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DE LA SERIE DE AZALIDAS

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Zagreb, Croacia.

74. APODERADO

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FORMULARIO UNICO DE SOLICITUD DE PATENTE**PCT****ENTRADA EN FASE NACIONAL****12-07-05****SOLICITUD DE:****1**☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☒ Capítulo I.☐ Capítulo II.**2****SOLICITANTE
(71)**

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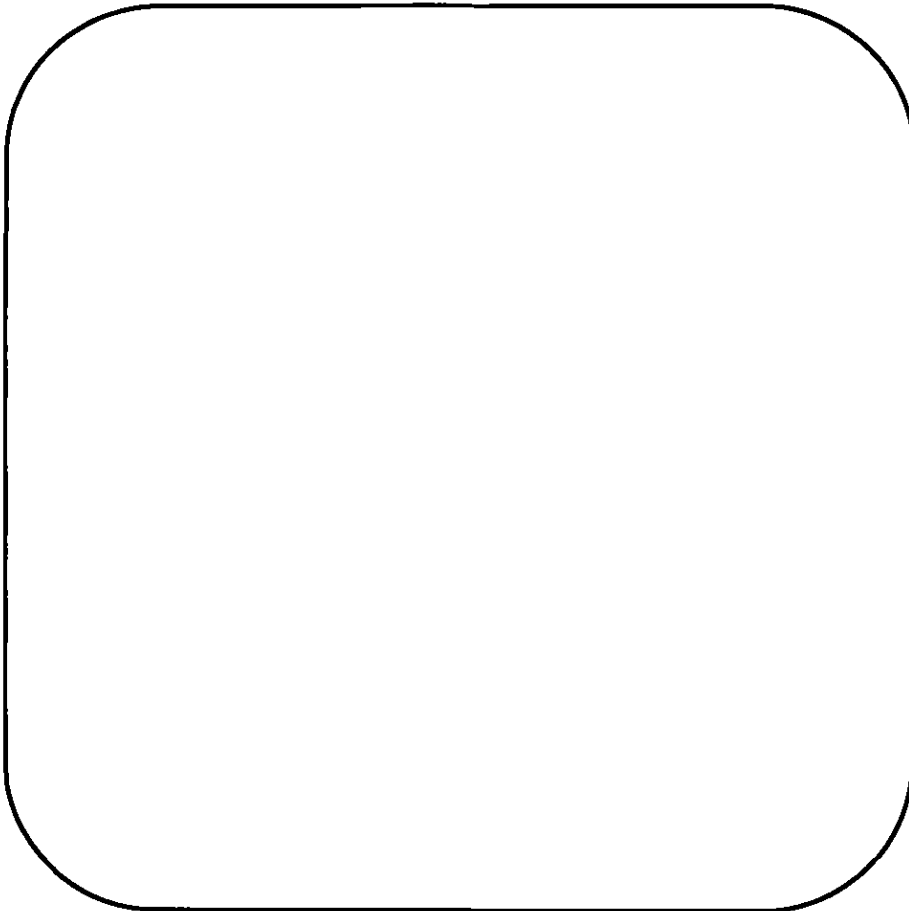
10

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11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

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DOCUMENTOS ANEXOS

1. ☒ **Publicación Internacional WO 2004/052904 A2**

Descripción:

Páginas 1 - 41 en el idioma original

Páginas 1 -59 en español

Reivindicaciones: Número (s) 56

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2. ☐ **Forma PCT/RO/101. PCT Request**
3. ☐ **Forma PCT/RO/106. Invitation to Correct Defects.**
4. ☒ **Forma PCT/ISA/210. Informe de Búsqueda Internacional.**
5. ☐ **Forma PCT/ISA/220. Notificación De La Transmisión Del Informe De Búsqueda Internacional Y De La Opinión Escrita De La Administración Encargada De La Búsqueda Internacional, O De La Declaración.**
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- (72) Inventors; and
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(54) Title: N⁶-Substituted 9a-N-(N⁶-carbamoyl-γ-aminopropyl), 9a-N-(N⁶-thiocarbamoyl-γ-aminopropyl), 9a-N-[N⁶-(β-cyanoethyl)-N⁶-carbamoyl-γ-aminopropyl] and 9a-N-[N⁶-(β-cyanoethyl)-N⁶-thiocarbamoyl-γ-aminopropyl] derivatives of 9-de

(57) Abstract: The invention relates to N⁶-substituted 9a-N-(N⁶-carbamoyl-γ-aminopropyl), 9a-N-(N⁶-thiocarbamoyl-γ-aminopropyl), 9a-N-[N⁶-(β-cyanoethyl)-N⁶-carbamoyl-γ-aminopropyl] and 9a-N-[N⁶-(β-cyanoethyl)-N⁶-thiocarbamoyl-γ-aminopropyl] derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series, of the general formula I, wherein R represents H or cladinosyl moiety, R¹ represents H or (β-cyanoethyl) moiety, R² represents isopropyl, 1-naphthyl, 2-naphthyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl, β-phenylethyl, ethoxycarbonylmethyl, 1-(1-naphthyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O and S, and their acceptable addition salts thereof with inorganic or organic acids, to the process for preparation of their pharmaceutical compositions as well as the use their compositions in the treatment of bacterial infections.

**N''-Substituted 9a-N-(N'-carbamoyl- γ -aminopropyl), 9a-N-(N'-thiocarbamoyl- γ -aminopropyl), 9a-N-[N'-(β -cyanoethyl)-N'-carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-thiocarbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-
9a-
-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-
-dihydro-9a-aza-9a-homoerithronolide A**

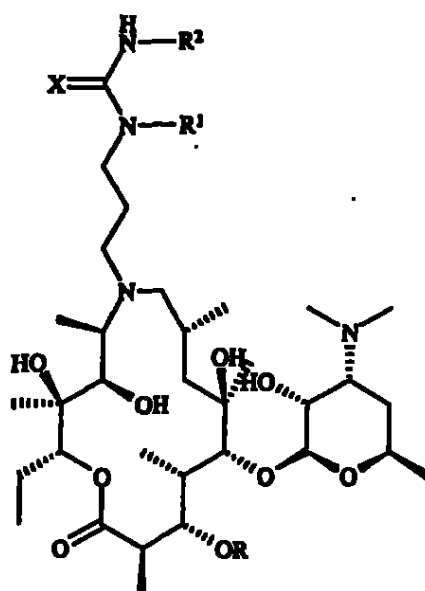
Technical field

Int. Cl. C 07H 17/08, A61K 31/71

Technical Problem

The present invention relates to N''-substituted 9a-N-(N'-carbamoyl- γ -aminopropyl), 9a-N-(N'-thiocarbamoyl- γ -aminopropyl), 9a-N-[N'-(β -cyanoethyl)-N'-carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-thiocarbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series having antibacterial activity, of the general formula 1,

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wherein R represents H or cladinosyl moiety, and R¹ represents H or β-cyanoethyl group, R² represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl, β-phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O or S, to pharmaceutically acceptable addition salts thereof with inorganic or organic acids, to a process for the preparation of the pharmaceutical compositions as well as to the use of the pharmaceutical compositions obtained in the treatment of bacterial infections.

Prior Art

Brithromycin A is a macrolide antibiotic, whose structure is characterized by 14-membered macrolactone ring having carbonyl group in C-9 position. It was found by McGuire in 1952 [*Antibiot. Chemother.*, 2 (1952) 281] and for over 40 years it has been considered as a reliable and effective antimicrobial agent in the treatment of diseases caused by Gram-positive and some Gram-negative microorganisms. However, in an acidic medium it is easily converted into anhydroerythromycin A, an inactive C-6/C-12 metabolite of a spiroketal structure [P. Kurath et al.,

