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CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO (E) DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA

27 AGO 2004

PABLO MENDEZ BARAJAS
NOTARIO (E)

COMO NOTARIO SEXTO DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA

13 AGO 2004

JUAN MANUEL ESTERO MEDINA
NOTARIO

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JOSE LLOREDA CAMACHO & CO.

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**ABBOTT LABORATORIES**.-Solicitud de Patente de Invención para **"9A-AZALIDAS CON ACTIVIDAD ANTIBACTERIAL"**-Clase **A.61K**.-Expediente número **00-063.018**.-

1. Me refiero a mi memorial de 12 de Febrero de 2001, mediante el cual se dividió la solicitud de la referencia en dos solicitudes.

2. De conformidad con lo señalado en el numeral 4 (1) c del mencionado escrito, anexo me permito presentar copia del nuevo capítulo reivindicatorio que comprende las reivindicaciones originales 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 y 18, renumeradas y una reivindicación 15, quedando así el capítulo reivindicatorio para la solicitud original, compuesto por **17** reivindicaciones.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

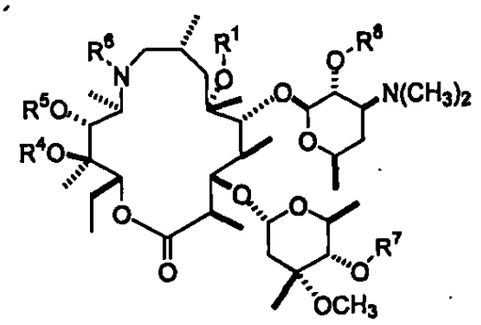
Señor Superintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

REIVINDICACIONES

LO QUE SE REIVINDICA ES:

1. Un compuesto de fórmula (I)



(I),

o sales farmacéuticamente aceptables del mismo, donde R^1 y R^6 son independientemente seleccionados del grupo que consiste de

(1) hidrógeno

(2) aquil -C_1-C_2-,

(3) alquenil -C_3-C_{12}-,

y

(4) alquinil -C_3-C_{12}-,

donde (2)-(4) pueden ser opcionalmente substituidos con uno, dos, o tres substituyentes independientemente seleccionados del grupo que consiste de

(a) halógeno,

(b) -OR^9, donde R^9 es seleccionado entre el grupo que consiste de

(i) hidrógeno

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(ii) alquil-C_1-C_{12}-,

(iii) heteroalquil -C_2-C_{12}-,

donde (ii) y (iii) pueden ser opcionalmente substituidos con uno, dos, o tres substituyentes independientemente seleccionados del grupo que consiste de

(1') aril,

(2') aril substituido por el reemplazo independiente de uno, dos o tres átomos de hidrógeno con -F, -Cl, -Br, -I, -OH, -NO_2, -CN, -(CO)-alquil-C_1-C_6, -C(O)-aril, -(CO)-heteroaril, -CO_2-alquil, -CO_2-aril, -CO_2-heteroaril, -$CONH_2$, -CONH-alquil-C_1-C_6-, -CONH-aril, -CONH-heteroaril, -OC(O)-alquil-C_1-C_6, -OC(O)-aril, -OC(O)-heteroaril, -OCO_2-alquil, -OCO_2-aril, -OCO_2-heteroaril, -$OCONH_2$, -OCONH-alquil-C_1-C_6-, -OCONH-aril, -OCONH-heteroaril, -NHC(O)-alquil-C_1-C_6-, -NHC(O)-aril, -NHC(O)-heteroaril, -$NHCO_2$-alquil, -$NHCO_2$-aril, -$NHCO_2$-heteroaril, -$NHCONH_2$, -NHCONH-alquil-C_1-C_6-, -NHCONH-aril, -NHCONH-heteroaril, -SO_2-alquil-C_1-C_6-, -SO_2-aril, SO_2-heteroaril, -SO_2NH_2, -SO_2NH-alquil-C_1-C_6-, -SO_2NH-aril, -SO_2NH-heteroaril, alquil-C_1-C_6-, cicloalquil-C_3-C_6-, -CF_3, -CH_2CF_3, $CHCl_2$, -CH_2OH, -CH_2CH_2OH, -CH_2NH_2, -$CH_2SO_2CH_3$, aril, heteroaril, bencil, benciloxi, ariloxi, heteroariloxi, alcoxi-C_1-C_6-, metoximetoxi, metoxietoxi, amino, bencilamino, arilamino, heteroarilamino, alquilamino-C_1-C_3-, tio, ariltio, heteroariltio, benciltio, alquiltio-C_1-C_6-, o metiltiometil.

(3') heteroaril,

y

(4') heteroaril substituido por el reemplazo independiente de uno, dos o tres átomos de hidrógeno con -F, -Cl, -Br, -I, -OH, $-NO_2$, -CN, -(CO)-alquil-C_1-C_6, -C(O)-aril, -(CO)-heteroaril, -CO_2-alquil, -CO_2-aril, -CO_2-heteroaril, $-CONH_2$, -CONH-alquil-C_1-C_6-, -CONH-aril, -CONH-heteroaril, -OC(O)-alquil-C_1-C_6, -OC(O)-aril, -OC(O)-heteroaril, -OCO_2-alquil, -OCO_2-aril, -OCO_2-heteroaril, $-OCONH_2$, -OCONH-alquil-C_1-C_6-, -OCONH-aril, -OCONH-heteroaril, -NHC(O)-alquil-C_1-C_6-, -NHC(O)-aril, -NHC(O)-heteroaril, -$NHCO_2$-alquil, -$NHCO_2$-aril, -$NHCO_2$-heteroaril, $-NHCONH_2$, -NHCONH-alquil-C_1-C_6-, -NHCONH-aril, -NHCONH-heteroaril, -SO_2-alquil-C_1-C_6-, -SO_2-aril, SO_2-heteroaril, $-SO_2NH_2$, -SO_2NH-alquil-C_1-C_6-, -SO_2NH-aril, -SO_2NH-heteroaril, alquil-C_1-C_6-, cicloalquil-C_3-C_6-, $-CF_3$, $-CH_2CF_3$, $CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2SO_2CH_3$, aril, heteroaril, bencil, benciloxi, ariloxi, heteroariloxi, alcoxi-C_1-C_6-, metoximetoxi, metoxietoxi, amino, bencilamino, arilamino, heteroarilamino, alquilamino-C_1-C_3-, tio, ariltio, heteroariltio, benciltio, alquiltio-C_1-C_6-, o metiltiometil.

(iv) aril,

(v) aril substituido, como se definió anteriormente.

(vi) heteroaril,

y

(xv) heteroaril substituido, como se definió anteriormente.

(c) $-NR^{11}R^{12}$, donde R^{11} y R^{12} son independientemente seleccionados del grupo que consiste de

(i) hidrógeno

(ii) alquil -C_1-C_{12}-,

(iii) heteroalquil -C_2-C_{12}-,

donde (ii) y (iii) pueden ser opcionalmente substituidos con uno, dos o tres substituyentes independientemente seleccionados del grupo que consiste de

(1') aril,

(2') aril substituido, como se definió anteriormente.

(3') heteroaril,

y

(4') heteroaril substituido, como se definió anteriormente.

(iv) aril,

(v) aril substituido, como se definió anteriormente.

(vi) heteroaril,

y

(xv) heteroaril substituido, como se definió anteriormente.

o

R^{11} y R^{12}, junto con el átomo al cual están unidos, forman un anillo heterocicloalquil, donde el anillo heterocicloalquil puede ser opcionalmente substituido por el reemplazo independiente de uno, dos o tres átomos de hidrógeno con -F, -Cl, -Br, -I, -OH, $-NO_2$, -CN, -(CO)-alquil-C_1-C_6, -C(O)-aril, -(CO)-heteroaril, -CO_2-alquil, -CO_2-aril, -CO_2-heteroaril, $-CONH_2$, -CONH-alquil-C_1-C_6-, -CONH-aril, -CONH-heteroaril, -OC(O)-alquil-C_1-C_6, -OC(O)-aril, -OC(O)-heteroaril, -OCO_2-alquil, -OCO_2-aril, -OCO_2-

heteroaril, -$OCONH_2$, -OCONH-alquil-C_1-C_6-, -OCONH-aril, -OCONH-heteroaril, -NHC(O)-alquil-C_1-C_6-, -NHC(O)-aril, -NHC(O)-heteroaril, -$NHCO_2$-alquil, -$NHCO_2$-aril, -$NHCO_2$-heteroaril, -$NHCONH_2$, -NHCONH-alquil-C_1-C_6-, -NHCONH-aril, -NHCONH-heteroaril, -SO_2-alquil-C_1-C_6-, -SO_2-aril, SO_2-heteroaril, -SO_2NH_2, -SO_2NH-alquil-C_1-C_6-, -SO_2NH-aril, -SO_2NH-heteroaril, alquil-C_1-C_6-, cicloalquil-C_3-C_6-, -CF_3, -CH_2CF_3, $CHCl_2$, -CH_2OH, -CH_2CH_2OH, -CH_2NH_2, -$CH_2SO_2CH_3$, aril, heteroaril, bencil, benciloxi, ariloxi, heteroariloxi, alcoxi-C_1-C_6-, metoximetoxi, metoxietoxi, amino, bencilamino, arilamino, heteroarilamino, alquilamino-C_1-C_3-, tio, ariltio, heteroariltio, benciltio, alquiltio-C_1-C_6-, o metiltiometil.

(d) =N-O-R^9, donde R^9 es definido arriba,

(e) aril,

(f) aril substituido, como se definió anteriormente.

(g) heteroaril,

(h) heteroaril substituido, como se definió anteriormente.

(i) cicloalquil -C_3-C_8-,

(j) cicloalquil -C_3-C_8- substituido por el reemplazo independiente de uno, dos o tres átomos de hidrógeno con -F, -Cl, -Br, -I, -OH, -NO_2, -CN, -(CO)-alquil-C_1-C_6, -C(O)-aril, -(CO)-heteroaril, -CO_2-alquil, -CO_2-aril, -CO_2-heteroaril, -$CONH_2$, -CONH-alquil-C_1-C_6-, -CONH-aril, -CONH-heteroaril, -OC(O)-alquil-C_1-C_6, -OC(O)-aril, -OC(O)-heteroaril, -OCO_2-alquil, -OCO_2-aril, -OCO_2-heteroaril, -$OCONH_2$, -OCONH-alquil-C_1-C_6-, -OCONH-aril, -OCONH-heteroaril, -NHC(O)-alquil-C_1-C_6- -NHC(O)-aril, -NHC(O)-heteroaril, -$NHCO_2$-alquil, -$NHCO_2$-aril, -$NHCO_2$-heteroaril, -$NHCONH_2$, -NHCONH-alquil-C_1-C_6-, -NHCONH-aril, -NHCONH-heteroaril, -SO_2-alquil-C_1-C_6-, -SO_2-aril, SO_2-heteroaril, -SO_2NH_2, -SO_2NH-alquil-C_1-C_6-, -SO_2NH-aril, -SO_2NH-heteroaril, alquil-C_1-C_6-, cicloalquil-

C_3-C_6-, $-CF_3$, $-CH_2CF_3$, $CHCl_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2NH_2$, $-CH_2SO_2CH_3$, aril, heteroaril, bencil, benciloxi, ariloxi, heteroariloxi, alcoxi-C_1-C_6-, metoximetoxi, metoxietoxi, amino, bencilamino, arilamino, heteroarilamino, alquilamino-C_1-C_3-, tio, ariltio, heteroariltio, benciltio, alquiltio-C_1-C_6-, o metiltiometil.

(k) heterocicloalquil,

(l) heterocicloalquil substituido, como se definió anteriormente.

(m) $-NHC(O)R^9$, donde R^9 es definido arriba,

(n) $-NHC(O)OR^{10}$, donde R^{10} es seleccionado entre el grupo que consiste de

(i) alquil -C_1-C_{12}-,

(ii) heteroalquil -C_1-C_{12}-,

donde (i) y (ii) pueden ser opcionalmente substituidos con uno, dos, o tres substituyentes independientemente seleccionados del grupo que consiste de

(1') aril,

(2') aril substituido, como se definió anteriormente.

(3') heteroaril,

y

(4') heteroaril substituido, como se definió anteriormente.

(iii) aril,

(iv) aril substituido, como se definió anteriormente.

(v) heteroaril,

y

(vi) heteroaril substituido, como se definió anteriormente.

(o) -NHC(O)$NR^{11}R^{12}$, donde R^{11} y R^{12} son definidos arriba,

(p) -OC(O)R^{10}, donde R^{10} es definido arriba,

(q) -OC(O)OR^{10}, donde R^{10} es definido arriba,

(r) -OC(O)$NR^{11}R^{12}$, donde R^{11} y R^{12} son definidos arriba,

(s) -C(O)R^{9}, donde R^{9} es definido arriba,

(t) -CO_2R^{9}, donde R^{9} es definido arriba,

y

(u) -C(O)$NR^{11}R^{12}$, donde R^{11} y R^{12} son definidos arriba;

R^4 y R^5 son hidrógeno;

o

R^4 y R^5 juntos son -C(O)- o -$(CH_2)_x$-, donde x es uno, dos, o tres;

o

R^5 y R^6 juntos son -C(O)- o -$(CH_2)_x$-, donde x es definido arriba;

R^7 es seleccionado del grupo que consiste de

(1) hidrógeno

(2) alquil -C_1-C_{12}-,

(3) alquenil -C_3-C_{12}-,

(4) alquinil -C_3-C_{12}-,

(5) heteroalquil -C_2-C_{12}-,

(6) heteroalquenil -C_4-C_{12}-,

(7) heteroalquinil -C_4-C_{12}-,

donde (2)-(7) pueden ser opcionalmente substituidos con uno, dos, o tres substituyentes independientemente seleccionados del grupo que consiste de

(a) halo,

(b) hidroxi,

(c) $-NR^{11}R^{12}$ donde R^{11} y R^{12} son definidos arriba,

(d) aril,

(e) aril substituido, como se definió anteriormente.

(f) heteroaril, y

(g) heteroaril substituido, como se definió anteriormente.

(8) $-C(O)R^9$, donde R^9 es definido arriba,

(9) $-CO_2R^9$, donde R^9 es definido arriba,

y

(10) $-C(O)NR^{11}R^{12}$, donde R^{11} y R^{12} son definidos arriba;

y

R^8 es hidrógeno o un grupo protector hidroxi

2. Un compuesto de acuerdo con la Reivindicación 1, en donde R^4 y R^5 son hidrógeno.

3. Un compuesto de acuerdo con la Reivindicación 1, en donde R^4 y R^5 juntos son -C(O)-.

4. Un compuesto de acuerdo con la Reivindicación 1, en donde R^6 es hidrógeno.

5. Un compuesto de acuerdo con la Reivindicación 1, en donde R^6 es metil.

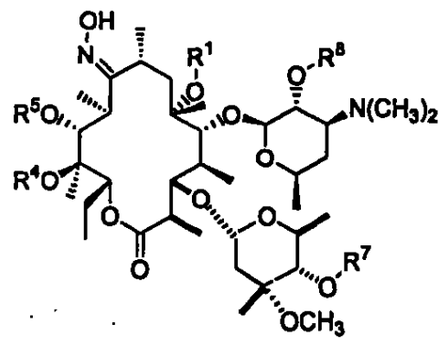
6. Un compuesto de acuerdo con la Reivindicación 1, en donde R^1 es $-CH_2-CH=CH_2$ o $-CH_2-CH=CH-$(3-quinolinil).

7. Un compuesto de acuerdo con la Reivindicación 6, en donde R^1 es $-CH_2-CH=CH_2$.

8. Un compuesto de acuerdo con la Reivindicación 6, en donde R^1 es CH_2-CH=CH-(3-quinolinil).

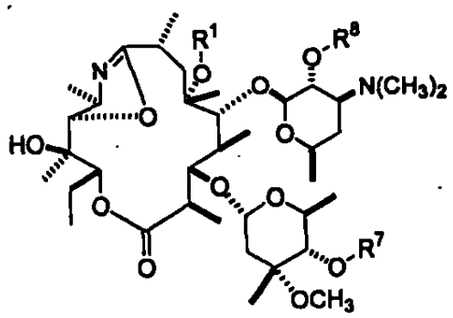
9. Un método para la preparación de los compuestos de acuerdo con la Reivindicación 1, el método comprende

(a) reacción de los compuestos de la fórmula (Ia)



(Ia)

En donde R^1, R4, R^5, R^7 y R^8 son como se definió en la Reivindicación 1, con un agente activador oxima para formar compuestos de fórmula (III)



(III),

(b) reacción del producto del paso (a) con un agente reductor;

(c) opcionalmente, alquilación del producto del paso (b); y

(d) opcionalmente desprotección del producto del Paso (c).

10. El método de acuerdo con la Reivindicación 9, en donde el agente activador oxima es un haluro de sulfonilo.

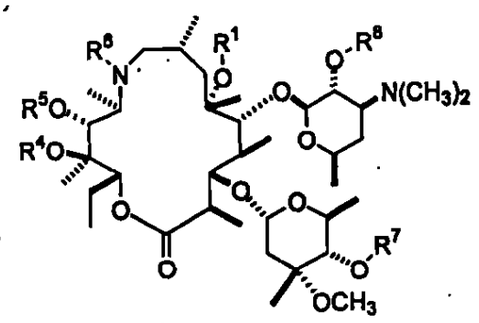
11. El método de acuerdo con la Reivindicación 10, en donde el haluro de sulfonilo es cloruro de para-toluensulfonilo, cloruro de metanosulfonilo, cloruro de para-bromosulfonilo, o cloruro de para-bromosulfonilo.