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Experientia 27 (1971) 362]. It is well-known that spirocyclisation of aglycone ring of erythromycin A is successfully inhibited by a chemical transformation of C-9 ketones or hydroxy groups in C-6 and/or C-12 position. By the oximation of C-9 ketones [S. Đokić et al., *Tetrahedron Lett.* 1967: 1945] and by subsequently modifying the obtained 9(E)-oxime into 9-[O-(2-methoxyethoxy)methyloxime]erythromycin A (ROXTITHROMYCIN) [G. S. Ambrieres, Fr. pat. 2,473,525, 1981] or 9(S)-erithromycylamine [R. S. Egan et al., *J. Org. Chem.* 39 (1974) 2492] or a more complex oxazine derivative thereof, 9-deoxo-11-deoxy-9,11-(imino[2-(2-methoxyethoxyethylidene)oxy]-9(S)-erythromycin A (DIRITHROMYCIN) [P. Lugar et al., *J. Crist. Mol. Struct.* 9 (1979) 329], novel semisynthetic macrolides were synthesized, whose basic characteristic, in addition to a greater stability in an acidic medium, is a better pharmacokinetics and a long half-time with regard to the parent antibiotic erythromycin A. In a third way for modifying C-9 ketones use is made of Beckmann rearrangement of 9(E)-oxime and of a reduction of the obtained imino ether (G. Kobrehel et al., U.S. Pat. 4,328,334, 1982.) into 11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9a-aza-9a-homoerythromycin A) under broadening the 14-member ketolactone ring into a 15-member azalactone ring. By reductive N-methylation of 9a-amino group according to Eschweiler-Clark process (G. Kobrehel et al., BB Pat. 892,397, 1982.) or by a preliminary protection of amino group by means of conversion into the corresponding N-oxides and then by alkylation and reduction [G. M. Bright, U.S. Pat., 4,474,768, 1984.] N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9a-methyl-9a-aza-9a-homoerithromycin A, AZITHROMYCIN) was synthesized, a prototype of azalide antibiotics, which, in addition to a broad antimicrobial spectrum including Gram-negative bacteria and intracellular microorganisms, are characterized by a specific mechanism of transport to the application site, a long biological half-time and a short therapy period. In EP A 0316128 (Bright G. M. et al.) novel 9a-allyl and 9a-propargyl derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A are disclosed and in U.S. Pat. 4,492,688, from 1985 (Bright G. M.) the synthesis and the antibacterial activity of the corresponding cyclic ethers are disclosed. In the there are further disclosed the synthesis and the activity spectrum of novel 9-deoxo-9a-aza-11-deoxy-9a-

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-homoerythromycin A 9a,11-cyclic carbamates and O-methyl derivatives thereof (G. Kobrehel et al., *J. Antibiot.* 46 (1993) 1239-1245).

By reaction of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A with isocyanates or isothiocyanates respectively [N. Kujundžić et al. Croat. Pat. 931480, 1993.], 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A with a certain antibacterial activity are obtained.

According to the known and established Prior Art, N"-substituted 9a-N-(N'-carbamoyl- γ -aminopropyl), 9a-N-(N'-thiocarbamoyl- γ -aminopropyl), 9a-N-[N'-(β -cyanoethyl)-N'-carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-thiocarbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, a process for the preparation thereof as well as the preparation methods and use in pharmaceutical preparations have not been disclosed as yet.

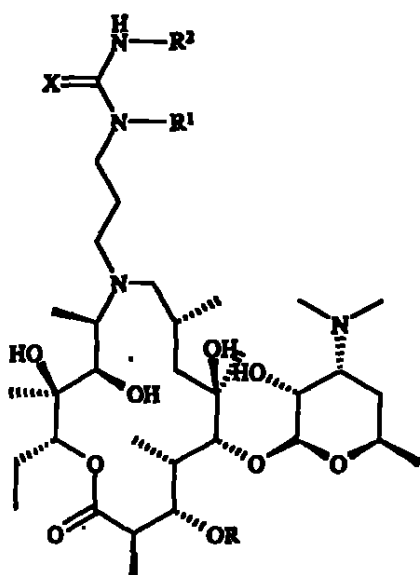
It has been found and it is object of the present invention, that N"-substituted 9a-N-(N'-carbamoyl- γ -aminopropyl), 9a-N-(N'-thiocarbamoyl- γ -aminopropyl), 9a-N-[N'-(β -cyanoethyl)-N'-carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-thiocarbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotic of the azalide series and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, may be prepared by reacting 9a-N-(γ -aminopropyl) and 9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A with isocyanates or isothiocyanates and optionally by reacting the obtained N"-substituted 9a-N-(N'-carbamoyl- γ -aminopropyl), 9a-N-(N'-thiocarbamoyl- γ -aminopropyl), 9a-N-[N'-(β -cyanoethyl)-N'-carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-thiocarbamoyl- γ -aminopropyl]

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derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A with organic and inorganic acids.

Technical Solution

It has been found that novel Nⁿ-substituted 9a-N-(Nⁿ-carbamoyl-γ-aminopropyl), 9a-N-(Nⁿ-thiocarbamoyl-γ-aminopropyl), 9a-N-[Nⁿ-(β-cyanoethyl)-Nⁿ-carbamoyl-γ-aminopropyl] and 9a-N-[Nⁿ-(β-cyanoethyl)-Nⁿ-thiocarbamoyl-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula 1,

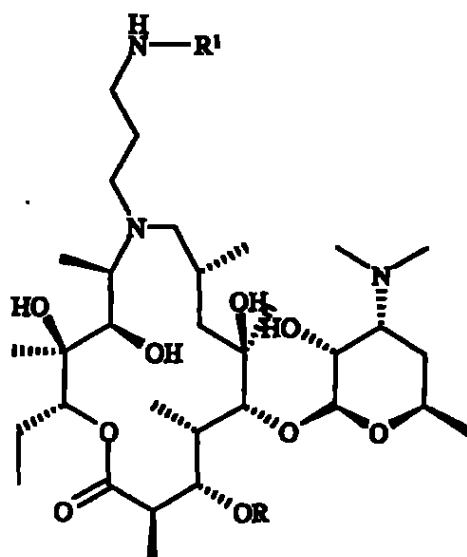


1

wherein R represents H or cladinოსyl group, R¹ represents H or β-cyanoethyl moiety, R² represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl, β-phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O or S, and their acceptable addition salts thereof with inorganic or organic acids, may be prepared by reacting 9a-N-(γ-aminopropyl) and 9a-N-[Nⁿ-(β-cyanoethyl)-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-

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-homocithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homocithronolide A general formula 2,



2

wherein R represents H or cladinosyl group and R¹ represents H or β-cyanoethyl moiety, with isocyanates or thioisocyanates general formula 3,



3

wherein R² and X have above meanings, in toluene, xylene or some other aprotic solvent, at a temperature 0° to 110°C.

Pharmaceutically acceptable acid addition salts, which also represent an object of present invention, were obtained by reaction N'-substituted 9a-N-(N'-carbamoyl-γ-aminopropyl), 9a-N-(N'-thiocarbamoyl-γ-aminopropyl), 9a-N-[N'-(β-cyanoethyl)-N'-carbamoyl-γ-aminopropyl] and 9a-N-[N'-(β-cyanoethyl)-N'-thiocarbamoyl-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homocithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homocithronolide A with an at least equimolar amount of the corresponding inorganic or organic acid such as hydrochloric acid, hydroiodic acid, sulfuric acid, phosphoric acid, acetic acid,

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trifluoroacetic acid, propionic acid, benzoic acid, benzenesulfonic acid, methane sulfonic acid, laurylsulfonic acid, stearic acid, palmitic acid, succinic acid, ethylsuccinic acid, lactobionic acid, oxalic acid, salicylic acid and similar acid, in a solvent inert to the reaction. Addition salts are isolated by evaporating the solvent or, alternatively, by filtration after a spontaneous precipitation or a precipitation by the addition of a non-polar cosolvent.

N"-Substituted 9a-N-(N'-carbamoyl- γ -aminopropyl), 9a-N-(N'-thiocarbamoyl- γ -aminopropyl), 9a-N-[N'-(β -cyanoethyl)-N'-carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-thiocarbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homocithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homocithronolide A of the general formula 1 and pharmaceutically acceptable addition salts with inorganic or organic acids thereof possess an antibacterial activity *in vitro*.

Minimal inhibitory concentration (MIC) is defined as the concentration which shows 90% growth inhibition, and was determined by broth dilution methods National Committee for Clinical Laboratory Standards (NCCLS, M7-A2 protocols). Final concentration of test substances were in range from 64 to 0.125 mg/l. MIC levels for all compound were determined on panel of susceptible and resistant Gram positive bacterial strains (*S. aureus*, *S. pneumoniae* and *S. pyogenes*) and on Gram negative strains (*E. coli*, *H. influenzae*, *E. faecalis*, *M. catarrhalis*).