12. El método de acuerdo con la Reivindicación 9, en donde el agente reductor es borano en tetrahidrofurano, borano•dimetil sulfuro, cianoborohidruro de sodio, o borohidruro de sodio, opcionalmente en presencia de un ácido.

13. El método de acuerdo con la reivindicación 12, en donde el agente reductor es cianoborohidruro de sodio en presencia de ácido.

14. El método de acuerdo con la Reivindicación 13, en donde el ácido es ácido acético.

15. Un compuesto intermediario en la preparación de los compuestos de acuerdo con la Reivindicación 1, el cual tiene la fórmula:



(I),

o sales farmacéuticamente aceptables del mismo, en donde R^1, R^7 y R^8 son como se definió en la Reivindicación 1.

16. Una composición farmacéutica que comprende una cantidad farmacéuticamente efectiva de un compuesto de la Reivindicación 1 o de la Reivindicación 15 en combinación con un portador farmacéuticamente aceptable.

17. Un compuesto de acuerdo con la Reivindicación 1 o la Reivindicación 15 seleccionado entre el grupo que consiste de

Compuesto de la fórmula (III): R^1 es $-CH_2CH=CH_2$, R^4 es hidrógeno, R^7 es hidrógeno, R^8 es hidrógeno,

Compuesto de la fórmula (I): R^1 es $-CH_2CH=CH_2$, R^4 es hidrógeno, R^5

es hidrógeno, R^6 es hidrógeno, R^7 es hidrógeno, R^8 es hidrógeno,

Compuesto de la fórmula (I): R^1 es $-CH_2CH=CH_2$, R^4 es hidrógeno, R^5

es hidrógeno, R^6 es metil, R^7 es hidrógeno, R^8 es hidrógeno

y

Compuesto de la fórmula (I): R^1 es $-CH_2CH=CH$-(3-quinolinil), R^4 es hidrógeno, R^5 es hidrógeno, R^6 es metil, R^7 es hidrógeno, R^8 es hidrógeno.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCI
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., 14 de diciembre de 2005

Apoderado: Alicia Lloreda Ricaurte Oficio: 99 13961

REFERENCIA: Radicación No. 00-63018
Tramite 002
Evento 001
Actuación 430
Folios

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:

Documentos estudiados:

◆Capítulo descriptivo folios 5 a 59;
◆Capitulo reivindicatorio, folios 198 a 208;
◆1° examen de forma, folio 152 a 154;
◆Solicitud de la cual se reivindica prioridad, folios 84 a 147;
◆2° examen de forma folio 181;
◆Solicitud del examen de patentabilidad, folios 183 a 188;

Objeto de la invención:

La presente solicitud cuyo título es "9A-AZALIDAS CON ACTIVIDAD ANTIBACTERIAL". El objeto de la solicitud son los compuestos de derivados de 9ª-azahomoeritromicina, con actividad bactericida.

El objeto de la invención se puede clasificar según la clasificación internacional como A61K 31/70, 31/71.

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comunidad Andina establece que: "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*".

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En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio. Reivindicaciones 1 a 17 de los folios 198 a 208, consultada la fuente de información con que cuenta este despacho se encontró el siguiente documento:

Item	Documento	Fecha de publicación	Titulo
D1	EP0109253	23-05-1984	Epimeric azahomoherythromycin A derivatives and intermediates therefor
D2	EP0259789	16-03-1986	Metal complex of N-methyl-11-aza-10-deoxo-10-dihydroerthromycin A, method for the manufacture thereof and their use in the manufacture of pharmaceuticals
D3	US4474768	02-oct-1984	N-methyl-11-aza-10-deoxo-10-dihydroerithromycin A, intermediates therefor
D4	US5686587	11-nov-1997	Intermediate for azithromycin
D5	WO9856801	17-dic-1998	C-4"-subtituted macrolide derivatives
D6	WO9856802	17-dic-1998	C-4"-subtituted-9-deoxo-9A-aza-9A-homoerithromycin A derivatives
D7	US4464527	07-ago-1984	Antibacterial 9-deoxo-9A alkyl-9A-homo-erythromycin A derivatives and intermediates thereof

Evaluación de la novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina dispone que: "*Una invención se considerará nueva cuando no está comprendida en el estado de la técnica*".

En la solicitud en estudio se reclaman compuestos que comprenden la fórmula general: (I)

-La anterioridad D1 enseña la síntesis total de epimericos de 9ª-azalidas con actividad antibacteriana, análogos de eritromicina A , modificados en N (9ª), en 4", en 11 y 12, con los mismos sustituyentes, o con otros análogos que conservan el ampliamente conocido efecto antibacterial de los macrólidos; los compuestos de la anterioridad caen dentro de lo que se reclama como nuevo con la formula general (I) en la solicitud en estudio; entonces los compuestos de la solicitud en estudio no son nuevos.

-Las anterioridades D2, D3, D4, D6 y D7 enseñan la síntesis total de derivados de 9ª-azalidas con actividad antibacteriana, análogos de eritromicina A , modificados en N (9ª), en 4", en 11 y 12, con los mismos sustituyentes, o con sustituyentes análogos; siendo específica la presente anterioridad respecto a la generalización de la formula (I) de la solicitud en estudio; entonces los compuestos de la solicitud en estudio no son nuevos.

-La anterioridad D5-La anterioridad D1 enseña la síntesis total de epimericos de 9ª-azalidas con actividad antibacteriana, análogos de eritromicina A, modificandos en N (9ª), en 4", en 11 y 12, con los mismos sustituyentes, o análogos, para conservar el ampliamente conocido efecto antibacterial de los macrólidos; los compuestos de la anterioridad caen dentro de lo que se reclama como nuevo con la formula general (I) en la solicitud en estudio; entonces los compuestos de la solicitud en estudio no son nuevos.

No	Documento:	Reivindicaciones afectadas:	Requisito afectado
D1	EP0109253	1 a 17	Novedad y nivel inventivo
D2	EP0259789	1 a 17	Novedad y nivel inventivo
D3	US4474768	1 a 17	Novedad y nivel inventivo
D4	US5686587	1 a 17	Novedad y nivel inventivo
D5	WO9856801	1 a 17	Novedad y nivel inventivo
D6	WO9856802	1 a 17	Novedad y nivel inventivo
D7	US4464527	1 a 17	Novedad y 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 numeral 5.2,literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.

CLARA CASTELLANOS DE JAIMES
Jefe de División de Nuevas Creaciones(E)

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El anterior requerimiento fue notificado por fijación en lista, de fecha

29 DIC. 2005

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Epimeric azahomoerythromycin A derivative and intermediates therefor.

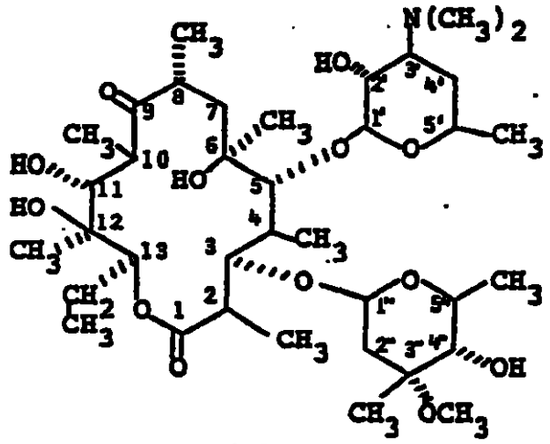
Antibacterial 4"-epi-9-deoxo-9a-methyl-9a-aza-9a-homo-erythromycin A, pharmaceutically-acceptable salts thereof, pharmaceutical compositions comprising antibacterially-effective amounts thereof, a method of treatment of bacterial infections with antibacterially effective amounts thereof, and intermediates for the synthesis thereof from erythromycin A.

EP 0 109 253 A2

EPIMERIC AZAHOMOERYTHROMYCIN A DERIVATIVE AND INTERMEDIATES THEREFOR

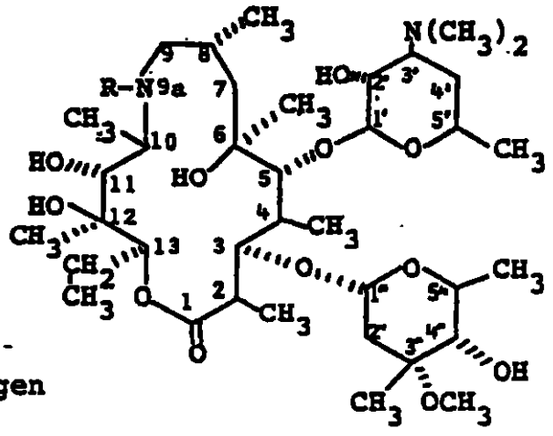
The present invention is concerned with antibacterial 4"-epi-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A, pharmaceutically-acceptable salts thereof, and intermediates useful in the preparation thereof from erythromycin A.

Erythromycin A is a well-known macrolide antibiotic, having the formula (I), which has found extensive clinical use.



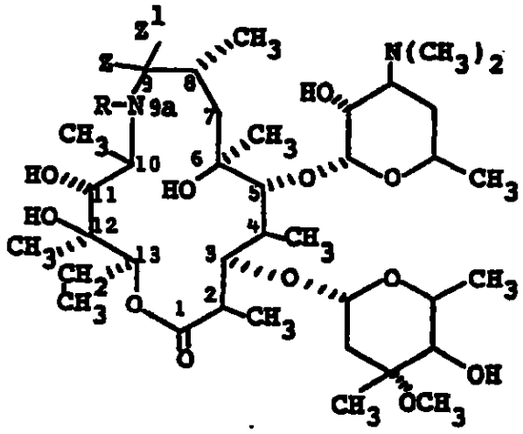
(I)

The present therapeutic compound is the 4"-epimer of the previously reported erythromycin A derivative of the formula (II), the



(II) R=methyl

(III) R=hydrogen



(IV) R=methyl, Z=Z^1=hydrogen

(V) R=hydrogen, Z and Z^1 together=oxygen

(VI) R=Z=Z^1=hydrogen

The present therapeutic compound (IV) shows a relatively broad spectrum of antibacterial activity which includes erythromycin A susceptible organisms and, in addition, fully incorporates the major respiratory pathogen Hemophilus influenzae. Its high oral absorption and extraordinarily long half-life in vivo renders compound (IV) of especial value in the oral treatment of susceptible bacterial infections in mammals.

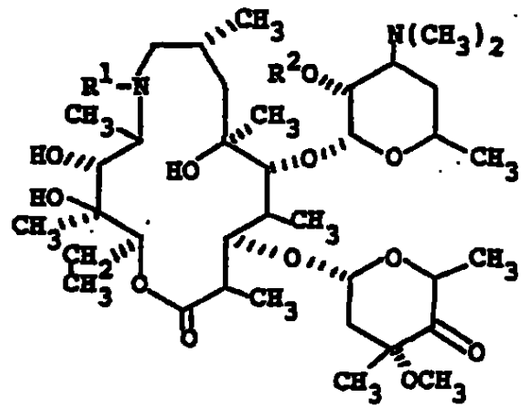
The present invention also encompasses intermediates useful in the synthesis of 4"-epi-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (IV) as follows:

(a) A compound selected from the group consisting of 4"-epi-9a-aza-9a-homoerythromycin A and the 9-deoxo derivative thereof; of the above formulae (V) and (VI), respectively.

(b) 4"-Epi-erythromycin A oxime.

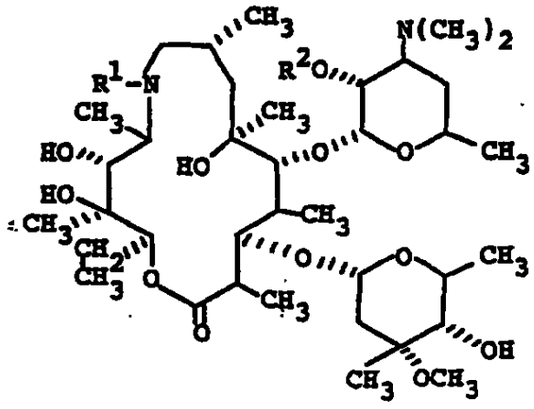
(c) A compound selected from the group consisting of 9a-benzyloxycarbonyl-9-deoxo-4"-deoxy-4"-oxo-9a-aza-9a-homoerythromycin A, of the formula (VII); 9-

deoxo-4"-deoxy-4"-oxo-9a-methyl-9a-aza-9a-homoerythromycin A, of the formula (VIIa); and the corresponding 2'-O-(C_2-C_3)alkanoyl derivatives thereof of the formulae (VIII) and (VIIIa). Acetyl is the preferred value of 2'-O-(C_2-C_3)alkanoyl.



(VII) R^1=benzyloxycarbonyl, R^2=H
(VIII) R^1=benzyloxycarbonyl, R^2=(C_2-C_3)alkanoyl
(VIIa) R^1=methyl, R^2=H
(VIIIa) R^1=methyl, R^2=(C_2-C_3)alkanoyl

(d) A compound selected from the group consisting of the 2'-O-acetyl- and the 2'-O-propionyl-9-deoxo-9a-benzoyloxycarbonyl-9a-aza-9a-homoerythromycin A, of the formula (IX). The 2'-O-acetyl derivative is of particular value.



(IX) R^1=benzyloxycarbonyl, R^2=(C_2-C_3)alkanoyl

(A)(B)(C)(D), (B)(A)(C)(D) or (B)(C)(D)(A). The various intermediates and final product are isolated by standard manipulative methods (e.g., extraction, precipitation, evaporation, chromatography, crystallization).

(A)(B)(C)(D)

The operational sequence (A)(B)(C)(D) involves initial conversion of erythromycin A (I) to 4-epi-erythromycin A, according to the method of Sciavolino et al. (supra). The latter is then converted, in virtually quantitative yield, to 4"-epi-erythromycin A oxime by reaction with hydroxylamine or preferably, a hydroxylamine salt such as the hydrochloride. Under presently discovered, preferred conditions, at least one molar equivalent, usually an excess, e.g., 10-30 equivalents, of the hydroxylamine is employed; in an excess of a weakly basic, tertiary amine (preferably pyridine) as solvent; at a temperature in the range 0-50°, conveniently at ambient temperature.

The resulting 4"-epi-erythromycin oxime is rearranged to the 4"-epi-9a-aza-9a-homo derivative (V) via a Beckman rearrangement. The preferred conditions employ an excess (e.g., 3-4 molar equivalents) of an organic sulfonyl chloride, preferably methane sulfonyl chloride, which is reacted with the oxime (as free base or as an acid salt) in a mixture of a lower ketone (e.g., methyl ethyl ketone, acetone) and water containing a large molar excess of sodium bicarbonate, at a temperature of 0-50°C., preferably at 0-30°C.

The C-9 amide carbonyl of (V) is then conveniently reduced to the corresponding dihydro derivative, i.e., 4"-epi-9-dedxo-9a-aza-9a-homoerythromycin A (VI) by reduction with sodium borohydride (preferably in excess to force the reaction to completion in a reasonable time period, but with at least two equivalents). The reduction is carried out in a suitable protic solvent, such as a lower alkanol (preferably methanol) at 0-50°

(preferably at or below 38°). Excess $NaBH_4$ is carefully decomposed by quenching the reaction in dilute aqueous acid.

Final methylation to yield the compound (IV) is accomplished by reductive methylation, using formaldehyde in the presence of a reducing agent, such as hydrogen and a noble metal catalyst, sodium cyanoborhydride, or, preferably, formic acid. The reaction is preferably carried out with at least one equivalent each of formaldehyde and formic acid in a reaction inert solvent at 20-100°C. The preferred solvent is chloroform. In this solvent, reactants are conveniently combined at ambient temperature and then heated at reflux to force the reaction to completion.

Alternatively, methylation of (VI) to (IV) is accomplished by oxidatively protecting the dimethylamino group as its N-oxide (simultaneously forming the 9a-N-hydroxy derivative), methylating with methyl iodide, with (at least in part) simultaneous 9a-N-deoxygenation, and reduction of the resulting 9a-methyl-3"-N-oxide. Oxidation of (VI) is readily accomplished by reaction with hydrogen peroxide, generally in excess of the minimum necessary two molar equivalents, in a reaction inert solvent at 10-50°C., conveniently at ambient temperature. In this manner 9a-hydroxy-3'-N-oxide (X) is formed. The latter is methylated and deoxygenated to (XI) with methyl iodide conveniently in a reaction inert solvent (e.g., methylene chloride) at 0-50°C. (conveniently at ambient temperature), preferably in the presence of a solvent insoluble base which will neutralize formed acid (e.g., HI when methyl iodide is the methylating agent). With methylene chloride as solvent, an excess of potassium

carbonate is the base of choice. Thus the excess base and formed sodium iodide are completely removed by simple filtration prior to isolation of the 9a-methyl-3'-N-oxide (XI). Finally, removal of the 3'-N-oxide group is readily accomplished by hydrogenation over a noble metal or Raney nickel catalyst. In this hydrogenation, temperature and pressure are not critical, e.g., suitably 0-100°C. and a pressure which ranges from subatmospheric to 100 atmospheres or more. Most convenient are ambient temperature and moderate pressures, e.g., 2-8 atmospheres. Suitable noble metal catalysts include palladium rhodium and platinum, of the supported or non-supported type, well known in the art of catalytic hydrogenation. The preferred catalysts are palladium supported on carbon and Raney nickel.

(B)(A)(C)(D)

The operational sequence (B)(A)(C)(D) involves initial conversion of erythromycin A (I) to 9-deoxo-9a-aza-9a-homoerythromycin (III), via erythromycin A oxime and 9a-aza-9a-homoerythromycin, according to the method of Kobrehel et al. (supra). In this connection, the novel process, described above for 4"-epi-erythromycin A oxime, is advantageously employed for the preparation of the intermediate erythromycin A oxime.

The 2'-hydroxy group of compound (III) is first protected in the form of its acetate or propionate ester. Acylation is selectively accomplished by reacting compound (III) with a limited excess of acetic or propionic anhydride in a reaction inert solvent (e.g., methylene chloride) at 0-30°C. (conveniently ambient temperature). The limited excess of anhydride is used to compensate for reagent consumed in side reactions, e.g., undesired acylation of other groups, particularly the 9a-nitrogen.

The resulting 2'-(C_2-C_3)alkanoyl derivative is then protected on 9a-nitrogen with a benzyloxycarbonyl group. Thus compound (IX) is formed by reaction of the above 2'-ester with carbobenzoxy chloride, in a reaction inert solvent in the presence of a base. Particularly well suited are Schotten-Baumann conditions, i.e., reaction of the 2'-ester with the acid chloride under aqueous, alkaline conditions, e.g., aqueous tetrahydrofuran, maintaining the pH 7.5-8.5 with dilute NaOH as the acid chloride is added and as the reaction proceeds. Temperature is not critical, but will generally be in the range 0-50°C., conveniently ambient.

The C-4" hydroxyl compound (IX) is then oxidized to C-4"-oxo compound (VIII) by the action of oxalyl chloride/ dimethylsulfoxide at low temperature (-40 to -80°C.) in a reaction inert solvent (e.g., methylene chloride), followed by treatment of the cold reaction mixture with an excess of a tertiary amine (e.g., triethylamine). The alkanoate ester protecting group is removed by solvolysis, preferably by contact with excess methanol at 0-100°C. thereby forming compound (VII).

Hydrogenation over Raney nickel catalyst, using conditions as described above, converts compound (VII) to 4"-epi-9-deoxo-9a-aza-9a-homoerythromycin A (VI). The latter is converted to the 9a-N-methyl derivative (IV) according to one of alternative methods as described above.

<u>(B)(C)(D)(A)</u>

This operational sequence involves initial conversion of erythromycin A to the above compound of the formula (II) according to my above cited copending application, using methods detailed in the Preparation section below. C-4" epimerization is then accomplished according to the steps and methods

described above. The 2'-hydroxy group is protected by acylation, the 4"-hydroxy group is oxidized to the 4"-oxo group, preferably substituting trifluoroacetic anhydride for oxalyl chloride; the protecting acyl group is removed; and the 4"-oxo group catalytically hydrogenated to the desired 4"-epimeric hydroxy group. In this case, the preferred catalyst is Raney nickel.

Since compound (IV) of the present invention contains two basic nitrogen atoms, pharmaceutically acceptable mono and di acid addition salts are formed by contacting the free base (IV), respectively, with substantially one equivalent of the acid or with at least two equivalents of the acid. Salts are generally formed by combining the reagents in a reaction inert solvent; if the salt does not precipitate directly, it is isolated by concentration and/or addition of a non-solvent. Suitable pharmaceutically acceptable acid addition salts include, but are not restricted to those with HCl, HBr, HNO_3, H_2SO_4, $HO_2CCH_2CH_2CO_2H$, cis- and trans-$HO_2CCHCHCO_2H$, CH_3SO_3H and p-$CH_3C_6H_4SO_3H$.

The antibacterial activity of the compound of the formula (IV) is demonstrated by measuring its minimum inhibitory concentrations (MIC's) in mcg./ml. against a variety of microorganisms in brain heart infusion (BHI) broth. Generally twelve 2 fold dilutions of the test compound are employed, with initial concentration of the test drug being in the range of 50 to 200 mcg./ml. The susceptibility (MIC) of the test organism is accepted as the lowest concentration of compound capable of producing complete inhibition of growth as judged by the naked eye. A comparison of the activity of 4"-epi-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (IV) with that of an erythromycin A control is shown in replicate in the Table I.

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(54) **Metal complexes of N-methyl-11-aza-10-deoxo-10-dihydro-erythromycin A or 11-aza-10-deoxo-10-dihydroerythromycin A, method for the manufacture thereof and their use in the manufacture of pharmaceuticals.**

(57) New 2:1 complexes of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A or 11-aza-10-deoxo-10-dihydroerythromycin A with bivalent metals chosen from the group comprising Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2} and Ca^{+2}, a process for their manufacture and their use in the manufacture of antibiotically active pharmaceuticals.

New 2:1 complexes of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A or 11-aza-10-deoxo-10-dihydroerythromycin A with bivalent metals chosen from the group comprising Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2} and Ca^{+2} are made by reacting N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A or 11-aza-10-deoxo-10-dihydroerythromycin A in its free base form or in its water-soluble salt form with salts of said bivalent metals. The compounds possess antibiotic activity.

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METAL COMPLEXES OF N-METHYL-11-AZA-10-DEOXO-10-DIHYDROERYTHROMYCIN A OR 11-AZA-10-DEOXO-10-DIHYDROERYTHROMYCIN A, METHOD FOR THE MANUFACTURE THEREOF AND THEIR USE IN THE MANUFACTURE OF PHARMACEUTICALS

The present invention relates to new, biologically active compounds of semisynthetic 15-membered macrolide antibiotics N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A or 11-aza-10-deoxo-10-dihydroerythromycin A with bivalent metals, to methods for the manufacture thereof and to their use in the manufacture of pharmaceuticals.

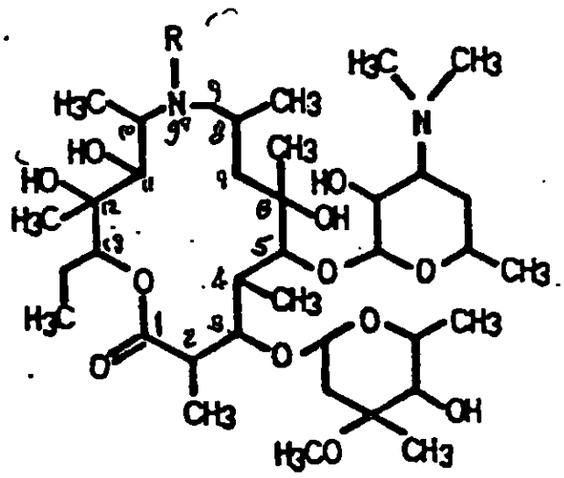
By means of chemical transformations of the C-9 keto group of erythromycin A there were synthetized 15-membered macrolides possessing a nitrogen atom in the aglycone ring, namely 11-aza-10-deoxo-10-dihydroerythromycin A (U.S. patent 4,328,334) and N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (Belgian patent 892,357 and GB patent 2,094,293 resp.), which is an effective antibacterial agent in the treatment of gram-positive and gram-negative microorganisms and exhibited an important activity in preliminary in vivo tests.

It has been known that the presence of metals and the formation of metal complexes resp. might substantially influence the stability, distribution, biotransformation, elimination and other characteristics of pharmaceuticals, especially of antibiotics.

According to the literature(J. Pharm. Pharmac. 18 (1966) 729) erythromycin A may theoretically yield a wax complex with Co^{+2}, but it does not yield any complexes with Cu^{+2}, Ca^{+2}, Mg^{+2}, Ni^{+2} and Zn^{+2} ions.

The metal complexes of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A and 11-aza-10-deoxo-10-dihydroerythromycin A have, according to the Applicant's own search of prior art, not been described as yet.

It has now been found that new useful complexes of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (Ia) and 11-aza-10-deoxo-10-dihydroerythromycin A (Ib)



Ia R = CH_3

Ib R = H

with bivalent metals chosen from the group comprising Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2} andCa^{+2} in the ratio of 2:1 may be obtained in a simple manner and in high yields by means of the claimed process.

One object of the present invention are new 2:1 complexes of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A and 11-aza-10-deoxo-10-dihydroerythromycin A of the above cited formulae Ia and Ib with Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2} and Ca^{+2}, which exhibit a superior pharmacological, specifically a superior antibiotic activity.

Another object of the present invention is a new process for the manufacture of said new metal complexes, which is performed in such a manner that N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A of the formula Ia or 11-aza-10-deoxo-10-dihydro erythromycin A of the formula Ib or salts thereof are reacted with salts of bivalent metals chosen from the group comprising Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2} andCa^{+2}, in a molar ratio of 2:1, at ambient temperature.

When the reaction is performed with the compounds Ia or Ib in their salt form, said compounds Ia or Ib are first converted into their water-soluble salts, e.g. a hydrochloride, by means of suitable acids, whereupon the reaction is performed in aqueous solution with a salt of said bivalent metals. The pH of the reaction solution is adjusted to 8-11 by adding alkali lyes (pH-stating) and the product is isolated by means of filtration (method A).

When the reactants Ia and Ib are used in their free base form, the reaction with the metal salt is performed in an alcohol-water mixture while adjusting the pH value by means of alkali lyes and evaporating the alcohol under reduced pressure. The product is isolated by filtration (method B).

The antibiotical activity was assessed on the test organism Sarcina lutea ATCC 9341 as evident from the following Examples. The new complexes exhibited a potent antibiotic activity. Therefore a further object of the present invention is a pharmaceutical composition comprising an effective amount of the new metal complexes of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A or 11-aza-10-deoxo-10-dihydroerythromycin A, a method of treating human and animal infections, and a method for the manufacture of pharmaceuticals comprising the metal complexes of the compounds of the formula Ia or Ib.

The present invention is illustrated but in no way limited by the following Examples.

Example 1 (Method A)

0.749 g N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A were charged into a 100 ml beaker and dissolved under stirring and the addition of 1 N HCl in 50 ml of water (0.02 M solution) (pH about 6).

Then there were added 0.086 g $CuCl_2 \times 2H_2O$ (0.01 M solution with respect to Cu^{+2}) and the stirring was continued under a stepwise addition of 0.1 N NaOH until the pH value of 8.5 was achieved. Subsequently, the reaction mixture was stirred for 2 hours at a constant pH value (pH-stating), then the violet-coloured precipitate was aspirated, washed three times with 10 ml of water and dried; and yield was 0.64 g of the product (81.8 %).

Cu-analysis: (polarographic method, 0.1 N HCl, $E_{1/2}$ = -0.25 V;
SCE - saturated calomel electrode)
Calc.: 4.07 %
Found: 4.1 %
Activity: 834 U/mg Sarcina lutea ATCC 9341.

Example 2 (Method B)

In 50 ml of a 0.02 M solution of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A in 80 % w/w methanol there were dissolved 0.086 g $CuCl_2 \times 2H_2O$ (0.01 M solution with respect to Cu^{+2}). After the adjustment of the pH value to 8.5 with 0.1 N NaOH it was kept stirring for two hours at ambient temperature. The reaction mixture was evaporated at reduced pressure to about half its volume, the violet-coloured precipitate was aspirated, washed three times with 10 ml of water, dried and afforded 0.62 g of the product (79.3 %).

The analysis of the product was identical as in Example 1.

Example 3

The process was performed as described in Example 1 with the sole exception that 0.068 g $ZnCl_2$ were added instead of $CuCl_2$ and the pH value was kept adjusted at 8.6. There were obtained 0.61 g of a white-coloured product (77.9 %).

Zn-analysis: (atom absorption spectrophotometric method)
Calc.: 4.18 %
Found: 4.5 %
Activity: 852 U/mg Sarcina lutea ATCC 9341.

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Example 4

The process was performed as described in Example 1 with the sole exception that 0.118 g $CoCl_2 \times 6H_2O$ were added instead of $CuCl_2$ and the pH value was kept adjusted at 8.6. There were obtained 0.63 g of a light green-coloured product (80.7 %).

Co-analysis: (polarographic method, 0.1 N HCl - 0.1 N KCl (1:25).

$E_{1/2}$ = -1.60 V; SCE)

Calc.: 3.79 %

Found: 4.1 %

Activity: 849 U/mg Sarcina lutea ATCC 9341.

Example 5

The process was performed as described in Example 1 with the sole exception that 0.119 g $NiCl_2 \times 6H_2O$ were added instead of $CuCl_2$ and the pH value was kept adjusted at 8.6. There were obtained 0.62 g (79.6 %) of a light green-coloured product.

Ni-analysis: (polarographic method, 0.1 N HCl - 0.1 N KCl (1:25).

$E_{1/2}$ = -1.55 V; SCE)

Calc.: 3.77 %

Found: 4.3 %

Activity: 852 U/mg Sarcina lutea ATCC 9341.

Example 6

The process was performed as described in Example 1 with the sole exception that 0.074 g $CaCl_2 \times 2H_2O$ were added instead of $CuCl_2$ and the pH value was kept adjusted at 8.6. There were obtained 0.60 g (77.9 %) of a white-coloured product.

Ca-analysis: (atom absorption spectrophotometric method)

Calc.: 2.60 %

Found: 3.3 %

Activity: 858 U/mg Sarcina lutea ATCC 9341.

Example 7

The process was performed as described in Example 1 with the sole exception that 0.735 g 11-aza-10-deoxo-10-dihydroerythromycin A were charged instead of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A and the pH value was kept adjusted at 9.0. There were isolated 0.62 g of a violet-coloured product (80.8 %).

Cu-analysis (polarographic method: 0.1 N HCl)

Calc.: 4.14 %

Found: 4.4 %

Activity: 945 U/mg Sarcina lutea; ATCC 9341.

Example 8

The process was performed as described in Example 2 except that there were charged 0.735 g 11-aza-10-deoxo-10-dihydroerythromycin A instead of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A and 0.068 g $ZnCl_2$ instead of $CuCl_2$, while keeping the pH value adjusted at 10.0 for three hours. There were isolated 0.53 g (69.0 %) of a white-coloured product.

Zn-analysis: (atom absorption spectrophotometric method)

Calc.: 4.10 %

Found: 4.6 %

Activity: 530 U/mg Sarcina lutea ATCC 9341.

225
227

Example 9

The process was performed as described in Example 4 except that 0.735 g 11-aza-10-deoxo-10-dihydroerythromycin A were charged instead of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A and the pH value was kept adjusted at 10. There were isolated 0.54 g (70.6 %) of a light green-coloured product.

Co-Analysis: (polarographic method, 0.1 N HCl - 0.1 N KCl)
Calc.: 3.72 %
Found: 4.1 %
Activity: 435 U/mg Sarcina lutea ATCC 9341.

Example 10

The process was performed as described in Example 9 with the sole exception that 0.118 g $NiCl_2 \times 6H_2O$ were charged instead of $CoCl_2$. There were isolated 0.58 g (73.2 %) of a light green-coloured product.

Ni-Analysis: (polarographic method, 0.1 N HCl - 0.1 N KCl)
Calc.: 3.70 %
Found: 4.1 %
Activity: 500 U/mg Sarcina lutea ATCC 9341.

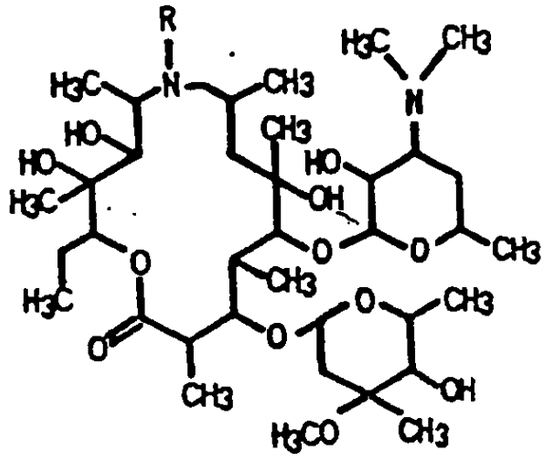
Example 11

The process was performed as described in Example 9 with the sole exception that 0.074 g $CaCl_2 \times 2H_2O$ were added instead of $CoCl_2$. There were isolated 0.52 g (68.9 %) of a white-coloured product.

Ca-analysis: (atom absorption spectrophotometric method)
Calc.: 2.55 %
Found: 3.0 %
Activity: 517 U/mg Sarcina lutea ATCC 9341.

Claims

1. A complex of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A of the formula (Ia) or 11-aza-10-deoxo-10-dihydroerythromycin A of the formula (Ib)

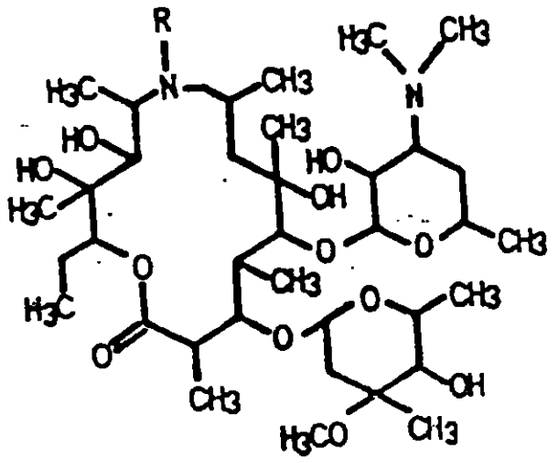


Ia R = CH_3

Ib R = H

with bivalent metals chosen from the group comprising Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2}, Ca^{+2} in the ratio of 2:1.