It is evident from Table 1 and Table 2 that standard strains are susceptible to newly synthesized compounds of general formula 1. Thus they may be used as therapeutic agents in the treatment of infective diseases in animals, especially mammals and humans, caused by a broad spectrum of Gram-positive and Gram-negative bacteria, mycoplasmas and generally pathogenic microorganisms that are susceptible to the compounds of the formula 1. To this purpose the above compounds and pharmaceutically acceptable acid addition salts thereof may be administered orally in usual doses from 0.2 mg/kg body weight daily to about 250 mg/kg/day, most

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preferably from 0.5-50 mg/kg/day, or parenterally in the form of subcutaneous and intramuscular injections.

Process for the preparation of Nⁿ-substituted 9a-N-(Nⁿ-carbamoyl-γ-aminopropyl), 9a-N-(Nⁿ-thiocarbamoyl-γ-aminopropyl), 9a-N-[Nⁿ-(β-cyanoethyl)-Nⁿ-carbamoyl-γ-aminopropyl] and 9a-N-[Nⁿ-(β-cyanoethyl)-Nⁿ-thiocarbamoyl-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of this invention is illustrated by the following Examples which should in no way be construed as a limitation of the scope thereof.

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TABLE 1. Antibacterial *in vitro* activity of novel N"-substituted 9a-N-(N'-carbamoyl-γ-aminopropyl) and 9a-N-(N'-thiocarbamoyl-γ-aminopropyl) derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A presented as MIC values in comperison with erythromycin A (Er).

Test organisms	MIK µg/ml												
Compound from example	1	2	3	4	5	6	7	8	9	10	11	12*	Er
<i>S. aureus</i> ATCC 13709	2	0.5	0.5	2	2	2	1	1	8	16	4	8	≤0.125
<i>S. pneumoniae</i>	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	8	≤0.125	16	≤0.125
<i>S. pyogenes</i>	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	0.25
<i>S. pyogenes</i> BMLS	8	2	4	2	4	8	4	4	16	8	32	2	>64
<i>S. pyogenes</i> M	32	4	8	4	4	32	8	8	64	16	64	8	8
<i>M. catarrhalis</i> ATCC 23246	0.5	0.25	1	1	2	8	1	1	4	4	16	0.5	-
<i>H. influenzae</i> ATCC 49247	32	1	2	2	2	16	2	2	32	2	16	2	2
<i>E. faecalis</i> ATCC 29212	32	4	16	8	4	64	16	16	>64	16	>64	8	1
<i>E. coli</i> ATCC 25922	16	8	16	16	8	32	16	32	>64	64	>64	32	32

TABLE 2. Antibacterial *in vitro* activity of novel N"-substituted 9a-N-[N'-(β-cyanoethyl)-N'-carbamoyl-γ-aminopropyl] and 9a-N-[N'-(β-cyanoethyl)-N'-thiocarbamoyl-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A presented as MIC values in comperison with erythromycin A (Er).

Test organisms	MIK µg/ml												
Compound from example	27	28	29	30	31	32	33	34	36	37	38	39*	Er
<i>S. aureus</i> ATCC 13709	4	1	2	1	4	4	1	1	2	4	1	1	≤0.125

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<i>S. pneumoniae</i> ATCC	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125
<i>S. pyogenes</i> ATCC	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	0.25
<i>S. pyogenes</i> IMLS	8	2	16	2	4	8	4	4	8	47	2	32	>64
<i>S. pyogenes</i> M	32	4	64	4	4	32	8	8	16	8	8	64	8
<i>M. catarrhalis</i> ATCC 23246	0.5	0.25	4	1	2	8	1	1	4	1	0.5	16	-
<i>H. influenzae</i> ATCC 49247	32	1	32	2	2	16	2	2	2	2	2	16	2
<i>E. faecalis</i> ATCC 29212	32	4	>64	8	4	64	16	16	16	16	8	>64	1
<i>E. coli</i> ATCC 25922	16	8	>64	16	8	32	16	32	64	16	32	>64	32

Example 1**9-Deoxo-9-dihydro-9a-N-(N'-isopropylcarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ-aminopropyl)-9a-homoerithromycin A and 0.1 g (1.3 mmol) of isopropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-(N'-isopropylcarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 877.

Example 2**9-Deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ-aminopropyl)-9a-homoerithromycin A and 0.22 g (1.26 mmol) of 1-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 961.

Example 3**9-Deoxo-9-dihydro-9a-N-(N'-benzylcarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ-aminopropyl)-9a-homoerithromycin A and 0.17 g (1.3 mmol) of benzylisocyanate in 10 ml dry

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toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-(N'-benzylcarbamoyl- γ -aminopropyl)-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 925.

Example 4

9-Deoxo-9-dihydro-9a-N-(N'-benzylthiocarbamoyl- γ -aminopropyl)-9a-aza-9a-homoerithromycin A

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.17 g (1.3 mmol) of benzylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-(N'-benzylthiocarbamoyl- γ -aminopropyl)-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 941.

Example 5

9-Deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.17 g (1.3 mmol) of 1-naphtylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 977.

Example 6**9-Deoxo-9-dihydro-9a-N-[N'-(2-trifluoromethyl)phenyl]carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.24 g (1.3 mmol) of 2-(trifluoromethyl)phenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(2-trifluoromethylphenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 979.

Example 7**9-Deoxo-9-dihydro-9a-N-[N'-(3-phenylpropyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.22 g (1.3 mmol) of 3-phenylpropylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(3-phenylpropyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 969.

Example 8**9-Deoxo-9-dihydro-9a-N-[N'-(β -phenylethyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A**

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A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.21 g (1.3 mmol) of β -phenylethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -phenylethyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.
MS(ES⁺)m/z = 979.

Example 9

9-Deoxo-9-dihydro-9a-N-(N'-ethoxycarbonylmethylcarbamoyl- γ -aminopropyl)-9a-aza-9a-homoerithromycin A

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.16 g (1.3 mmol) of ethoxycarbonylmethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-(N'-ethoxycarbonylmethylcarbamoyl- γ -aminopropyl)-9a-aza-9a-homoerithromycin A was obtained.
MS(ES⁺)m/z = 921.

Example 10

9-Deoxo-9-dihydro-9a-N-[N'-[1-(1-naphtyl)ethylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.25 g (1.3 mmol) of 1-(1-naphtyl)ethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on

silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-{N'-[1-(1-naphthyl)ethyl carbamoyl- γ -aminopropyl]}-9a-aza-9a-homoerithromycin A was obtained.
MS(ES⁺)m/z = 989.

Example 11

9-Deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.26 g (1.3 mmol) of 3,4,5-trimethoxyphenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1001.

Example 12

9-Deoxo-9-dihydro-9a-N-[N'-(2-naphthyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.23 g (1.3 mmol) of 2-naphthylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 :

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: 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(2-naphtyl)carbamoyl- γ -aminopropyl]-9a-
-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 961.

Example 13

**9-Deoxo-9-dihydro-9a-N-[N'-(2,4-dichlorophenyl)carbamoyl- γ -aminopropyl]-9a-
-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-
-homoerithromycin A and 0.23 g (1.3 mmol) of 2,4-dichlorophenylisocyanate in 10
ml dry toluene was stirred for 30 minutes at room temperature to complete the
reaction. The crystals of the crude product were filtered, wherefrom by
chromatography on silica gel column using the solvent system methylene-chloride :
: methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(2,4-
-dichlorophenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was
obtained.

MS(ES⁺)m/z = 979.

Example 14

**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-(N'-isopropylcarbamoyl- γ -
-aminopropyl)-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -
-aminopropyl)-9a-aza-homoerithronolide A and 0.13 g (1.57 mmol) of
isopropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room
temperature to complete the reaction. The crystals of the crude product were filtered,
wherefrom by chromatography on silica gel column using the solvent system
methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-
-deoxo-9-dihydro-9a-N-(N'-isopropylcarbamoyl- γ -aminopropyl)-9a-aza-9a-
-homoerithronolide A was obtained.

MS(ES⁺)m/z = 719.

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Example 15**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-naphthyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.13 g (1.57 mmol) of 1-naphthylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-naphthyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 803.

Example 16**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-(N'-benzylcarbamoyl- γ -aminopropyl)-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.21 g (1.57 mmol) of benzylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(N'-benzylcarbamoyl- γ -aminopropyl)-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 767.

Example 17**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-(N'-benzylthiocarbamoyl- γ -aminopropyl)-9a-aza-9a-homoerithronolide A**

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A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.24 g (1.57 mmol) of benzyliothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(N'-benzylthiocarbamoyl- γ -aminopropyl)-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 783.

Example 18

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.29 g (1.57 mmol) of 1-naphtyliothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-naphtyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 819.