2. A process for preparing a complex of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (Ia) or 11-aza-10-deoxo-10-dihydroerythromycin A (Ib)



Ia R = CH_3

Ib R = H

with bivalent metals chosen from the group comprising Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2} andCa^{+2} in the ratio of 2:1, which comprises:

A) the reaction of a compound of the formula (Ia) or (Ib) in the form of its water-soluble salt with a salt of a bivalent metal chosen from the group comprising Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2} and Ca^{+2}, in a molar ratio of 2:1, in an aqueous solution and at ambient temperature while keeping the pH value adjusted at 8-11, and the isolation of the product by means of filtration, or

B) the reaction of a compound of the formula (Ia) or (Ib) with a salt of a bivalent metal chosen form the group comprising Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2} and Ca^{+2}, in a molar ratio of 2:1, at ambient temperature, in an alcohol-aqueous solution while keeping the pH value adjusted at 8-11 by the addition of alkali lyes, the evaporation of the alcohol under reduced pressure after the performed reaction and the isolation of the product by filtration.

3. A process as claimed in claim 2, wherein the water-soluble salt of the compound (Ia) or (Ib) is a hydrochloride.

4. A process as claimed in claims 2 or 3, wherein the metal salt is a chloride.

5. The use of 2:1 complexes of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A or 11-aza-10-deoxo-10-dihydroerythromycin A with bivalent metals chosen from the group comprising Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2} and Ca^{+2} in the manufacture of antibiotically active pharmaceuticals.

D3

2/3

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United States Patent [19]

Bright

[11] **Patent Number: 4,474,768**

[45] **Date of Patent: Oct. 2, 1984**

[54] **N-METHYL 11-AZA-10-DEOXO-10-DIHYDROERYTHROMYCIN A, INTERMEDIATES THEREFOR**

[75] Inventor: **Gene M. Bright, Groton, Conn.**

[73] Assignee: **Pfizer Inc., New York, N.Y.**

[21] Appl. No.: **441,981**

[22] Filed: **Nov. 15, 1982**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 399,401, Jul. 19, 1982, abandoned.

[51] Int. Cl.³ A61K 31/71; C07H 17/08

[52] U.S. Cl. 424/180; 536/7.4

[58] Field of Search 536/7.4; 424/180

[56] **References Cited**

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4,110,531	8/1978	Sciavolino	536/7.4
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4,328,334	5/1982	Kobrehel et al.	536/7.4

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Migridichian *Organic Synthesis*, vol. 1, New York: Reinhold Pub. Corp. 1957, p. 476.

Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., N.Y., 1981, p. 281.

Primary Examiner—Johnnie R. Brown
Assistant Examiner—Elli Peselev
Attorney, Agent, or Firm—Charles J. Knuth; Albert E. Frost; Peter C. Richardson

[57] **ABSTRACT**

Antibacterial N-methyl 11-aza-10-deoxo-10-dihydroerythromycin A and pharmaceutically acceptable acid addition salts thereof, intermediates therefor, and processes for their preparation.

8 Claims, No Drawings

N-METHYL 11-AZA-10-DEOXO-10-DIHYDROERYTHROMYCIN A, INTERMEDIATES THEREFOR

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of copending application Ser. No. 399,401, filed July 19, 1982, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to a novel derivative of 11-aza-10-deoxo-10-dihydroerythromycin A useful as an antibacterial agent, to intermediates therefor, and to processes for their preparation. More particularly it relates to the N-methyl derivative of 11-aza-10-deoxo-10-dihydroerythromycin A, to pharmaceutically acceptable acid addition salts thereof, and to certain alkanoyl derivatives thereof useful as antibacterial agents, to intermediates therefor, and to processes for their preparation.

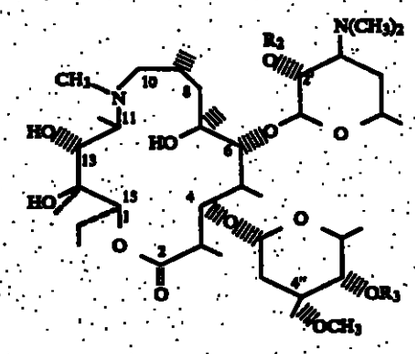
Erythromycin A is a macrolide antibiotic produced by fermentation and described in U.S. Pat. No. 2,653,899. Numerous derivatives of erythromycin A have been prepared in efforts to modify its biological and/or pharmacodynamic properties. Erythromycin A esters with mono- and dicarboxylic acids are reported in Antibiotics Annual, 1953–1954, Proc. Symposium Antibiotics (Washington, D.C.), pages 500–513 and 514–521, respectively. U.S. Pat. No. 3,417,077 describes the cyclic carbonate ester of erythromycin A, the reaction product of erythromycin A and ethylene carbonate, as an active and antibacterial agent.

U.S. Pat. No. 4,328,334, issued May 4, 1982, describes 11-aza-10-deoxo-10-dihydroerythromycin A, certain N-acyl- and N-(4-substituted benzenesulfonyl) derivatives thereof having antibacterial properties, and a process for their preparation.

The alkylation of primary and/or secondary amine groups of compounds which include a tertiary amine group is generally complicated. However, it is common practice to protect tertiary amine groups in such compounds by converting them to N-oxides prior to alkylation (Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., N.Y., 1981, pg. 281).

SUMMARY OF THE INVENTION

It has now been found that the N-methyl derivative of 11-aza-10-deoxo-10-dihydroerythromycin A and its 2'-, 4''- and/or 2',4''-acetyl-, propionyl- and 3-carbethoxypropionyl derivatives are effective antibacterial agents against gram-positive and gram-negative bacteria. The compounds have formula I

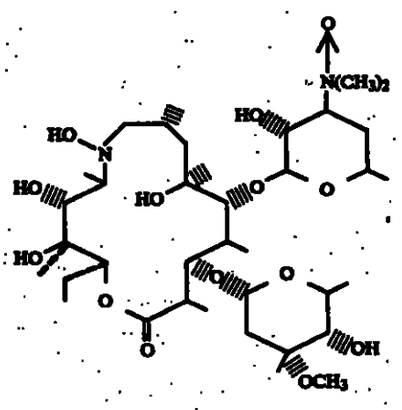


I

wherein R_2 is hydrogen, alkanoyl having from 2 to 3 carbon atoms or 3-carbethoxypropionyl; and R_3 is hydrogen, alkanoyl having from 2 to 3 carbon atoms or 3-carbethoxypropionyl.

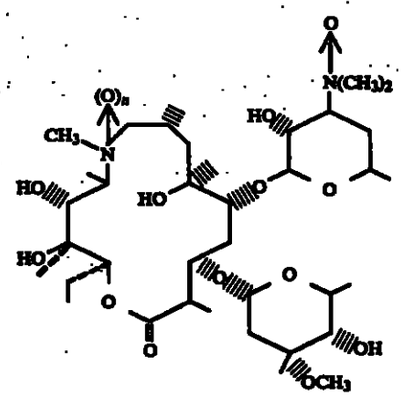
Also valuable for the same purpose as formula I compounds are the pharmaceutically acceptable acid addition salts thereof. Included among said salts, but by no means limited to said salts, are those enumerated below: hydrochloride, hydrobromide, sulfate, phosphate, formate, acetate, propionate, butyrate, citrate, glycolate, lactate, tartrate, malate, maleate, fumarate, gluconate, stearate, mandelate, pamoate, benzoate, succinate, lactate, p-toluenesulfonate and aspartate.

This invention also includes the intermediates of formulae II, III and III-A:



II

and



III
III-A

n = 1

-continued

n = 0

The compounds of this invention of formula I can be named as N-methyl-11-aza-4-O-(L-cladinosyl)-6-O-(D-desosaminyl)-15-ethyl-7,13,14-trihydroxy-3,5,7,9,12,14-hexamethyloxacyclopentadecane-2-ones. However, for simplicity, they are referred to herein as N-methyl derivatives of 11-aza-10-deoxo-10-dihydroerythromycin A, the nomenclature used in U.S. Pat. No. 4,328,334.

The compound of formula II (R_2=R_3=H) is named in like manner as N-hydroxy-11-aza-10-deoxo-10-dihydroerythromycin A N'-oxide, the term "N'-oxide" referring to oxide formation on the dimethylamino group of the desosaminyl moiety. The alkylated structure of formula III (R_2=R_3=H) is named as N-methyl-11-aza-10-deoxo-10-dihydroerythromycin bis N-oxide. The stereochemistry at the 11-aza atom of formula III is not yet known. However, said formula III is intended to embrace the diastereomers.

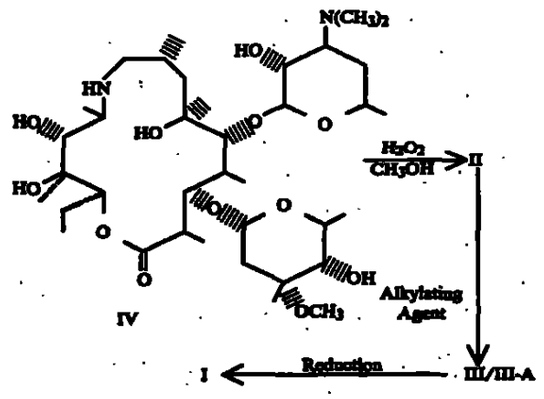
As an alternative to the nomenclature used above, the parent compound of formula IV below can be named as 9-deoxo-9a-aza-9a-homoerythromycin A. Using this system the compounds of formula I wherein each of R^2 and R^3 is hydrogen is named 9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A.

Compounds of formula I and pharmaceutically acceptable acid addition salts thereof are effective antibacterial agents against gram-positive microorganisms, e.g. *Staphylococcus aureus* and *Streptococcus pyogenes*, and against gram-negative microorganisms, e.g. *Pasturella multocida* and *Neisseria sicca*. Additionally, they exhibit significant activity against *Haemophilus in vitro*. The N-methyl derivative (formula I, R_2=R_3=H), is superior to erythromycin A and 11-aza-10-deoxo-10-dihydroerythromycin A in its in vitro activity against Haemophilus.

The N-methyl derivatives (formula I) surprisingly and unexpectedly exhibit oral activity against gram-positive and gram-negative microorganisms. The N-methyl derivative of formula I (R_2=R_3=H) exhibits significant oral activity in vivo whereas no practical oral in vivo activity is exhibited by 11-aza-10-deoxo-10-dihydroerythromycin A.

DETAILED DESCRIPTION OF THE INVENTION

The N-methyl derivative of 11-aza-10-deoxo-10-dihydroerythromycin A (formula I) is prepared from 11-aza-10-deoxo-10-dihydroerythromycin A (formula IV) by the following reaction sequence:



The oxidation of 11-aza-10-deoxo-10-dihydroerythromycin A is conducted in a reaction-inert solvent, i.e., one which does not react with reactants or products to produce undesired substances, under the conditions of the reaction, using as oxidizing agent hydrogen peroxide or a per acid such as peracetic acid, perbenzoic acid, m-chloroperbenzoic acid, permaleic acid and perphthalic acid.

The choice of solvent depends, in part, upon the oxidizing agent used. When using a water soluble oxidizing agent such as hydrogen peroxide or peracetic acid, a water miscible solvent should be used. When using oxidizing agents of low water solubility, e.g. perbenzoic or m-chloroperbenzoic acid, an aqueous reaction mixture is generally avoided in order to maintain a single phase reaction mixture.

Suitable solvents for use with the latter oxidizing agents are methylene chloride, chloroform, ethers, e.g. dioxane, tetrahydrofuran.

The oxidation is carried out at ambient temperature, i.e., from about 18°-25° C., for reaction periods of up to 24 hours. An excess of oxidizing agent is used to ensure maximum conversion of 11-aza-10-deoxo-10-dihydroerythromycin A, the limiting reactant. In general, from about 1.0 mole to about 35 moles of oxidant per mole of said limiting reactant is used. In practice, for the sake of economy, from about 5 to about 15 moles of oxidant are used per mole of the limiting reactant. Hydrogen peroxide is favored as oxidizing agent because of its availability. The amine oxide of formula II is isolated by extraction following removal of destruction of the excess oxidizing agent.

The amine oxide of formula II thus produced is then alkylated by reaction with an appropriate alkylating agent such as methyl iodide or bromide in a reaction-inert solvent and in the presence of an acid acceptor. Representative of reaction-inert solvents useful in this step are methylene chloride, chloroform, tetrahydrofuran and toluene. Suitable acid acceptors are inorganic bases such as alkali metal hydroxides and carbonates, and organic amines such as hindered amine bases, e.g. 2,6-lutidine, said substances being used in at least stoichiometric amount based on the alkylating agent used.

The alkylating agents are generally used in amounts based upon the amine oxide reactant ranging from equimolar to up to 100% excess.

The alkylation reaction, when methyl iodide is used as alkylating agent, is conveniently carried out at ambient temperature. Alkylation by means of methyl bro-

D4

216

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US005686587A

United States Patent [19]

Yang

[11] Patent Number: 5,686,587

[45] Date of Patent: Nov. 11, 1997

[54] **INTERMEDIATE FOR AZITHROMYCIN**

[75] Inventor: Bingwei V. Yang, Waterford, Conn.

[73] Assignee: Pfizer Inc., New York, N.Y.

[21] Appl. No.: 537,741

[22] PCT Filed: Mar. 14, 1994

[86] PCT No.: PCT/US94/02547

§ 371 Date: Nov. 13, 1995

§ 102(e) Date: Nov. 13, 1995

[87] PCT Pub. No.: WO94/26758

PCT Pub. Date: Nov. 24, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 64,610, May 19, 1993, abandoned.

[51] Int. Cl.[6] C07H 17/08; C08B 01/00

[52] U.S. Cl. 536/7.1; 514/29; 536/18.5; 536/125

[58] Field of Search 536/7.2, 17.2, 536/17.3, 17.4, 17.9, 18.5, 7.1, 125; 514/29

[56] **References Cited**

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4,512,982	4/1985	Hauske et al.	514/29
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Djokic et al., J. Chem. Soc. Perkin Trans. I, (1986), 1881–1890.

Jones, J. Org. Chem., vol. 57, 4361–4367 (1992).

Primary Examiner—John Kight
Assistant Examiner—Howard C. Lee
Attorney, Agent, or Firm—Peter C. Richardson; Gregg C. Benson; James T. Jones

[57] **ABSTRACT**

A compound having formula (III). Also, a process of making azithromycin comprising reducing the compound of formula (III) and N-methylating the reduced product.

11 Claims, No Drawings

INTERMEDIATE FOR AZITHROMYCIN

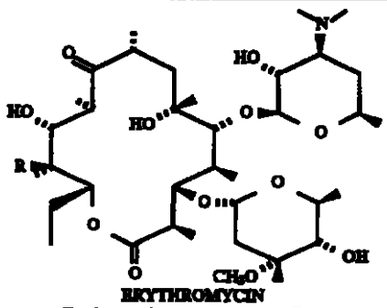
This is a §371 national stage application of PCT/US94/02547 filed internationally on Mar. 14, 1994, which is a continuation of U.S. application Ser. No. 08/064,610, filed May 19, 1993, now abandoned.

FIELD OF THE INVENTION

This invention relates to antibiotics, and particularly relates (1) to an intermediate per se, useful for making the known antibiotic azithromycin, (2) to a process for making azithromycin with the intermediate, and (3) to processes for making the intermediate.

BACKGROUND OF THE INVENTION

Erythromycin is an antibiotic formed during the culturing of a strain of *Streptomyces erythreus* in a suitable medium as taught in U.S. Pat. No. 2,653,899. Erythromycin, which is produced in two forms, A and B, is represented by the following structure (I):



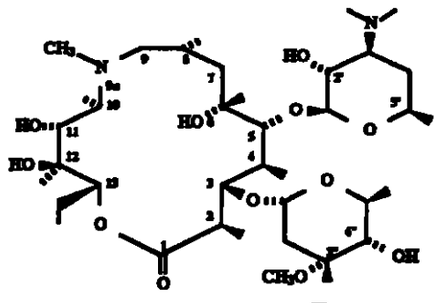
(I)

ERYTHROMYCIN

Erythromycin	R
A	—OH
B	—H

The structure reveals that the antibiotic is comprised of three main portions: a sugar fragment known as cladinose, a second sugar moiety containing a basic amino substituent known as desosamine and a fourteen membered lactone ring referred to as erythronolide A or B or as the macrolide ring.

Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antibacterial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359, and was named N-methyl-11-aza-10-deoxo-10-dihydro-erythromycin A in these patents. It has the following structure (II) wherein the numbering system conventionally employed is shown:



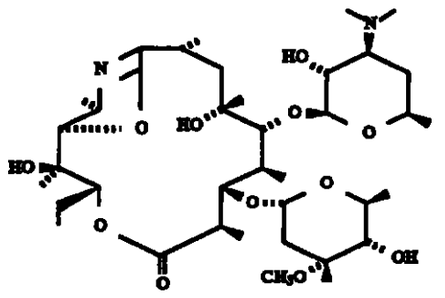
(II)

The above patents also disclose that (II) and certain derivatives thereof possess antibacterial properties.

In particular, the procedure for making azithromycin from erythromycin A involves relatively strong reaction conditions as described, for example, in Djokic et al., *J. Chem. Soc. Perkin Trans. I*, 1881, (1986), wherein the preparation of 10-dihydro-10-deoxo-11-azaerythromycin A from an imino ether precursor was effected by catalytic hydrogenation in acetic acid under 70 atm of H_2.

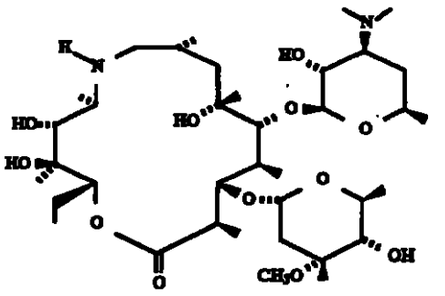
SUMMARY OF THE INVENTION

In a first aspect, this invention provides a compound having formula III



(III)

Compound III, 9-deoxo-11-deoxy-9,11-epoxy-9,9a-didehydro-9a-aza-9a-homoerythromycin A, herein also referred to as a 9,11-imino ether, has utility as an intermediate for making azithromycin, and can be reduced to a direct precursor of azithromycin having formula IV, shown below. The precursor of Formula IV need only be N-methylated (position 9a) to produce azithromycin. Accordingly, in a further aspect, this invention provides a process of making azithromycin, comprising reducing the (9,11-imino ether) compound of formula III to 9a-aza-9-deoxo-9a-homoerythromycin A, a compound having formula IV

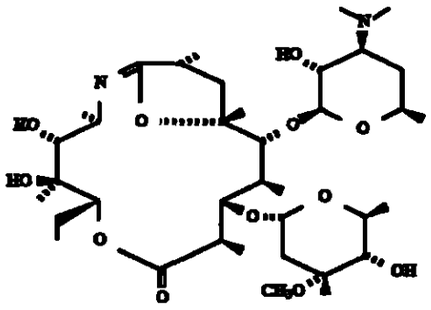


(IV)

and thereafter N-methylating the said compound of formula IV.

In a further aspect, this invention provides a process of making an intermediate of formula III, comprising isomerizing a compound of formula V, 9-deoxo-6-deoxy-6,9-epoxy-9,9a-didehydro-9a-aza-homoerythromycin A:

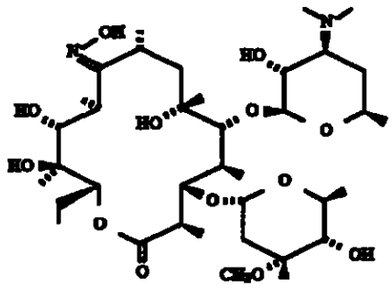
(V)



in a suitable solvent.

In still a further aspect, this invention provides an additional process of making an intermediate of formula III, comprising treating a compound of formula VI

(VI)



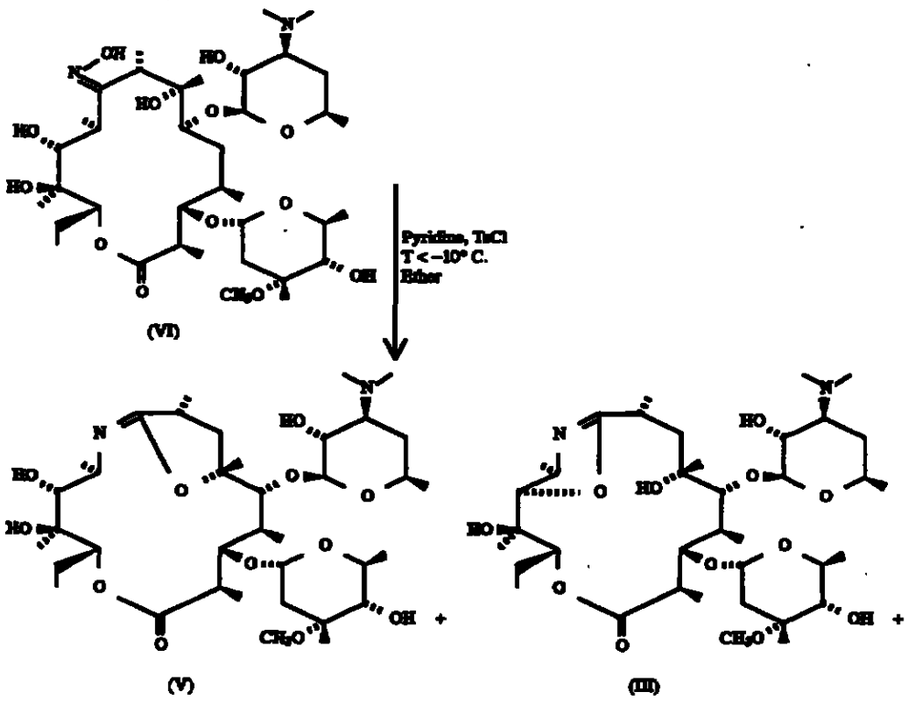
with tosyl chloride and pyridine in diethyl ether at a temperature of less than about 10° C. for a time between about 0.5 and about 50 hours.

DETAILED DESCRIPTION

A general reaction scheme for (1) making the intermediate 9,11-imino ether and (2) using the intermediate 9,11-imino ether to make azithromycin is shown in Scheme 1:

Scheme 1

STEP A



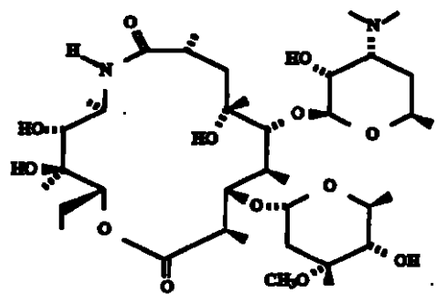
(VI)

(V)

(III)

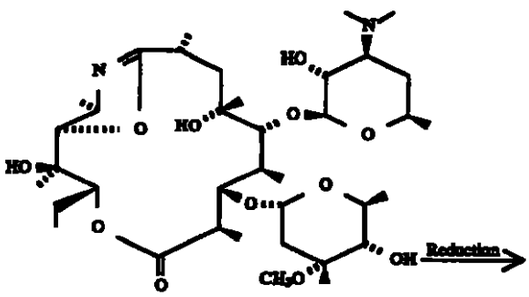
-continued

Scheme I

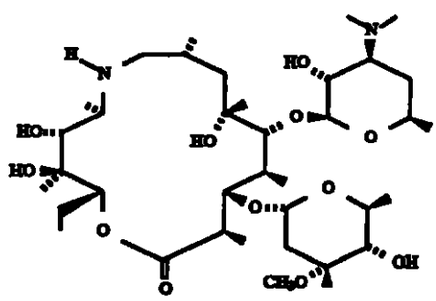


(VII)

STEP B

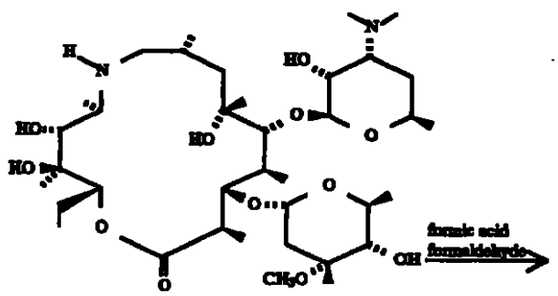


(III)



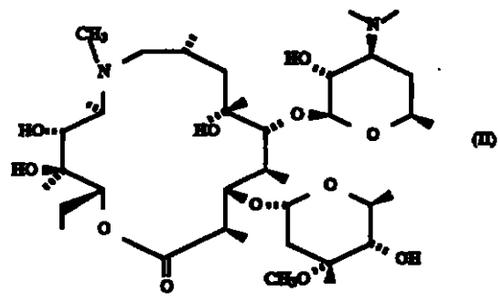
(IV)

STEP C



(IV)

-continued
Scheme I



(II)

In the above scheme the starting material in step A, compound (VI) is the E-isomer of 9-deoxo-9-hydroxyimino erythromycin A and can be made by known procedures such as the straightforward reaction of Erythromycin A with hydroxylamine to produce the erythromycin E-oxime as the major isomer. The oxime is treated with tosyl chloride in the presence of pyridine as a base and in a suitable solvent such as a dialkyl ether (e.g. diethyl ether), thereby initially forming a corresponding O-tosyl oxime which is a suitable precursor in the Beckmann rearrangement of ketoximes. Importantly, the temperature should be maintained below −10° C. to favor formation of the 9,11 imino ether, compound III, over compound V, the 6,9 imino ether, and compound VII. Generally it is preferred to maintain the said temperature below −20° C., and most preferred to maintain the temperature below −40 ° C. At the low temperatures employed, and depending on the exact temperature employed, the reaction can take as long as several days to go to completion, although appreciable amounts of 9,11-imino ether III are available from workup of the reaction medium after much shorter reaction times, e.g., on the order of a day. The amount of tosyl chloride employed is at least equivalent to the amount of erythromycin A 9-E-oxime. To ensure completion of the reaction within a reasonable time the tosyl chloride can be used in excess, with a 2:1 equivalents ratio being preferred. The mixture will typically contain a mixture of compounds V, III, and VII, per Scheme I, Step A, which can be conventionally resolved by column chromatography separation, typically employing silica gel having a particle size of 230–400 mesh ASTM (commercially available, for example, as Silica Gel 60 from EM Science, Gibbstown, N.J.) with toluene, chloroform and triethylamine mixed in a ratio, respectively, of 20:1:1 as the eluting solvent system.

The fact that 9,11-imino ether III is made per Step A is surprising in view of literature precedent (Djokic et al., supra) wherein the erythromycin A 9-E-oxime of erythromycin A yielded 6,9-imino ether V only.

If appreciable amounts of 6,9-imino ether V are formed, it can be isomerized to compound III by dissolving it in a suitable solvent. Any of a number of solvents can be employed such as tetrahydrofuran, (THF), lower alcohols, (e.g. methanol, ethanol, or propanol) and halogenated hydrocarbons, with chlorinated hydrocarbons such as chloroform and methlene chloride being preferred. Deuterated analogs of the chlorinated solvents (e.g. deuterochloroform) can also be employed. To speed the rate of isomerization a catalytic amount of acid can be added to the reaction medium. The acid employed is not critical so long as it is not used in an amount which results in cleavage of either of the sugar fragments from the macrolide ring. Organic acids (e.g. trifluoroacetic acid, p-toluenesulfonic acid) or inorganic (hydrochloric, sulfuric) acids may be employed. It is preferred to use camphorsulphonic acid in an amount of 0.1 equivalent per equivalent of compound V at a temperature of from 15° C. to reflux, typically room temperature, for a period sufficient for isomerization to occur, typically a period of from about 12 hours to about 7 days or longer. Conversions of essentially 100% after about 7 days in deuterochloroform are feasible using this novel procedure. Total yields of the intermediate III of over 90%, based on the weight of the starting material, are facilely obtainable by combining compound III obtained directly from scheme I with compound III obtained by isomerizing compound V (also obtained from scheme I) in deuterochloroform.

Compound III can be reduced to compound IV, the direct precursor of azithromycin, by any of a number of conventional methods, but advantageously under much milder conditions than those known in the art for reducing macrolide imino ethers. Reduction can be effected under a hydrogen pressure of about 50 psi in the presence of platinum dioxide catalyst and in glacial acetic acid solvent. Yields approaching 90% are obtainable within reaction times of 48 hrs. Other methods of reduction employing conventional reducing agents such as sodium borohydride are also feasible. Reactions employing borohydride are typically conducted with stirring in a suitable solvent such as methanol at a temperature of 0° to room temperature, and employing at least one equivalent of borohydride. Workup can proceed as in Djokic et al., supra.

Compound IV can be methylated to obtain azithromycin as conventionally known in the art, for example by the Eschweiler-Clark reaction in which compound IV is reacted with a combination of formic acid and formaldehyde, most suitably performed with a 1–3 molar excess of formaldehyde and formic acid in an appropriate solvent, preferably in a halogenated hydrocarbon, e.g., chloroform or carbon tetrachloride. The reaction is generally conducted at reflux for a period of 2 to 8 hours. The azithromycin can be isolated by conventional means such as by simple solvent evaporation. If further purification is desired, such can be effected conventionally, for example column chromatography through silica gel employing an eluting solvent comprising, by volume, 3–10% chloroform, and 0.1–1% ammonium hydroxide.

The invention will now be illustrated by means of the following examples which are not, however, to be taken as limiting:

EXAMPLE 1

9-Deoxo-11-deoxy-9,11-epoxy-9,9a-dihydro-9a-aza-9a-homoerythromycin A (compound III)

METHOD A:

(Step A in Scheme I): Erythromycin A 9-oxime (6.11 g, 8.16 mmol) was dissolved in pyridine (45 ml) and cooled to −45° C. To this solution was added a precooled (−45° C.) solution of p-toluenesulfonyl chloride (3.2 g, 16.9 mmol) and pyridine (10 ml) in ether (25 ml). The reaction mixture was stirred at −45° C. for six hours and stood at −20° C. for 12 hours. The mixture was poured into cold water and stirred while the pH was adjusted to 5 with aqueous 2M HCl. The solution was extracted with 75 mL quantities of methylene chloride twice. After separation, the aqueous layer was extracted with 75 mL of chloroform at pH 7 and 9, respectively (pH adjusted with saturated aqueous solution of potassium carbonate). Each extract was separately washed with brine and dried over magnesium sulfate. The extract from pH 7, upon evaporation in vacuo, gave a slightly yellow solid, containing a mixture of 9-deoxo-11-deoxy-9,11-epoxy-9,9a-dihydro-9a-aza-9a-homoerythromycin A (compound III) and 9-deoxo-6-deoxy-6,9-epoxy-9,9a-dihydro-9a-aza-9a-homoerythromycin A (compound V) at 1.2/1 ration (4.69 g, 6.42 mmol, yield: 78.6%). The pH 9 extract was evaporated to yield a white solid containing 9a-aza-9a-homoerythromycin cyclic lactam (compounds VII) and 9-deoxo-6-deoxy-6,9-epoxy-9,9a-dihydro-9a-aza-9a-homoerythromycin A (V) at 2/1 ratio (0.49 g). A pure sample of III was obtained as follows: The mixture of V and III was dissolved in deuterochloroform and stirred at room temperature for 12 hours. After removal of solvent in vacuo, the residue was chromatographed on silica gel (eluent:toluene/$CHCl_3$/Et_3N 20:1:1) to afford the pure title compound as a white solid. ^{13}CNMR($CDCl_3$) 176.3, 102.2, 95.3, 83.0, 82.3, 81.1, 77.7, 76.7, 76.4, 75.1, 73.2, 72.7, 70.7, 69.4, 65.9, 65.1, 63.5, 49.3, 43.4, 40.3, 39.6, 34.6, 34.6, 29.8, 28.7, 25.0, 24.2, 21.7, 21.66, 21.0, 19.3, 18.1, 17.4, 11.3, 10.9. ^{1}HNMR ($CDCl_3$, partial): 5.03 (br d, 1H), 4.81 (dd, J=10.1, 1.8 Hz, 1h), 4.61(d, J=7.3 Hz, 1h), 4.50 (D, J=4.7 Hz, 1H), 4.39 (d, J=8.5 Hz, 1H), 4.14 (m, 1H), 3.95 (m, 1H), 3.69 (d, J=5.9 Hz, 1H), 3.67 (s, 1H), 3.54 (m, 1H), 3.31 (s, 3H), 3.24 (m, 1H), 3.00 (t, J=9.7 Hz, 1H), 2.70 (m, 1H), 2.66 (m, 1H), 2.25 (s, 6H), 1.97 (s, 3H), 1.38 (d, J=6.6 Hz, 3H), 1.28 (s, 3H), 1.25 (d, J=6.4 Hz, 3H), 1.22 (s, 3H), 1.21 (S, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.175 (s, 3H), 1.14 (d, J=7.2 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H). FAB-mass:m/e:731, 573, 398, 158; high resolution mass calcd for $C_{37}H_{67}N_2)_{12}$: 731.4696; found 731.4744.

Method B:

A solution of 9-deoxo-6-deoxy-6,9-epoxy-9,9a-dihydro-9a-aza-9a-homoerythromycin A (compound V) (100 mg, 3.57 mmol) in $CDCl_3$ (1.5 ml) was stirred at room temperature for 36 hours. ^{1}HNMR spectrum of an aliquot sample indicated that the reaction mixture contained 9-deoxo-6-deoxy-6,9-epoxy-9,9a-dihydro-9a-aza-9a-homoerythromycinA (compound V) and 9-deoxo-11-deoxy-9,11-deoxy-9,11-epoxy-9,9a-dihydro-9a-aza-9a-homoerythromycin A (compound III) at ratio 1.7/1. After seven days, the isomerization of compound V to III was complete, as indicated by ^{1}HNMR spectrum. Evaporation of the solvent afforded the title compound in quantitative yield; it was identical with that obtained according to method A.

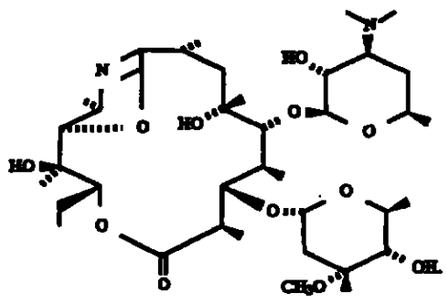
EXAMPLE 2

9-Deoxo-9a-aza-9a-homoerythromycin A (compound IV)

A solution of the title compound of example 1 (231 mg, 0.316 mmol) in acetic acid (20 ml) was hydrogenated over PtO_2 (13.1 mg, 0.058 mmol) under hydrogen (50 psi) at room temperature for 48 hours. The catalyst and the solvent were removed. The residue oil was dissolved in methylene chloride and washed with 10% aqueous potassium carbonate and brine, and dried over magnesium sulfate. The solvent evaporated in vacuo to afford the title compound pure (199 mg, 0.27 mmol, yield:85.8%); it was identical by comparison with a known sample of the title compound.