Example 19

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(2-(trifluoromethyl)phenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

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A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.30 g (1.57 mmol) of 2-(trifluoromethyl)phenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(2-(trifluoromethyl)phenylcarbamoyl- γ -aminopropyl)]-9a-aza-9a-homoerithronolide A was obtained.
MS(ES⁺)m/z = 821.

Example 20

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3-phenylpropyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.28 g (1.57 mmol) of 3-phenylpropylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3-phenylpropyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.
MS(ES⁺)m/z = 811.

Example 21

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -phenylethyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.26 g (1.57 mmol) of β -phenylethylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered,

wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β-phenylethyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 797.

Example 22

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-(N'-ethoxykarbonylmethyl-carbamoyl-γ-aminopropyl)-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.20 g (1.57 mmol) of ethoxykarbonylmethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(N'-ethoxykarbonylmethylcarbamoyl-γ-aminopropyl)-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 763.

Example 23

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(2-naphtyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.27 g (1.57 mmol) of 2-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(2-naphtyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 803.

Example 24

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-(1-naphtyl)ethyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.31 g (1.57 mmol) of 1-(1-naphtyl)ethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(1-(1-naphtyl)ethyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 831.

Example 25

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.31 g (1.57 mmol) of 3,4,5-trimethoxyphenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 843.

Example 26**5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(2,4-dichlorophenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A**

A mixture of 1.0 g (1.57 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.31 g (1.57 mmol) of 2,4-dichlorophenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(3,4,5-trimethoxyphenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 821.

Example 27**9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-isopropylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.06 g (0.591 mmol) of isopropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-isopropylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 931.

Example 28**9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(1-naphthyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A**

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A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.11 g (0.591 mmol) of 1-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(1-naphtyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z =.

Example 29

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-benzylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.08 g (0.591 mmol) of benzylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-benzylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 931.

Example 30

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-benzylthiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.09 g (0.591 mmol) of benzylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered,

wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-benzylthiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 995.

Example 31

9-Deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(1-naphtyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-γ-aminopropyl]-9a-aza-9a-homoerithromycin A and 0.12 g (0.591 mmol) of 1-naphtylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(1-naphtyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1029.

Example 32

9-Deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(2-(trifluoromethyl)phenyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-γ-aminopropyl]-9a-aza-9a-homoerithromycin A and 0.08 g (0.591 mmol) of 2-(trifluoromethyl)phenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-

-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2-(trifluoromethyl)phenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1033.

Example 33

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(3-phenylpropyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.10 g (0.591 mmol) of 3-phenylpropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(3-phenylpropyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1022.

Example 34

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(β -phenylethyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.10 g (0.591 mmol) of β -phenylethylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(β -phenylethyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1008.

Example 35

9-Deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-ethoxycarbonylmethyl-carbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-γ-aminopropyl]-9a-aza-9a-homoerithromycin A and 0.10 g (0.591 mmol) of ethoxycarbonylmethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-ethoxycarbonylmethylcarbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 974.

Example 36

9-Deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-[1-(1-naphtyl)ethyl]carbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-γ-aminopropyl]-9a-aza-9a-homoerithromycin A and 0.11 g (0.591 mmol) of 1-(1-naphtyl)ethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-[1-(1-naphtyl)ethyl]carbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1042.

Example 37

9-Deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(3,4,5-trimethoxyphenyl)carbamoyl]-γ-aminopropyl]-9a-aza-9a-homoerithromycin A

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A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.12 g (0.591 mmol) of 3,4,5-trimethoxyphenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(3,4,5-trimethoxyphenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1053.

Example 38

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2-naphtyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.11 g (0.591 mmol) of 2-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2-naphtyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1014.

Example 39

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2,4-dichlorophenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

A mixture of 0.5 g (0.591 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.11 g (0.591 mmol) of 2-naphtylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room

temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2,4-dichlorophenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1033.

Example 40

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-isopropylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.06 g (0.728 mmol) of isopropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-isopropylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 771.

Example 41

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(1-naphthyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.12 g (0.728 mmol) of 1-naphthylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered,

wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(1-naphtyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 855.

Example 42

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-benzylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.10 g (0.728 mmol) of benzylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-benzylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 819.

Example 43

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-benzylthiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.11 g (0.728 mmol) of benzylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-benzylthiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 835.

Example 44

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(1-naphthyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.14 g (0.728 mmol) of 1-naphthylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(1-naphthyl)thiocarbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 855.

Example 45

5-O-Desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(2-(trifluoromethyl)phenyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-(γ-aminopropyl)-9a-aza-homoerithronolide A and 0.14 g (0.728 mmol) of 2-(trifluoromethyl)phenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(2-(trifluoromethyl)phenyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 873.

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Example 46

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(3-phenylpropyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.13 g (0.728 mmol) of 3-phenylpropylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(3-phenylpropyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 863.

Example 47

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(β -phenylethyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.12 g (0.728 mmol) of β -phenylethylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(β -phenylethyl)thiocarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = .

Example 48

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-ethoxycarbonylmethylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.09 g (0.728 mmol) of β -phenylethylisothiocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-ethoxycarbonylmethylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 815.

Example 49

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2-naphthyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.12 g (0.728 mmol) of 2-naphthylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2-naphthyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 855.

Example 50

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-[1-(1-naphthyl)ethylcarbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

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A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxy-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.15 g (0.728 mmol) of 1-(1-naphthyl)ethylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxy-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(1-(1-naphthyl)ethyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 883.

Example 51

5-O-Desosaminy-9-deoxy-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(3,4,5-trimethoxyphenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxy-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.14 g (0.728 mmol) of 3,4,5-trimethoxyphenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-desosaminy-9-deoxy-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(3,4,5-trimethoxyphenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 895.

Example 52

5-O-Desosaminy-9-deoxy-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2,4-dichlorophenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

A mixture of 0.5 g (0.728 mmol) 5-O-desosaminy-9-deoxy-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-homoerithronolide A and 0.14 g (0.728 mmol) of 2,4-dichlorophenylisocyanate in 10 ml dry toluene was stirred for 30 minutes at room

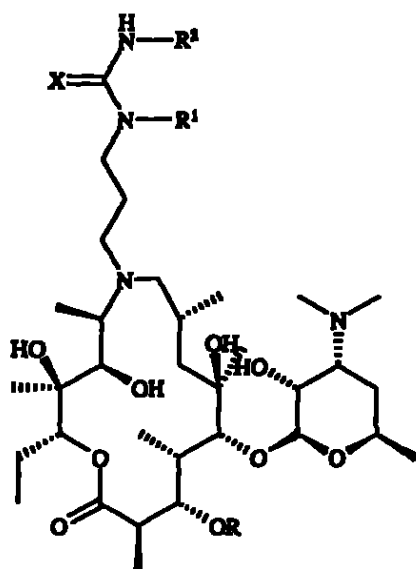
temperature to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : ammonia= 90 : 20 : 1.5, pure 5-O-deosaminy-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2,4-dichlorophenyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 874.

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CLAIMS

1. N⁷-Substituted 9a-N-(N⁷-carbamoyl-γ-aminopropyl), 9a-N-(N⁷-thiocarbamoyl-γ-aminopropyl), 9a-N-[N⁷-(β-cyanoethyl)-N⁷-carbamoyl-γ-aminopropyl] and -9a-N-[N⁷-(β-cyanoethyl)-N⁷-thiocarbamoyl-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series of the general formula 1,



1

- wherein R represents H or cladinosyl moiety, R¹ represents H or β-cyanoethyl moiety, R² represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl, β-phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O and S, and their acceptable addition salts thereof with inorganic or organic acids.
2. Substance according to claim 1, characterized in that R represents cladinosyl group and R¹ represents H, R² represents isopropyl group and X is O.
 3. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 1-naphtyl group and X is O.

4. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 2-naphtyl group and X is O.
5. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents benzyl group and X is O.
6. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 2-(trifluoromethyl)phenyl group and X represents O.
7. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 3-phenylpropyl group and X is S.
8. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents β-phenylethyl group and X is S.
9. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents etoxycarbonylmethyl group and X is O.
10. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 1-(1-naphtyl)ethyl group and X is O.
11. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 3,4,5-trimethoxyphenyl group and X is O.
12. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 2,4-dichlorophenyl group and X is O.
13. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents benzyl group and X is S.
14. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 1-naphtyl group and X is S.
15. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents isopropyl group and X is O.
16. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents 1-naphtyl group and X is O.

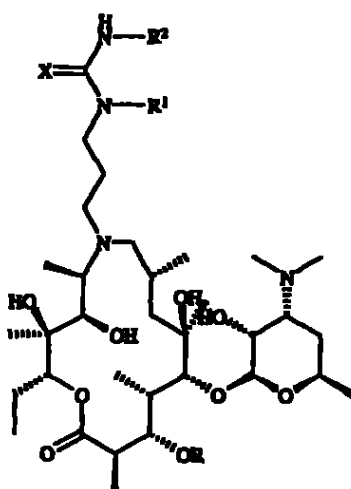
SUBSTITUTE SHEET (RULE 26)

- 2/1
17. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents 2-naphtyl group and X is O.
 18. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents benzyl group and X is O.
 19. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents 2-(trifluoromethyl)phenyl group and X is O.
 20. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents 3-phenylpropyl group and X is S.
 21. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents β-phenylethyl group and X is S.
 22. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents ethoxycarbonylmethyl group and X is O.
 23. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents 1-(1-naphtyl)ethyl group and X is O.
 24. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents 3,4,5-trimethoxyphenyl group and X is O.
 25. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, R² represents 2,4-dichlorophenyl group and X is O.
 26. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl group, R² represents benzyl group and X is S.
 27. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl group, R² represents 1-naphtyl group and X is S.

28. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents isopropyl group and X is O.
29. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents 1-naphtyl group and X is O.
30. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents 2-naphtyl group and X is O.
31. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents benzyl group and X is O.
32. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents 2-(trifluoromethyl)phenyl group and X is O.
33. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents 3-phenylpropyl group and X is S.
34. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents β-phenylethyl group and X is S.
35. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents ethoxycarbonylmethyl group and X is O.
36. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents 1-(1-naphtyl)ethyl group and X is O.
37. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents 3,4,5-trimethoxyphenyl group and X is O.
38. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents 2,4-dichlorophenyl group and X is O.
39. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents benzyl group and X is S.
40. Substance according to claim 1, characterized in that R and R¹ represent H, R² represents 1-naphtyl group and X is S.
41. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl, R² represents isopropyl group and X is O.
42. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl, R² represents 1-naphtyl group and X is O.
43. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl, R² represents 2-naphtyl group and X is O.

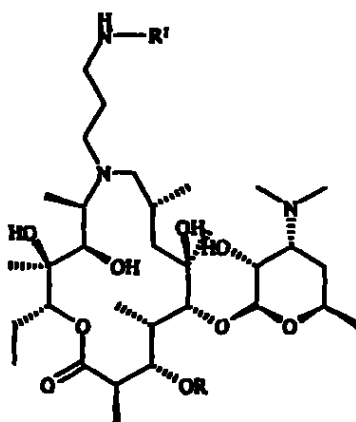
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44. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents benzyl group and X is O.
45. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents 2-(trifluoromethyl)phenyl group and X is O.
46. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents 3-phenylpropyl group and X is S.
47. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents β -phenylethyl group and X is O.
48. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents ethoxycarbonylmethyl group and X is O.
49. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents 1-(1-naphtyl)ethyl group and X is O.
50. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents 3,4,5-trimethoxyphenyl group and X is O.
51. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents 2,4-dichlorophenyl group and X is O.
52. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents benzyl group and X is S.
53. Substance according to claim 1, characterized in that R represents H, R¹ represents β -cyanoethyl, R² represents 1-naphtyl group and X is S.
54. Process for the preparation of N'-substituted 9a-N-(N'-carbamoyl- γ -aminopropyl), 9a-N-(N'-thiocarbamoyl- γ -aminopropyl), 9a-N-[N'-(β -cyanoethyl)-N'-carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-thiocarbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, of the general formula 1,



1

wherein R represents H or cladinosyl moiety, R¹ represents H or β-cyanoethyl moiety, R² represents isopropyl, 1-naphthyl, 2-naphthyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl, β-phenylethyl, ethoxycarbonylmethyl, 1-(1-naphthyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O and S, characterized in that 9a-N-(γ-aminopropyl) and 9a-N-[N'-(β-cyanoethyl)-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homocerrithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homocerrithronolide A general formula 2,



2

wherein R represents H and cladinosyl group and R¹ represents H and β-cyanoethyl group is reacted with isocyanates or isothiocyanates general formula 3



3

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wherein R^2 represents isopropyl, 1-naphtyl, 2-naphtyl, benzyl, 2-(trifluoromethyl)phenyl, 3-phenylpropyl, β -phenylethyl, ethoxycarbonylmethyl, 1-(1-naphtyl)ethyl, 3,4,5-trimethoxyphenyl and 2,4-dichlorophenyl group, and X represents O and S, in toluene, xylene or some others aprotic solvents at a temperature 0°-110°C and then, if appropriate, to a reaction with inorganic or organic acids.

55. Pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an antibacterially effective amount of the substances according to claim 1.
56. Use of a substance according to any claims 1 to 51 in the treatment of bacterial infections.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P-482/WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/HR 03/00062	International filing date (day/month/year) 10/12/2003	(Earliest) Priority Date (day/month/year) 12/12/2002
Applicant PLIVA D.D.		

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

This International Search Report consists of a total of 3 sheets.

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

1. Basis of the report

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

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

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

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

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

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

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

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

NOVEL SEMISYNTHETIC MACROLIDE ANTIBIOTICS OF THE AZALIDE SERIES

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

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

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

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/HR 03/00062

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H17/00 A61K31/70 A61P31/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 492 688 A (BRIGHT GENE M) 8 January 1985 (1985-01-08) claim 9	1-56
A	WO 97/35590 A (PLATT CHRIS E) 2 October 1997 (1997-10-02) claim 4	1-56
A	EP 0 132 944 A (PFIZER) 13 February 1985 (1985-02-13) claim 1	1-56



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

21 June 2004

Date of making of the international search report

02/07/2004

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentkan 2
NL - 2280 LV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Bard111, W

PATENT COOPERATION TREATY

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PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

SARCEVIC, Kresimir, LLB
Pliva- Research Institute Ltd.
Legal and Patent Affairs
Prilaz baruna Filipovica 29
10000 Zagreb
Croatia

Date of mailing (day/month/year) 29 July 2004 (29.07.2004)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference P-482/WO	
International application No. PCT/HR2003/000062	International filing date (day/month/year) 10 December 2003 (10.12.2003)

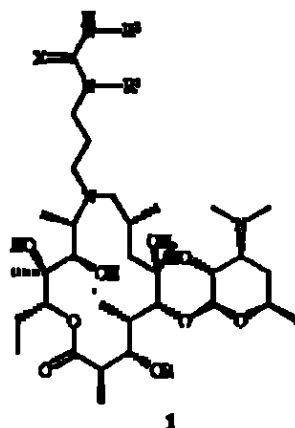
1. The following indications appeared on record concerning:		
☒ the applicant	☐ the inventor	☐ the agent ☐ the common representative
Name and Address PLIVA D.D. Ulica grada Vukovara 49 10000 Zagreb Croatia	State of Nationality HR	State of Residence HR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
☒ the person	☐ the name	☐ the address ☐ the nationality ☐ the residence
Name and Address PLIVA - ISTRAZIVACKI INSTITUT D.O.O. Prilaz baruna Filipovica 29 10000 Zagreb Croatia	State of Nationality HR	State of Residence HR
	Telephone No. 385 1 372 1246	
	Facsimile No. 385 1 372 1249	
	Teleprinter No.	
3. Further observations, if necessary: Please send all future correspondence to the address indicated in the addressee box of this notification.		
4. A copy of this notification has been sent to:		
☒ the receiving Office	☒ the designated Offices concerned	
☐ the International Searching Authority	☐ the elected Offices concerned	
☐ the International Preliminary Examining Authority	☐ other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Céline Faust (Fax 338-8995)
Facsimile No. (41-22) 338.89.85	Telephone No. (41-22) 338 8728

**NUEVOS ANTIBIÓTICOS MACRÓLIDOS SEMISINTÉTICOS
DE LA SERIE DE AZALIDAS**

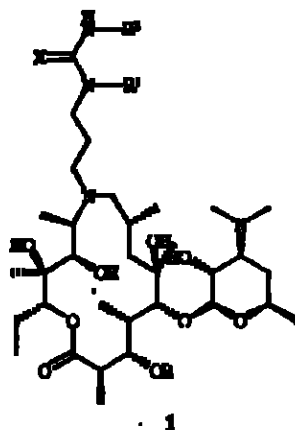
RESUMEN

La invención se refiere a derivados N" sustituidos 9a-N- (N'-carbamoil-γ-aminopropil), 9a-N- (N'-tiocarbamoil-γ-aminopropil), 9a-N- [N'-(β-cianoetil)-N'-carbamoil-γ-aminopropil] y 9a-N- [N'-(β-cianoetil)-N'-tiocarbamoil-γ-aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A, nuevos antibióticos macrólidos semisintéticos de la serie de azalidas de fórmula general 1,



donde R representa H o una parte cladinósilo, R¹ representa H o una parte β-cianoetilo, R² representa un grupo isopropilo, 1-naftilo, 2-naftilo, bencilo, 2-(trifluorometil)fenilo, 3-fenilpropilo, β-feniletilo, etoxycarbonil-metilo, 1-(1-naftil)etilo, 3,4,5-trimetoxifenilo y 2,4-diclorofenilo, y X representa O y S, y sus sales de adición aceptables con ácidos inorgánicos u orgánicos, al procedimiento para la preparación de sus composiciones farmacéuticas, como así también al uso de sus composiciones para el tratamiento de infecciones bacterianas.