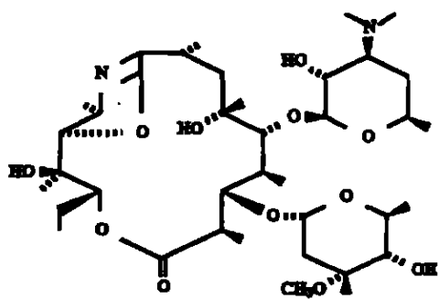
What is claimed is:

1. A compound having formula III



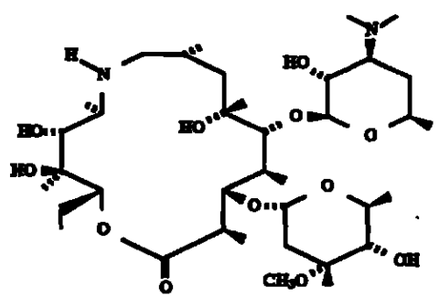
(III)

2. A process of making azithromycin, comprising reducing a compound of formula III



(III)

to a compound of formula IV



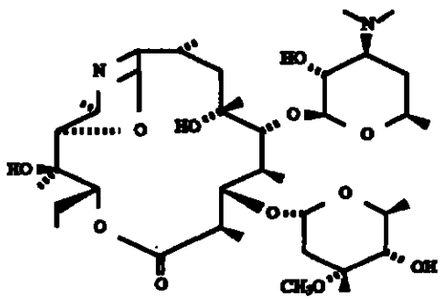
(IV)

and thereafter N-methylating the said compound of formula IV at position 9a.

3. A process as defined in claim 2, wherein said compound of formula III is reduced with hydrogen in the presence of platinum dioxide catalyst.

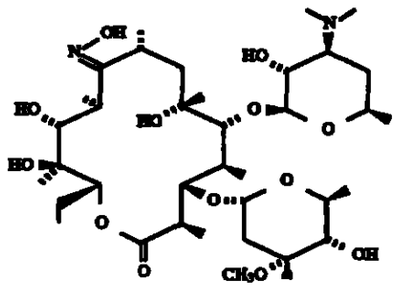
4. A process as defined in claim 2, wherein said compound of formula IV is N-methylated by treating said compound of formula IV with a combination of formic acid and formaldehyde.

5. A method of making a compound having formula III



(III)

comprising treating a compound of formula VI comprising treating the E-isomer of formula VI



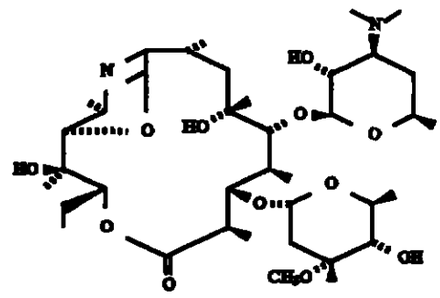
(VI)

with tosyl chloride in the presence of pyridine at a temperature less than about −10° C.

6. A process as defined in claim 5, wherein said temperature is less than about −20° C.

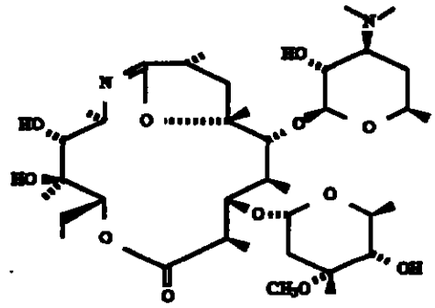
7. A process as defined in claim 6, wherein said temperature is less than about −40° C.

8. A process of making a compound having formula III



(III)

comprising dissolving a compound of formula V



(V)

in a solvent for a time sufficient to produce said compound of formula III.

9. A process as defined in claim 8, wherein said isomerization is conducted for between about 12 hours and about 7 days.

10. A process as defined in claim 8, wherein said isomerization is conducted at a temperature between about 15° C. and the reflux temperature of deuterochloroform.

11. A process as defined in claim 10, wherein said isomerization is conducted at room temperature.

* * * * *

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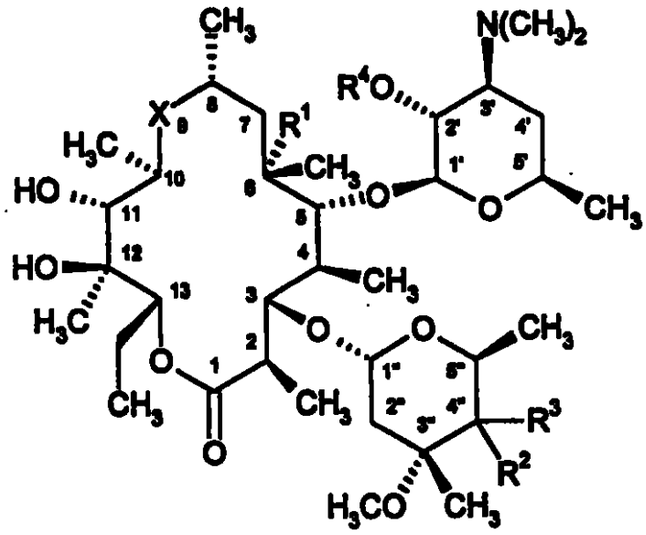
(54) Title: C-4''-SUBSTITUTED MACROLIDE DERIVATIVES

(57) Abstract

This invention relates to compounds of formula (1) and to pharmaceutically acceptable salts thereof. The compounds of formula (1) are potent antibacterial agents that may be used to treat various bacterial infections and disorders related to such infections. The invention also relates to pharmaceutical compositions containing the compounds of formula (1) and to methods of treating bacterial infections by administering the compounds of formula (1). The invention also relates to methods of preparing the compounds of formula (1) and to intermediates useful in such preparation.



(1)

C-4"-SUBSTITUTED MACROLIDE DERIVATIVES

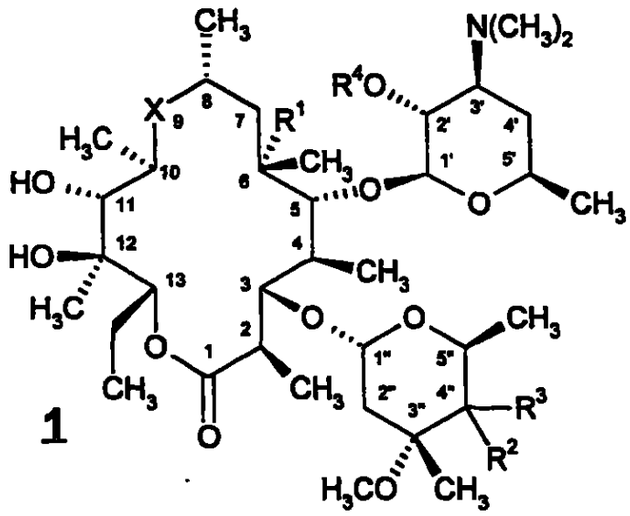
Background of the Invention

This invention relates to novel C-4" substituted macrolide derivatives that are useful as antibacterial and antiprotozoa agents in mammals, including man, as well as in fish and birds. This invention also relates to pharmaceutical compositions containing the novel compounds and to methods of treating bacterial and protozoa infections in mammals, fish and birds by administering the novel compounds to mammals, fish and birds requiring such treatment.

Macrolide antibiotics are known to be useful in the treatment of a broad sprectrum of bacterial and protozoa infections in mammals, fish and birds. Such antibiotics include various derivatives of erythromycin A such as azithromycin which is commercially available and is referred to in United States patents 4,474,768 and 4,517,359, both of which are incorporated herein by reference in their entirety. Like azithromycin and other macrolide antibiotics, the novel macrolide compounds of the present invention possess potent activity against various bacterial and protozoa infections as described below.

Summary of the Invention

The present invention relates to compounds of the formula



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and to pharmaceutically acceptable salts thereof, wherein:

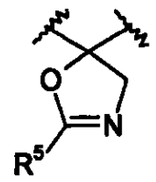
X is $-CH(NR^9R^{10})-$, $-C(O)-$, $-C(=NOR^9)-$, $-CH_2NR^9-$, or $-N(C_1-C_6\ alkyl)CH_2-$ wherein the first dash of each of the foregoing X groups is attached to the C-10 carbon of the compound of formula 1 and the last dash of each group is attached to the C-8 carbon of the of the compound of formula 1;

R^1 is H, hydroxy or methoxy;

R^2 is hydroxy;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, $-CH_2S(O)_nR^8$ wherein n is an integer ranging from 0 to 2, $-CH_2OR^8$, $-CH_2N(OR^9)R^8$, $-CH_2NR^8R^{15}$, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^3 groups are optionally substituted by 1 to 3 R^{16} groups;

or R^2 and R^3 are taken together to form an oxazolyl ring as shown below



R^4 is H, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^9R^{10}$ or a hydroxy protecting group;

R^5 is $-SR^8$, $-(CH_2)_nC(O)R^8$ wherein n is 0 or 1, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^5 groups are optionally substituted by 1 to 3 R^{16} groups;

each R^6 and R^7 is independently H, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

each R^8 is independently H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$ wherein q and r are each independently an integer ranging from 0 to 3 except q and r are not both 0, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^8 groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or where R^8 is as $-CH_2NR^8R^{15}$, R^{15} and R^8 may be taken together to form a 4-10 membered saturated monocyclic or polycyclic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and $-N(R^8)-$, in addition to the nitrogen to which R^{15} and R^8 are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

each R^9 and R^{10} is independently H or C_1-C_6 alkyl;

each R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_m(C_6$-C_{10} aryl), and $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^{11}, R^{12}, R^{13} and R^{14} groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or R^{11} and R^{13} are taken together to form $-(CH_2)_p-$ wherein p is an integer ranging from 0 to 3 such that a 4-7 membered saturated ring is formed that optionally includes 1 or 2 carbon-carbon double or triple bonds;

or R^{13} and R^{14} are taken together to form a 4-10 membered monocyclic or polycyclic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and -N(R^8)-, in addition to the nitrogen to which R^{13} and R^{14} are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

R^{15} is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl, wherein the foregoing R^{15} groups are optionally substituted by 1 to 3 substituents independently selected from halo and -OR^9;

each R^{16} is independently selected from halo, cyano, nitro, trifluoromethyl, azido, -C(O)R^{17}, -C(O)OR^{17}, -C(O)OR^{17}, -$OC(O)OR^{17}$, -$NR^6C(O)R^7$, -C(O)NR^6R^7, -NR^6R^7, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, -$(CH_2)_m$(C_6-C_{10} aryl), and -$(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein said aryl and heteroaryl subsituents are optionally substituted by 1 or 2 substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -C(O)R^{17}, -C(O)OR^{17}, -C(O)OR^{17}, -$OC(O)OR^{17}$, -$NR^6C(O)R^7$, -C(O)NR^6R^7, -NR^6R^7, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each R^{17} is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -$(CH_2)_m$(C_6-C_{10} aryl), and -$(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

with the proviso that R^8 is not H where R^3 is -$CH_2S(O)_nR^8$.

Preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is -$CH_2NR^8R^{15}$ or -CH_2SR^8, and R^4 is H.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is -$CH_2NR^8R^{15}$, R^4 is H, R^{15} and R^8 are each selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^{15} and R^8 groups, except H, are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1-C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^{15} is either H or is selected from the following groups from which R^8 is also independently selected: methyl, ethyl, allyl, n-butyl, isobutyl, 2-methoxyethyl, cyclopentyl, 3-methoxypropyl, 3-ethoxypropyl, n-propyl, isopropyl, 2-hydroxyethyl, cyclopropyl, 2,2,2-trifluoroethyl, 2-propynyl, *sec*-butyl, *tert*-butyl, and n-hexyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is -CH_2NHR^8, R^4 is H, and R^8 is -$(CH_2)_m$(C_6-C_{10} aryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^8 is phenyl or benzyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is -$CH_2NR^{15}R^8$, R^4 is H, and R^{15} and R^8 are taken together to form a saturated ring.

Specific preferred compounds having the foregoing general structure include those wherein R^{15} and R^8 are taken together to form a piperidino, trimethyleneimino, or morpholino ring.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NR^{15}R^8$, R^4 is H, and R^{15} and R^8 are taken together to form a heteroaryl ring optionally substituted by 1 or 2 C_1-C_6 alkyl groups. Specific preferred compounds having the foregoing general structure include those wherein R^{15} and R^8 are taken together to form a pyrrolidino, triazolyl, or imidazolyl ring wherein said heteroaryl groups are optionally substituted by 1 or 2 methyl groups.

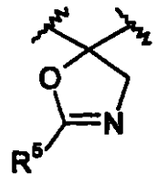
Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2SR^8$, R^4 is H, and R^8 is selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^8 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1-C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^8 is methyl, ethyl, or 2-hydroxyethyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^3 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, $-C(O)R^{17}$, $-NR^6R^7$, halo, cyano, azido, 5-10 membered heteroaryl, and C_1-C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^3 is methyl, allyl, vinyl, ethynyl, 1-methyl-1-propenyl, 3-methoxy-1-propynyl, 3-dimethylamino-1-propynyl, 2-pyridylethynyl, 1-propynyl, 3-hydroxy-1-propynyl, 3-hydroxy-1-propenyl, 3-hydroxypropyl, 3-methoxy-1-propenyl, 3-methoxypropyl, 1-propynyl, n-butyl, ethyl, propyl, 2-hydroxyethyl, formylmethyl, 6-cyano-1-pentynyl, 3-dimethylamino-1-propenyl, or 3-dimethylaminopropyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is $-(CH_2)_m$(5-10 membered heteroaryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^3 is 2-thienyl, 2-pyridyl, 1-methyl-2-imidazolyl, 2-furyl, or 1-methyl-2-pyrrolyl.

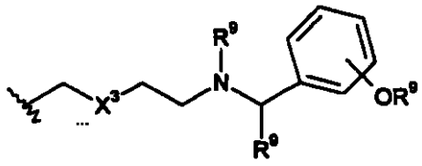
Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is $-(CH_2)_m$(C_6-C_{10} aryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^3 is phenyl.

Specific compounds of formula 1 include those wherein R^2 and R^3 are taken together to form an oxazolyl ring as shown below



wherein R^5 is as defined above.

Specific compounds of formula 1 include those wherein R^3 is selected from the following:



wherein X^3 is O, S or -N(R^{15})-, and wherein the -OR^9 group may be attached at any available carbon on the phenyl group.

The invention also relates to a pharmaceutical composition for the treatment of a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention also relates to a method of treating a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt thereof.

The term "treatment", as used herein, unless otherwise indicated, includes the treatment or prevention of a bacterial infection or protozoa infection as provided in the method of the present invention.

As used herein, unless otherwise indicated, the terms "bacterial infection(s)" and "protozoa infection(s)" include bacterial infections and protozoa infections that occur in mammals, fish and birds as well as disorders related to bacterial infections and protozoa infections that may be treated or prevented by administering antibiotics such as the compounds of the present invention. Such bacterial infections and protozoa infections, and disorders related to such infections, include the following: pneumonia, otitis media, sinusitus, bronchitis, tonsillitis, and mastoiditis related to infection by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Peptostreptococcus* spp.; pharynigitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Clostridium diptheriae*, or *Actinobacillus haemolyticum;* respiratory tract infections related to infection by *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Streptococcus*

The term "5-10 membered heteroaryl", as used herein, unless otherwise indicated, includes aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 5 to 10 atoms in its ring system. Examples of suitable 5-10 membered heteroaryl groups include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, oxazolyl, pyrrolyl and thiazolyl.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and, particularly, the calcium, magnesium, sodium and potassium salts of the compounds of the present invention.

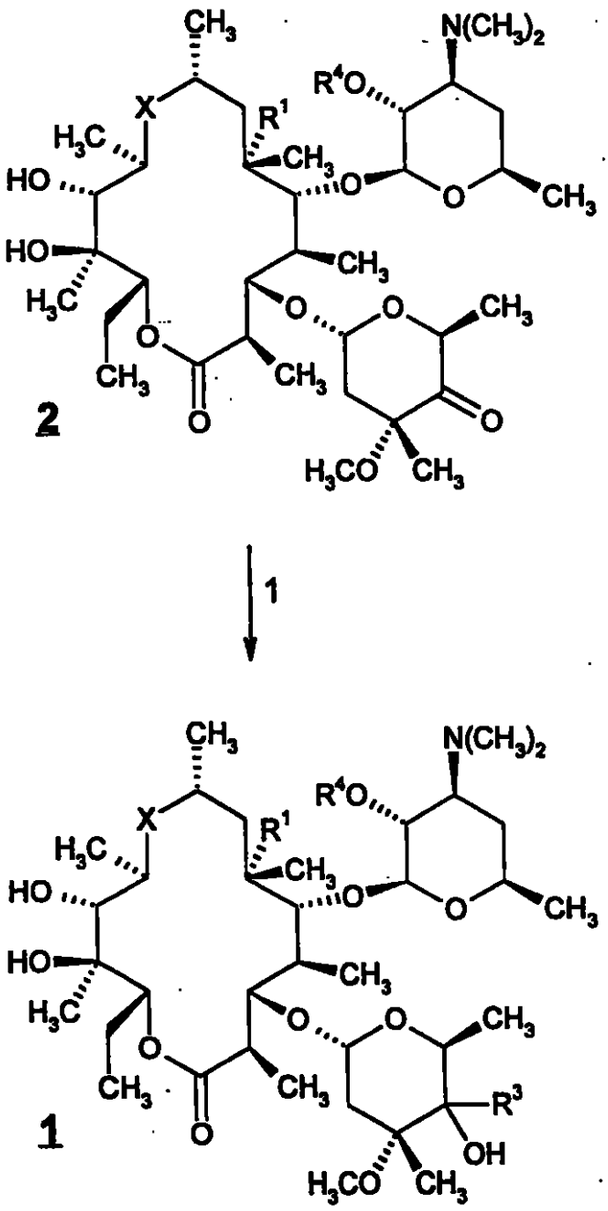
Certain compounds of the present invention may have asymmetric centers and therefore exist in different enantiomeric and diastereomic forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them.