La invención se refiere a derivados N" sustituidos de 9a-N-(N'-carbamoil-γ-aminopropil), 9a-N-(N'-tiocarbamoil-γ-aminopropil), 9a-N-[N'-(β-cianoetil)-N'-carbamoil-γ-aminopropil] y 9a-N-[N'-(β-cianoetil)-N'-tiocarbamoil-γ-aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A, nuevos antibióticos macrólidos semisintéticos de la serie de azalidas con actividad antibacteriana de fórmula general 1,



donde R representa H o una parte cladinósilo, R¹ representa H o un grupo β-cianoetilo, R² representa un grupo isopropilo, 1-naftilo, 2-naftilo, bencilo, 2-(trifluorometil)fenilo, 3-fenilpropilo, β-feniletilo, etoxycarbonil-metilo, 1-(1-naftil)etilo, 3,4,5-trimetoxifenilo y 2,4-diclorofenilo, y X representa O y S, y sus sales de adición farmacéuticamente aceptables con ácidos inorgánicos u orgánicos, al procedimiento para la preparación de sus composiciones farmacéuticas, como así también al uso de las composiciones farmacéuticas obtenidas para el tratamiento de infecciones bacterianas.

La eritromicina A es un antibiótico macrólido cuya estructura se caracteriza por un anillo de macrolactona de 14 miembros con el grupo carbonilo en la posición C-9. Fue descubierto por McGuire en 1952 [Antibiot. Chemother., 2 (1952) 281] y durante más de 40 años se lo ha considerado un agente antimicrobiano confiable y efectivo para el tratamiento de enfermedades causadas por microorganismos

Gram-positivos y algunos Gram-negativos. Sin embargo, en un medio ácido se convierte fácilmente en anhidroeritromicina A, un metabolito inactivo C-6/C-12 de estructura espirocetal [P. Kurath et al., *Experientia* 27 (1971) 362]. Es bien sabido que la espirociclización del anillo de aglicona de eritromicina A se inhibe con éxito mediante una transformación química de C-9 cetonas o grupos hidroxilo en las posiciones C-6 y/o C-12. Mediante la oximación de C-9 cetonas [S. Doki et al., *Tetrahedron Lett.* 1967:1945] y modificando seguidamente la 9(E)-oxima obtenida en 9-[O-(2-metoxietoxi)metiloxima] eritromicina A (ROXITHROMYCIN) [G. S. Ambrieres, Pat. Fr. 2.473.525, 1981] o 9(S)-eritromicilamina [R. S. Egan et al., *J. Org. Chem.* 39 (1974) 2492] o un derivado de oxazina más complejo de la misma 9-deoxo-11-deoxi-9,11-{imino[2-(2-metoxietoxietiliden)-oxi]-9(S)-eritromicina A (DI-RITHROMYCIN) [P. Lugar i sur., *J. Crist. Mol. Struct.* 9 (1979) 329], se sintetizaron nuevos macrólidos semisintéticos, cuya característica básica, aparte de una mayor estabilidad en un medio ácido, es una mejor farmacocinética y una semivida más larga en comparación con el antibiótico madre eritromicina A. En una tercera forma de modificación de C-9 cetonas se utiliza el reordenamiento de Beckmann de la 9(E)-oxima y una reducción del iminoéter obtenido (G. Kobrehel i sur., Pat. US 4.328.334, 1982.) en 11-

aza-10-deoxo-10-dihidroeritromicina A (9-deoxo-9a-aza-9a-homoeritromicina A) bajo ampliación del anillo de cetolactona de 14 miembros a un anillo de azalactona de 15 miembros. Mediante la N-metilación reductora de un grupo 9a-amino de acuerdo con el procedimiento de Eschweiler-Clark (G. Kobrehel et al., Pat. BE 892.397, 1982) o mediante protección preliminar del grupo amino mediante la conversión en los correspondientes N-óxidos y luego por alquilación y reducción [G. M. Bright et al., Pat.US 4.474.768, 1984] se sintetizó N-metil-11-aza-10-deoxo-10-dihidroeritromicina A (9-deoxo-9a-metil-9a-aza-9a-homoeritromicina A, AZITHROMYCIN), un prototipo de antibióticos azalida que, además de un amplio espectro antimicrobiano, incluyendo bacterias Gram-negativas y microorganismos intercelulares, se caracterizan por un mecanismo de transporte específico al sitio de aplicación, una larga semivida biológica y un período terapéutico breve. En la EP A 0316128 (G. M. Bright et al.) se divulgan nuevos derivados 9a-alilo y 9a-propargilo de 9-deoxo-9a-aza-9a-homoeritromicina A y en la Pat. US 4.492.688, 1/1985 (Bright G. M.) se divulgan la síntesis y la actividad antibacteriana de los correspondientes éteres cíclicos. En J. Antibiotics 46 (1993) 1239 (G. Kobrehel et al.) se divulgan además la síntesis y el espectro de actividad de nuevos carbamatos cíclicos de 9-deoxo-9a-aza-11-deoxi-9a-homoeritromicina A

9a,11 y sus derivados de O-metilo.

Por reacción de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A con isocianatos o isotiocianatos respectivamente [N. Kujundzi et al., Pat. Croat. 931480, 1993.], se obtienen derivados 9a-N-(N'-carbamoilo) y 9a-N-(N'-tiocarbamoilo) de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A con determinada actividad antibacteriana.

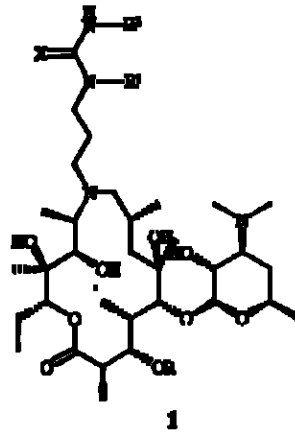
De acuerdo con el arte previo conocido y establecido, no se han divulgado aun los derivados N" sustituidos de 9a-N-(N'-carbamoil- γ -aminopropil), 9a-N-(N'-tiocarbamoil- γ -aminopropil), 9a-N-[N'-(β -cianoetil)-N'-carbamoil- γ -aminopropil] y 9a-N-[N'-(β -cianoetil)-N'-tiocarbamoil- γ -aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A, y sus sales de adición farmacéuticamente aceptables con ácidos inorgánicos u orgánicos, un procedimiento para la preparación de los mismos, y los métodos de elaboración y uso de preparaciones farmacéuticas.

Se ha descubierto y es objeto de la presente invención que los derivados N"-sustituidos 9a-N-(N'-carbamoil- γ -aminopropil), 9a-N-(N'-tiocarbamoil- γ -aminopropil), 9a-N-[N'-(β -cianoetil)-N'-carbamoil- γ -aminopropil] y 9a-N-[N'-(β -cianoetil)-N'-tiocarbamoil- β -aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-

deoxo-9-dihidro-9a-aza-9a-homoeritronolida A, nuevos antibióticos macrólidos semisintéticos de la serie azalida y sus sales de adición farmacéuticamente aceptables con ácidos inorgánicos u orgánicos pueden prepararse haciendo reaccionar derivados 9a-N-(γ -aminopropilo) y 9a-N-[N'-(β -cianoetil)- γ -aminopropilo] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A con isocianatos o isotiocianatos y opcionalmente haciendo reaccionar los derivados N" sustituidos 9a-N-(N'-carbamoil- γ -aminopropil), 9a-N-(N'-tiocarbamoil- γ -aminopropil), 9a-N-[N'-(β -cianoetil)-N'-carbamoil- γ -aminopropil] y 9a-N-[N'-(β -cianoetil)-N'-tiocarbamoil- γ -aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A obtenidos con ácidos orgánicos e inorgánicos.

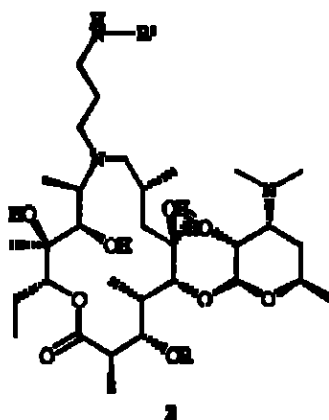
Se ha descubierto que los nuevos derivados N" sustituidos 9a-N-(N'-carbamoil- γ -aminopropil), 9a-N-(N'-tiocarbamoil- γ -aminopropil), 9a-N-[N'-(β -cianoetil)-N'-carbamoil- γ -aminopropil] y 9a-N-[N'-(β -cianoetil)-N'-tiocarbamoil- γ -aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A de fórmula general 1,

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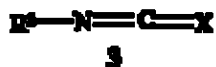


donde R representa H o un grupo cladinósilo, R¹ representa H o una parte β-cianoetilo, R² representa un grupo isopropilo, 1-naftilo, 2-naftilo, bencilo, 2-(trifluorometil)fenilo, 3-fenilpropilo, β-feniletilo, etoxycarbonil-metilo, 1-(1-naftil)etilo, 3,4,5-

trimetoxifenilo y 2,4-diclorofenilo, y X representa O o S, y sus sales de adición aceptables con ácidos inorgánicos u orgánicos, pueden ser preparados haciendo reaccionar los derivados 9a-N-(γ -aminopropil), y 9a-N-[N'-(β -cianoetil)- γ -aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A de fórmula general 2,



donde R representa H o un grupo cladinosilo y R¹ representa H o una parte β -cianoetilo, con isocianatos o tioisocianatos de fórmula general 3,



donde R^2 y X tienen los significados que anteceden, en tolueno, xileno u otro solvente aprótico, a una temperatura comprendida entre 0°C y 110°C.

Se obtuvieron sales de adición de ácidos farmacéuticamente aceptables, que también representan un objeto de la presente invención, mediante la reacción de derivados N'' sustituidos 9a-N-(N'-carbamoil- γ -aminopropil), 9a-N-(N'-tiocarbamoil- γ -aminopropil), 9a-N-[N'-(β -cianoetil)-N'-carbamoil- γ -aminopropil] y 9a-N-[N'-(β -cianoetil)-N'-tiocarbamoil- γ -aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A con una cantidad al menos equimolar del ácido inorgánico u orgánico correspondiente tal como ácido clorhídrico, ácido yodhídrico, ácido sulfúrico, ácido fosfórico, ácido acético, ácido trifluoroacético, ácido propiónico, ácido benzoico, ácido benzensulfónico, ácido metansulfónico, ácido laurilsulfónico, ácido esteárico, ácido palmítico, ácido succínico, ácido etilsuccínico, ácido lactobiónico, ácido oxálico, ácido salicílico y ácidos similares, en un solvente inerte a la reacción. Las sales de adición se aíslan evaporando el solvente o, alternativamente, por filtración luego de una precipitación espontánea o una precipitación por adición de un cosolvente no polar.

Los derivados N'' sustituidos 9a-N-(N'-carbamoil- γ -

aminopropil), 9a-N-(N'-tiocarbamoil- γ -aminopropil), 9a-N-[N'-(β -cianoetil)-N'-carbamoil- γ -aminopropil] y 9a-N-[N'-(β -cianoetil)-N'-tiocarbamoil- γ -aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A de fórmula general 1 y sus sales de adición farmacéuticamente aceptables con ácidos inorgánicos u orgánicos poseen actividad antibacteriana *in vitro*.

La concentración inhibitoria mínima (MIC) se define como la concentración que muestra el 90% de inhibición de desarrollo, y se determinó mediante métodos de dilución de caldo de acuerdo con protocolos del National Committee for Clinical Laboratory Standards (NCCLS, M7-A2). La concentración final de sustancias de prueba estaba comprendida entre 64 y 0,125 mg/l. Los niveles de MIC para todo el compuesto se determinaron en un panel de cepas bacterianas Gram-positivas susceptibles y resistentes (*S. aureus*, *S. pneumoniae* y *S. pyogenes*) y en cepas Gram-negativas (*E. coli*, *H. influenzae*, *E. faecalis*, *M. catarrhalis*).

Es evidente a partir de la Tabla 1 y la Tabla 2 que las cepas estándar son susceptibles a nuevos compuestos sintetizados de fórmula general 1. Por lo tanto, pueden emplearse como agentes terapéuticos en el tratamiento de

enfermedades infectivas en animales, especialmente mamíferos y humanos, causadas por un amplio espectro de bacterias gram-positivas y gram-negativas, micoplasmas y microorganismos generalmente patogénicos susceptibles a los compuestos de fórmula 1. Con este fin, los mencionados compuestos y sus sales de adición de ácidos farmacéuticamente aceptables pueden administrarse oralmente en dosis usuales comprendidas entre 0,2 mg/kg de peso corporal diariamente y alrededor de 250 mg/kg/día, más preferentemente 0,5-50 mg/kg/día, o parenteralmente en forma de inyecciones subcutáneas e intramusculares.

El procedimiento para la preparación de derivados N^o sustituidos 9a-N-(N'-carbamoil-γ-aminopropil), 9a-N-(N'-tiocarbamoil-γ-aminopropil), 9a-N-[N'-(β-cianoetil)-N'-carbamoil-γ-aminopropil] y 9a-N-[N'-(β-cianoetil)-N'-tiocarbamoil-γ-aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A de esta invención es ilustrado por los siguientes ejemplos que de ninguna manera se considerarán una limitación de su alcance.

TABLA 1. Actividad antibacteriana in vitro de nuevos derivados N"-sustituidos 9a-N-(N'-carbamoil- γ -aminopropil), 9a-N-(N'-tiocarbamoil- γ -aminopropil) de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A presentada como valores MIC en comparación con la eritromicina A (Er).

Organismos de prueba	MIK $\mu\text{g/ml}$												
	1	2	3	4	5	6	7	8	9	10	11	12*	Er
<i>S. aureus</i> ATCC 13789	2	0.5	0.5	2	2	2	1	1	8	16	4	8	0.125
<i>S. pneumoniae</i>	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	8	0.125	16	0.125
<i>S. pyogenes</i>	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.25
<i>S. pyogenes</i> IMLS	8	2	4	2	4	8	4	4	16	8	32	2	>64
<i>S. pyogenes</i> M	32	4	8	4	4	32	8	8	64	16	64	8	8
<i>M. catarrhalis</i> ATCC 23246	0.5	0.25	1	1	2	8	1	1	4	4	16	0.5	-
<i>M. influenzae</i> ATCC 49247	32	1	2	2	2	16	2	2	32	2	16	2	2
<i>E. faecalis</i> ATCC 29212	32	4	16	8	4	64	16	16	>64	16	>64	8	1
<i>E. coli</i> ATCC 25922	16	8	16	16	8	32	16	32	>64	64	>64	32	32

TABLA 1. Actividad antibacteriana in vitro de nuevos derivados N^m-sustituidos 9a-N-[N'-(β-cianoetil)-N'-carbamoil-γ-aminopropil] y 9a-N-[N'-(β-cianoetil)-N'-tiocarbamoil-γ-aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A presentada como valores MIC en comparación con la eritromicina A (Er).