The present invention includes the compounds of the present invention, and the pharmaceutically acceptable salts thereof, wherein one or more hydrogen, carbon or other atoms are replaced by isotopes thereof. Such compounds may be useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

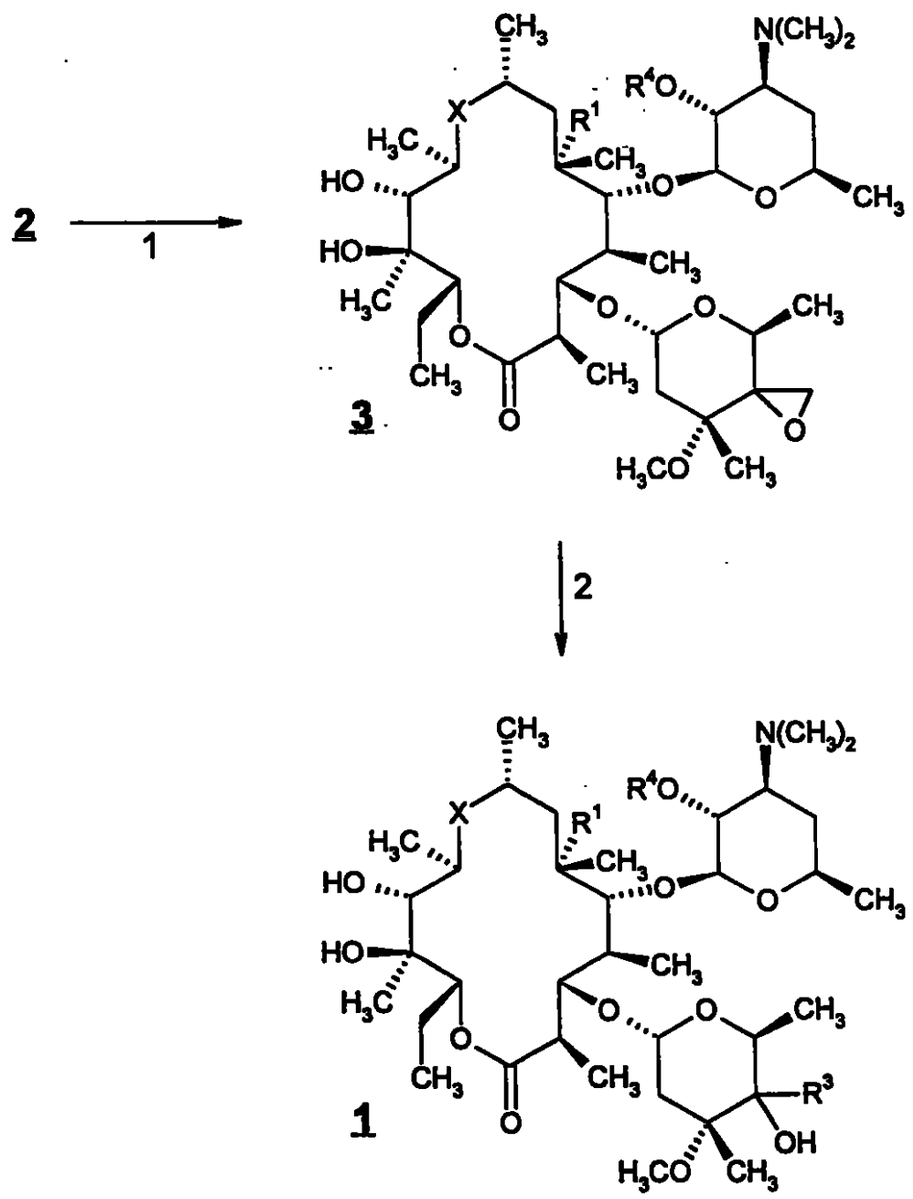
Detailed Description of the Invention

The compounds of of the present invention may be prepared according to Schemes 1-3 below and the description that follows. In the following Schemes, unless otherwise indicated, substituents X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are as defined above.

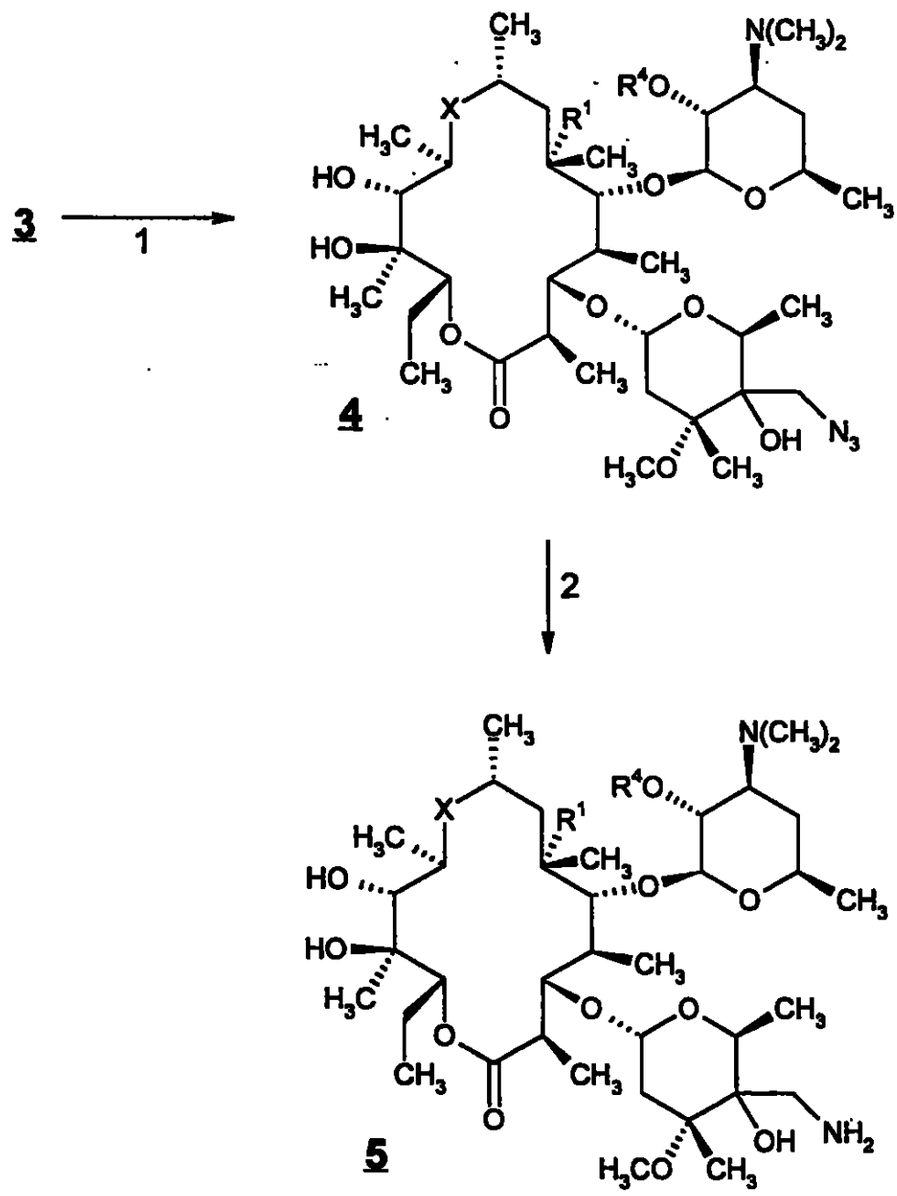
Scheme 1


CH3
N(CH3)2
R4O
X
R1
H3C
CH3
HO
O
O
CH3
HO
CH3
H3C
O
O
CH3
O
CH3
CH3
O
2
O
H3CO
CH3
1
CH3
N(CH3)2
R4O
X
R1
H3C
CH3
HO
O
O
CH3
HO
CH3
H3C
O
O
CH3
O
CH3
CH3
R3
O
1
OH
H3CO
CH3

Scheme 2



Scheme 3



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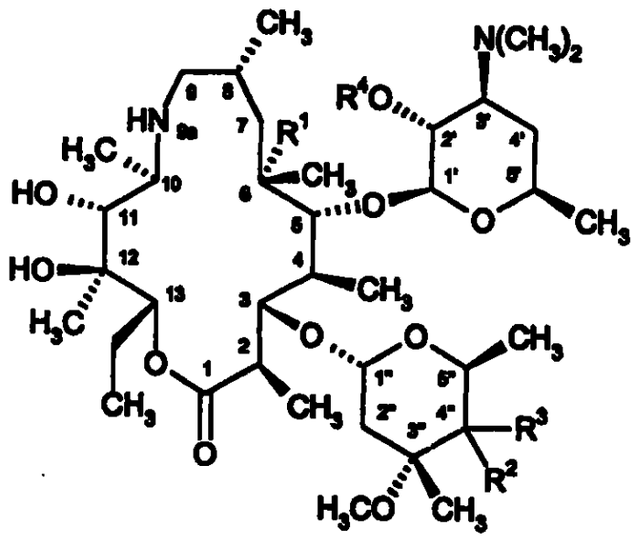
(54) Title: 4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES



(1)

(57) Abstract

The invention relates to compounds of formula (1) and to pharmaceutically acceptable salts thereof. The compounds of formula (1) are antibacterial agents that may be used to treat various bacterial and protozoa infections. The invention also relates to pharmaceutical compositions containing the compounds of formula (1) and to methods of treating bacterial protozoa infections by administering the compounds of formula (1). The invention also relates to methods of preparing the compounds of formula (1) and to intermediates useful in such preparation.

4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES

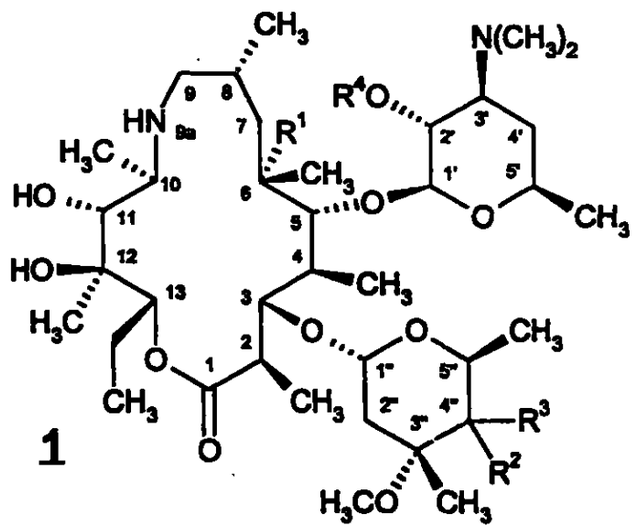
Background of the Invention

This invention relates to novel C-4" substituted derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A that are useful as antibacterial and antiprotozoa agents in mammals, including man, as well as in fish and birds. This invention also relates to pharmaceutical compositions containing the novel compounds and to methods of treating bacterial infections and protozoa infections in mammals, fish and birds by administering the novel compounds to mammals, fish and birds requiring such treatment.

Macrolide antibiotics are known to be useful in the treatment of a broad sprectrum of bacterial infections and protozoa infections in mammals, fish and birds. Such antibiotics include various derivatives of erythromycin A such as azithromycin which is commercially available and is referred to in United States patents 4,474,768 and 4,517,359, both of which are incorporated herein by reference in their entirety. Like azithromycin and other macrolide antibiotics, the novel macrolide compounds of the present invention possess potent activity against various bacterial infections and protozoa infections as described below.

Summary of the Invention

The present invention relates to compounds of the formula



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and to pharmaceutically acceptable salts thereof, wherein:

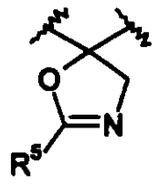
R^1 is H, hydroxy or methoxy;

R^2 is hydroxy;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, $-CH_2S(O)_nR^8$ wherein n is an integer ranging from 0 to 2, $-CH_2OR^8$, $-CH_2N(OR^9)R^8$, $-CH_2NR^8R^{10}$, $-(CH_2)_m(C_6$-C_{10} aryl), or

$-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^3 groups are optionally substituted by 1 to 3 R^{16} groups;

or R^2 and R^3 are taken together to form an oxazolyl ring as shown below



R^4 is H, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^9R^{10}$ or a hydroxy protecting group;

R^5 is $-SR^8$, $-(CH_2)_nC(O)R^8$ wherein n is 0 or 1, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_m$(C_6-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^5 groups are optionally substituted by 1 to 3 R^{16} groups;

each R^6 and R^7 is independently H, hydroxy, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(CH_2)_m$(C_6-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

each R^8 is independently H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$ wherein q and r are each independently an integer ranging from 0 to 3 except q and r are not both 0, $-(CH_2)_m$(C_6-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^8 groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or where R^8 is as $-CH_2NR^8R^{15}$, R^{15} and R^8 may be taken together to form a 4-10 membered monocyclic or polycyclic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and $-N(R^8)-$, in addition to the nitrogen to which R^{15} and R^8 are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

each R^9 and R^{10} is independently H or C_1-C_8 alkyl;

each R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_m$(C_6-C_{10} aryl), and $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^{11}, R^{12}, R^{13} and R^{14} groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or R^{11} and R^{13} are taken together to form $-(CH_2)_p-$ wherein p is an integer ranging from 0 to 3 such that a 4-7 membered saturated ring is formed that optionally includes 1 or 2 carbon-carbon double or triple bonds;

or R^{13} and R^{14} are taken together to form a 4-10 membered monocyclic or polycyclic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings

optionally include 1 or 2 heteroatoms selected from O, S and -N(R^8)-, in addition to the nitrogen to which R^{13} and R^{14} are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

R^{15} is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl, wherein the foregoing R^{15} groups are optionally substituted by 1 to 3 substituents independently selected from halo and -OR^8;

each R^{16} is independently selected from halo, cyano, nitro, trifluoromethyl, azido, -$C(O)R^{17}$, -$C(O)OR^{17}$, -$C(O)OR^{17}$, -$OC(O)OR^{17}$, -$NR^8C(O)R^7$, -$C(O)NR^8R^7$, -NR^8R^7, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, -$(CH_2)_m$(C_6-C_{10} aryl), and -$(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein said aryl and heteroaryl subsituents are optionally substituted by 1 or 2 substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -$C(O)R^{17}$, -$C(O)OR^{17}$, -$C(O)OR^{17}$, -$OC(O)OR^{17}$, -$NR^8C(O)R^7$, -$C(O)NR^8R^7$, -NR^8R^7, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each R^{17} is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -$(CH_2)_m$(C_6-C_{10} aryl), and -$(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

with the proviso that R^8 is not H where R^3 is -$CH_2S(O)_nR^8$.

Preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is -$CH_2NR^{15}R^8$ or -CH_2SR^8, and R^4 is H.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is -$CH_2NR^8R^{15}$, R^4 is H, R^{15} and R^8 are each selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^{15} and R^8 groups, except H, are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1-C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^{15} is either H or is selected from the following groups from which R^8 is also independently selected: methyl, ethyl, allyl, n-butyl, isobutyl, 2-methoxyethyl, cyclopentyl, 3-methoxypropyl, 3-ethoxypropyl, n-propyl, isopropyl, 2-hydroxyethyl, cyclopropyl, 2,2,2-trifluoroethyl, 2-propynyl, *sec*-butyl, *tert*-butyl, and n-hexyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is -CH_2NHR^8, R^4 is H, and R^8 is -$(CH_2)_m$(C_6-C_{10} aryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^8 is phenyl or benzyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is -$CH_2NR^{15}R^8$, R^4 is H, and R^{15} and R^8 are taken together to form a saturated ring.

Specific preferred compounds having the foregoing general structure include those wherein R^6 and R^8 are taken together to form a piperidino, trimethyleneimino, or morpholino ring.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NR^{15}R^8$, R^4 is H, and R^{15} and R^8 are taken together to form a heteroaryl ring optionally substituted by 1 or 2 C_1-C_6 alkyl groups. Specific preferred compounds having the foregoing general structure include those wherein R^{15} and R^8 are taken together to form a pyrrolidino, triazolyl, or imidazolyl ring wherein said heteroaryl groups are optionally substituted by 1 or 2 methyl groups.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2SR^8$, R^4 is H, and R^8 is selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^8 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1-C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^8 is methyl, ethyl, or 2-hydroxyethyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^3 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, $-C(O)R^{17}$, $-NR^6R^7$, halo, cyano, azido, 5-10 membered heteroaryl, and C_1-C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^3 is methyl, allyl, vinyl, ethynyl, 1-methyl-1-propenyl, 3-methoxy-1-propynyl, 3-dimethylamino-1-propynyl, 2-pyridylethynyl, 1-propynyl, 3-hydroxy-1-propynyl, 3-hydroxy-1-propenyl, 3-hydroxypropyl, 3-methoxy-1-propenyl, 3-methoxypropyl, 1-propynyl, n-butyl, ethyl, propyl, 2-hydroxyethyl, formylmethyl, 6-cyano-1-pentynyl, 3-dimethylamino-1-propenyl, or 3-dimethylaminopropyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is $-(CH_2)_m$(5-10 membered heteroaryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^3 is 2-thienyl, 2-pyridyl, 1-methyl-2-imidazolyl, 2-furyl, or 1-methyl-2-pyrrolyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is $-(CH_2)_m$(C_6-C_{10} aryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^3 is phenyl.

Specific compounds of formula 1 include those wherein R^2 and R^3 are taken together to form an oxazolyl ring as shown below

United States Patent [19]

Bright

[11] **Patent Number: 4,464,527**

[45] **Date of Patent: Aug. 7, 1984**

[54] **ANTIBACTERIAL 9-DEOXO-9A-ALKYL-9A-AZA-9A-HOMO-ERYTHROMYCIN A DERIVATIVES AND INTERMEDIATES THEREFORE**

[75] Inventor: **Gene M. Bright, Groton, Conn.**

[73] Assignee: **Pfizer Inc., New York, N.Y.**

[21] Appl. No.: **509,538**

[22] Filed: **Jun. 30, 1983**

[51] **Int. Cl.³** **C07H 17/08**

[52] **U.S. Cl.** **536/7.4**; 424/180; 536/7.2

[58] **Field of Search** 536/7.2, 7.4; 424/180

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Primary Examiner—Johnnie R. Brown

Attorney, Agent, or Firm—Charles J. Knuth; Albert E. Frost; James M. McManus

[57] **ABSTRACT**

Antibacterial 9-deoxo-9a-ethyl and propyl-9a-aza-9a-homoerythromycin A compounds, pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising antibacterially effective amounts thereof and a pharmaceutically acceptable carrier, the treatment of bacterial infections with antibacterially effective amounts thereof, and intermediates and processes for their preparation.

5 Claims, No Drawings

ANTIBACTERIAL 9-DEOXO-9A-ALKYL-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES AND INTERMEDIATES THEREFORE

BACKGROUND OF THE INVENTION

This invention relates to novel derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A, to intermediates therefor and to processes for their preparation. More particularly it relates to 9a-ethyl and 9a-n-propyl derivatives of 9-deoxo-9-a-aza-9a-homoerythromycin A, to pharmaceutically acceptable acid addition salts thereof and the use of said compounds as antibacterial agents, to intermediates therefor, and to processes for their preparation.

Erythromycin A is a macrolide antibiotic produced by fermentation and described in U.S. Pat. No. 2,653,899. Numerous derivatives of erythromycin A have been prepared in efforts to modify its biological and/or pharmacodynamic properties. Erythromycin A esters with mono- and dicarboxylic acids are reported in Antibiotics Annual, 1953–1954, Proc. Symposium Antibiotics (Washington, D.C.), pages 500–513 and 514–521, respectively. U.S. Pat. No. 3,417,077 describes the cyclic carbonate ester of erythromycin A, the reaction product of erythromycin A and ethylene carbonate, as an active antibacterial agent.

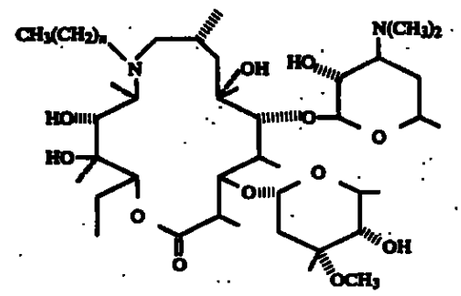
U.S. Pat. No. 4,328,334, issued May 4, 1982 describes 9-deoxo-9a-aza-9a-homoerythromycin A and refers to it by the name 11-aza-10-deoxo-10-dihydroerythromycin A. Since said compound is a ring expanded (homo) derivative of erythromycin A, nitrogen (aza) being the additional atom of the ring system, the nomenclature 9-deoxo-9a-aza-9a-homoerythromycin A is preferred for the parent ring system of the compounds of this invention.

Belgian Pat. No. 892,357, published July 1, 1982, and its British counterpart, Application No. 2,094,293A, published Sept. 15, 1982, disclose the N-methyl derivative of 9-deoxo-9a-aza-9a-homoerythromycin A, as does my co-pending U.S. application Ser. No. 441,981, filed Nov. 15, 1982, which claims priority from U.S. application Ser. No. 399,401, filed July 19, 1982, now abandoned. The 4''-epimer of said N-methyl derivative is the subject of my co-pending U.S. application Ser. No. 441,979, filed Nov. 15, 1982. My co-pending U.S. application Ser. No. 497,473 filed May 23, 1983 and now abandoned, claims cyclic ether derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A and its 4''-epimer.

U.S. Pat. No. 4,382,085, issued May 3, 1983 describes 4''-epi erythromycin A; i.e., the 4''—OH group has the axial configuration. The 4''—OH in erythromycin A has the equatorial configuration.

SUMMARY OF THE INVENTION

It has now been found that 9a-ethyl and 9a-n-propyl derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A are effective antibacterial agents against Gram-positive and Gram-negative bacteria. The compounds have the formula (I)

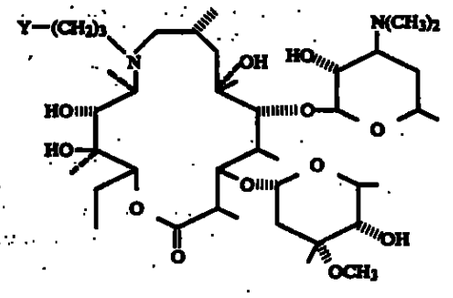


(I)

wherein n is 1 or 2.

Also included in this invention, and useful for the same purpose as formula (I) compounds, are the pharmaceutically acceptable acid addition salts thereof. Included among said salts, but by no means limited to said salts, are those enumerated below: hydrochloride, hydrobromide, sulfate, phosphate, formate, acetate, propionate, butyrate, citrate, glycolate, lactate, tartrate, malate, maleate, fumarate, gluconate, stearate, mandelate, pamoate, benzoate, succinate, lactate, p-toluenesulfonate and asparate.

The present invention also embraces processes and intermediates useful for the preparation of compounds of formula (I). The intermediates are represented by formula (II) below:



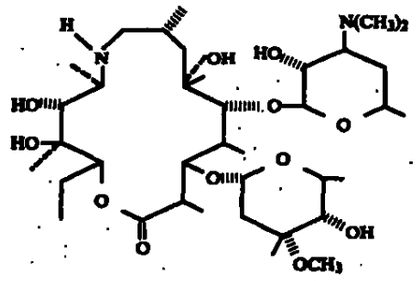
(II)

wherein Y is —NHCHO or

The first process for preparing a compound of formula (I) wherein n is 2 comprises reacting a compound of formula (II) wherein Y is

with tri-n-butyl tin hydride and azobisisobutylnitrile in a reaction-inert solvent at a reaction temperature of about 125° C. The preferred solvent is xylene.

The other process of this invention leading to a compound of formula (I) wherein n is 1 comprises reacting a compound of the formula



with

(a) aqueous acetaldehyde in the presence of hydrogen and palladium-on-charcoal in a reaction-inert solvent, wherein the preferred solvent is ethanol, or alternately,

(b) acetaldehyde and sodium cyanoborohydride in a reaction-inert solvent at a pH of about 5.9, wherein the preferred solvent is methanol.

Also within the scope of the present invention is a pharmaceutical composition comprising an antibacterial amount of a compound of formula (I) and a pharmaceutical carrier, and a method for treating a bacterial infection in a mammal which comprises administering to said mammal an antibacterial effective amount of a compound of formula (I).

Compounds of formula (I) and pharmaceutically acceptable acid addition salts thereof are effective antibacterial agents against Gram-positive microorganisms, e.g. *Staphylococcus aureus* and *Streptococcus pyogenes*, and against Gram-negative microorganisms, e.g., *Pasturella multocida* and *Neisseria sicca* in vitro. Additionally, compounds of formula (I) exhibit significant activity against *Neisseria gonorrhea* and Haemophilus in vitro and against many Gram-positive and Gram-negative microorganisms in vivo. In their useful oral activity and unexpectedly long serum half-life in mammals, the formula (I) compounds are like 9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A, and quite unlike the corresponding 9a-desmethyl compound 9-deoxo-9a-aza-9a-homoerythromycin A which exhibits no practical oral activity in vivo, and a substantially shorter serum half-life.

DETAILED DESCRIPTION OF THE INVENTION

The compound of formula (I) wherein n is 1 is prepared by the reductive alkylation of 9-deoxo-9a-aza-9a-homoerythromycin A using aqueous acetaldehyde and hydrogen in the presence of a palladium-on-charcoal catalyst in a reaction-inert solvent.

In practice, the 9-deoxo-9a-aza-9a-homoerythromycin A is combined with at least a ten fold excess of acetaldehyde in a reaction solvent containing about an equal weight of 5% palladium-on-charcoal. The resulting mixture is shaken at room temperature in a hydrogen atmosphere at an initial pressure of about 50 psi. Under these conditions the reaction is usually complete in about twelve to sixteen hours.

On completion of the reaction the catalyst is filtered and the product obtained by conventional means. If a purer product is desired it may be so purified by conventional means such as recrystallization or chromatography.

It is preferable to employ aqueous acetaldehyde, for example, a 37% solution of acetaldehyde in water.

The reaction-inert solvent employed in the aforementioned process should be one which amply solubilizes the reactants and does not react to any appreciable extent with the starting reagents or product. In this particular process the preferred solvent is ethanol although it is appreciated that a large number of other solvents may be employed with similar results.

A second type of reductive alkylation reaction used to prepare a compound of formula (I) wherein n is 1 comprises reacting 9-deoxo-9a-aza-9a-homoerythromycin A with acetaldehyde and sodium cyanoborohydride in a reaction-inert solvent at a pH of about 5.9.

In practice, 9-deoxo-9a-aza-9a-homoerythromycin A is combined with a one hundred fold molar excess of acetaldehyde in an appropriate reaction-inert solvent, and the pH adjusted to about 5.9 with acetic acid. To the resulting mixture is added over a period of about ten minutes a five fold molar amount of sodium cyanoborohydride. If needed the pH is adjusted by the addition of acetic acid.

The preferred reaction-inert solvent, having the aforementioned characteristics for this reaction is methanol, although many other solvents can be used with similar results.

At ambient temperatures the reaction is generally complete in about sixteen to eighteen hours. Shorter reaction times are possible if the reaction temperature is raised above room temperature.

The product is obtained by means familiar to those skilled in the art. Further purification can be achieved by normal methods such as recrystallization or chromatography.

Preparation of a compound of formula (I) wherein n is 2 comprises treating a compound of formula (II) wherein Y is

with tri-n-butyl tin hydride in a reaction-inert solvent.

In practice, 9-deoxo-9a-(gamma-isonitrilopropyl)-9a-aza-9a-homoerythromycin A

(II; Y = —N≡C)

is combined with a fifty fold molar amount of tri-n-butyl tin hydride in an appropriate solvent, and the temperature raised to about 125° C. To the hot reaction mixture is added over a period of one hour a five fold molar amount of azobisisobutylnitrile. The reaction temperature is maintained for about forty-five minutes after completion of the addition.

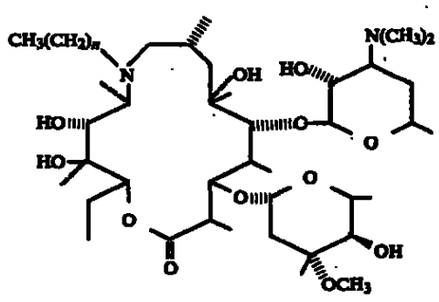
The preferred reaction-inert solvent for the aforedescribed process is xylene, although many other solvents can be employed with similar results.

On completion of the reaction the product is isolated by conventional means and purified by chromatographing on silica gel.

The preparation of the compound of formula (II) wherein Y is

and other necessary intermediates useful for this process are described hereafter in the examples.

Also considered part of the present invention are the 4"-epimers of the compounds of formula (I) as follows:



wherein n=1 or 2

Thus, for any given value of n, the epimeric forms of said compound differ structurally only in the configuration of the chiral center at the 4"-position; i.e., the 4"—OH group is either axial or equatorial. The axial configuration is represented by a solid or wedged shape line and the equatorial by a broken line of attachment of the OH group to the 4"-position.

Acid addition salts of the compounds of this invention are readily prepared by treating compounds having formula (I) with at least an equimolar amount of the appropriate acid in a reaction-inert solvent or, in the case of the hydrochloride salts, with pyridinium hydrochloride. Since more than one basic group is present in a compound of formula (I), the addition of sufficient acid to satisfy each basic group permits formation of polyacid addition salts. The acid addition salts are recovered by filtration if they are insoluble in the reaction-inert solvent, by precipitation by addition of a non-solvent for the acid addition salt, or by evaporation of the solvent.

A variety of Gram-positive microorganisms and certain Gram-negative microorganisms, such as those of spherical or ellipsoidal shape (cocci), are susceptible to compounds of formula (I). Their in vitro activity is readily demonstrated by in vitro tests against various microorganisms in a brain-heart infusion medium by the usual two-fold serial dilution technique. Their in vitro activity renders them useful for topical application in the form of ointments, creams and the like, for sterilization purposes, e.g. sick room utensils; and as industrial antimicrobials, for example, in water treatment, slime control, paint and wood preservation.

For in vitro use, e.g. for topical application, it will often be convenient to compound the selected product by methods well known in the pharmacist's art into lotions, salves, ointments, creams, gels or the like. For such purposes, it will generally be acceptable to employ concentrations of active ingredients of from about 0.01 percent up to about 10 percent by weight based on total composition. The dosage form is applied at the site of infection ad libitum, generally at least once a day.

Additionally, formula (I) compounds of this invention are active versus Gram-positive and certain Gram-negative microorganisms in vivo via the oral and/or parenteral routes of administration in animals, including man. Their in vivo activity is more limited as regards susceptible organisms and is determined by the usual procedure which comprises infecting mice of substantially uniform weight with the test organism and subsequently treating them orally or subcutaneously with the test compound. In practice, the mice, e.g. 10, are given an intraperitoneal inoculation of suitably diluted cultures containing approximately 1 to 10 times the LD_{100} (the lowest concentration of organisms required to produce 100% deaths). Control tests are simultaneously run in which mice receive inoculum of lower dilutions as a check on possible variation in virulence of the test organism. The test compound is administered 0.5 hour post-inoculation, and is repeated 4, 24 and 48 hours later. Surviving mice are held for 4 days after the last treatment and the number of survivors is noted.

When used in vivo, these novel compounds can be administered orally or parenterally, e.g. by subcutaneous or intramuscular injection, at a dosage of from about 1 mg/kg. to about 200 mg/kg. of body weight per day. The favored dosage range is from about 5 mg/kg. to about 100 mg/kg. of body weight per day and the preferred range from about 5 mg/kg. to about 50 mg/kg. of body weight per day. Vehicles suitable for parenteral injection may be either aqueous such as water, isotonic saline, isotonic dextrose, Ringer's solution or non-aqueous such as fatty oils of vegetable origin (cotton seed, peanut oil, corn, sesame), dimethylsulfoxide and other non-aqueous vehicles which will not interfere with therapeutic efficiency of the preparation and are non-toxic in the volume or proportion used (glycerol, propylene glycol, sorbitol). Additionally, compositions suitable for extemporaneous preparation of solutions prior to administration may advantageously be made. Such compositions may include liquid diluents; for example, propylene glycol, diethyl carbonate, glycerol, sorbitol, etc.; buffering agents, hyaluronidase, local anesthetics and inorganic salts to afford desirable pharmacological properties. These compounds may also be combined with various pharmaceutically acceptable inert carriers including solid diluents, aqueous vehicles, non-toxic organic solvents in the form of capsules, tablets, lozenges, troches, dry mixes, suspensions, solutions, elixirs and parenteral solutions or suspensions. In general, the compounds are used in various dosage forms at concentration levels ranging from about 0.5 percent to about 90 percent by weight of the total composition.

In the examples presented herein, no effort was made to recover the maximum amount of product produced or to optimize the yield of a given product. The Examples are merely illustrative of the process and of the products obtainable thereby.

In all examples, the terms "vanillin/ethanol/H_3PO_4 spray" and "vanillin/H_3PO_4 spray" refer to a solution of 1.0 g. of vanillin, 100 ml. of ethanol and 100 ml. of H_3PO_4.

The term "xylene" refers to the commercial mixture of xylene isomers, boiling range 137°–144° C.

EXAMPLE 1

9-Deoxo-9a-ethyl-9a-aza-9a-homoerythromycin A

To 10 ml. of methanol was added 1.0 g. (1.36 mmoles) of 9-deoxo-9a-aza-9a-homoerythromycin A (U.S. Pat. No. 4,328,334) and 5.95 g. (0.135 mole) of acetaldehyde, and the pH of the resulting solution adjusted to 5.95 with a 10% methanolic solution of acetic acid. To the reaction mixture was added 427 mg. (6.8 mmoles) of sodium cyanoborohydride portionwise over a period of ten minutes. After a final adjustment of the pH from 6.3