Organismo de prueba	MIK µg/ml												
Compuesto del ejemplo	27	28	29	30	31	32	33	34	36	37	38	39*	Er
<i>E. aureus</i> ATCC 13709	4	1	2	1	4	4	1	1	2	4	1	1	≤0.125
<i>E. pneumoniae</i> ATCC	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125
<i>E. pyogenes</i> ATCC	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	0.25
<i>E. pyogenes</i> IMLS	8	2	16	2	4	8	4	4	8	47	2	32	>64
<i>E. pyogenes</i> M	32	4	64	4	4	32	8	8	16	8	8	64	8
<i>M. catarrhalis</i> ATCC 23246	0.5	0.25	4	1	2	8	1	1	4	1	0.5	16	-
<i>M. influenzae</i> ATCC 49247	32	1	32	2	2	16	2	2	2	2	2	16	2
<i>E. faecalis</i> ATCC 29212	32	4	>64	8	4	64	16	16	16	16	8	>64	1
<i>E. coli</i> ATCC 25922	16	8	>64	16	8	32	16	32	64	16	32	>64	32

Ejemplo 1**9-Deoxo-9-dihidro-9a-N-(N'-isopropilcarbamoil- γ -aminopropil)-9a-aza-9a-homoeritromicina A**

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ -aminopropil)-9a-homoeritromicina A y 0,1 g (1,3 mmol) de isopropilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-(N'-isopropilcarbamoil- γ -aminopropil)-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 877.

Ejemplo 2**9- Deoxo-9-dihidro-9a-N-[N'-(1- naftil)carbamoil- γ -amino propil]-9a-aza-9a-homoeritromicina A**

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ -aminopropil)-9a-homoeritromicina A y 0,22 g (1,26 mmol) de 1-naftilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para

completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(1-naftil)carbamoil-γ-amino propil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 961.

Ejemplo 3

9-Deoxo-9-dihidro-9a-N-(N'-benzilcarbamoil-γ-aminopropil)-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ-aminopropil)-9a-homoeritromicina A y 0,17 g (1,3 mmol) de benzilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-(N'-benzilcarbamoil-γ-aminopropil)-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 925.

Ejemplo 4

9-Deoxo-9-dihidro-9a-N-(N'-benziltiocarbamoil-γ-aminopropil)-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ -aminopropil)-9a-homoeritromicina A y 0,17 g (1,3 mmol) de benzilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-(N'-benziltiocarbamoil- γ -aminopropil)-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 941.

Ejemplo 5

9-Deoxo-9-dihidro-9a-N-[N'-(1-naftil)tiocarbamoil- γ -aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ -aminopropil)-9a-homoeritromicina A y 0,17 g (1,3 mmol) de 1-naftilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(1-naftil)tiocarbamoil- γ -aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 977.

Ejemplo 6

9-Deoxo-9-dihidro-9a-N-[N'-(2-trifluorometil)

fenilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ-aminopropil)-9a-homoeritromicina A y 0,24 g (1,3 mmol) de 2-(trifluorometil)-fenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(2-trifluorometil)fenilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 979.

Ejemplo 7

9-Deoxo-9-dihidro-9a-N-[N'-(3-fenilpropil)tiocarbamoil-

γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ-aminopropil)-9a-homoeritromicina A y 0,22 g (1,3 mmol) de 3-fenilpropilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de

gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(3-fenilpropil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 969.

Ejemplo 8

9-Deoxo-9-dihidro-9a-N-[N'-(β-feniletíl)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ-aminopropil)-9a-homoeritromicina A y 0,21 g (1,3 mmol) de β-feniletílisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-feniletíl)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 979.

Ejemplo 9

9-Deoxo-9-dihidro-9a-N-(N'-etoxicarbonilmetilcarbamoil-1-aminopropil)-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ-aminopropil)-9a-homoeritromicina A y 0,16 g

(1,3 mmol) de etoxycarbonilmetilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-(N'-etoxycarbonilmetilcarbamoil-1-aminopropil)-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 921.

Ejemplo 10

9-Deoxo-9-dihidro-9a-N-{N'-[1-(1-naftil)etilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ-aminopropil)-9a-homoeritromicina A y 0,25 g (1,3 mmol) de 1-(1-naftil)etilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-{N'-[1-(1-naftil)etilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 989.

Ejemplo 11

9-Deoxo-9-dihidro-9a-N-[N'-(3,4,5-trimetoxifenil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ-aminopropil)-9a-homoeritromicina A y 0,26 g (1,3 mmol) de 3,4,5-trimetoxifenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(3,4,5-trimetoxifenil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 1001.

Ejemplo 12

9-Deoxo-9-dihidro-9a-N-[N'-(2-naftil)carbamoil-γ-amino propil]-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ-aminopropil)-9a-homoeritromicina A y 0,23 g (1,3 mmol) de 2-naftilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(2-

naftil)carbamoil- γ -amino propil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 961.

Ejemplo 13

9-Deoxo-9-dihidro-9a-N-[N'-(2,4-diclorofenil)carbamoil- γ -aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 1,0 g (1,26 mmol) de 9-deoxo-9-dihidro-9a-aza-9a-(γ -aminopropil)-9a-homoeritromicina A y 0,23 g (1,3 mmol) de 2,4-diclorofenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(2,4-diclorofenil)carbamoil- γ -aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 979.

Ejemplo 14

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-(N'-isopropil carbamoil- γ -aminopropil)-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,13 g (1,57 mmol) de isopropilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura

ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(N'-isopropil carbamoil-γ-aminopropil)-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 719.

Ejemplo 15

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(1-naftil) carbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,13 g (1,57 mmol) de 1-naftilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(1-naftil) carbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 803.

Ejemplo 16

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-(N'-benzilcarbamoil-γ-aminopropil)-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,21 g (1,57 mmol) de benzilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(N'-benzilcarbamoil- γ -aminopropil)-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 767.

Ejemplo 17

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-(N'-benziltio-carbamoil- γ -aminopropil)-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,24 g (1,57 mmol) de benzilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(N'-benziltio-carbamoil- γ -aminopropil)-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 783.

Ejemplo 18

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(1-naftil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,29 g (1,57 mmol) de 1-naftilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(1-naftil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 819.

Ejemplo 19

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(2-(trifluorometil)fenilcarbamoil)-γ-aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,30 g (1,57 mmol) de 2-trifluorometil)fenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la

temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(2-(trifluoro metil)fenilcarbamoil)-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 821.

Ejemplo 20

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(3-fenilpropil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,28 g (1,57 mmol) de 3-fenilpropilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(3-fenilpropil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 811.

Ejemplo 21

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-feniletil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,26 g (1,57 mmol) de β-feniletilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-feniletil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 797.

Ejemplo 22

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-(N'-etoxicarbonilmetil-carbamoil-γ-aminopropil)-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,20 g (1,57 mmol) de etoxicarbonilmetilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los

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cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(N'-etoxicarbonilmetil-carbamoil-γ-aminopropil)-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 763

Ejemplo 23

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-(N'-(2-naftil)carbamoil-γ-aminopropil)-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,27 g (1,57 mmol) de 2-naftilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(N'-(2-naftil)carbamoil-γ-aminopropil)-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 803.

Ejemplo 24

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-{N'-(1-(1-naftil)etil)carbamoil-γ-aminopropil)-9a-aza-9a-

homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,31 g (1,57 mmol) de 1-(1-naftil)etilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-{N'-(1-(1-naftil)etil)carbamoil- γ -aminopropil)-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 831.

Ejemplo 25

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-{N'-(3,4,5-trimetoxifenil)-carbamoil- γ -aminopropil)-9a-aza-9a-homoeritronolida A

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,31 g (1,57 mmol) de 3,4,5-trimetoxifenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema

solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5,
5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(3,4,5-
trimetoxifenil)-carbamoil-γ-aminopropil]-9a-aza-9a-
homoeritronolida A pura.

MS(ES+)m/z = 843.

Ejemplo 26

**5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(2,4-dicloro
fenil)carbamoil-γ-aminopropil]-9a-aza-9a- homoeritronolida A**

Una mezcla de 1,0 g (1,57 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,31 g (1,57 mmol) de 2,4-diclorofenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(3,4,5-trimetoxifenil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 821.

Ejemplo 27

**9-Deoxo-9-dihidro-9a-N-[N'-(2-cianoetil)-N'-isopropil
carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A**

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-

9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,06 g (0,591 mmol) de isopropilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-isopropil carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 931.

Ejemplo 28

9-Deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(1-naftil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,11 g (0,591 mmol) de 1-naftilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(1-naftil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

pura.

MS(ES+)m/z = .

Ejemplo 29

9-Deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-benzilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,08 g (0,591 mmol) de benzilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-benzilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 931.

Ejemplo 30

9-Deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-benziltiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,09 g (0,591 mmol) de benzilisotiocianato en 10 ml de tolueno seco se agitó durante

30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-benziltiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 995.

Ejemplo 31

9-Deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(1-naftil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,12 g (0,591 mmol) de 1-naftilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(1-naftil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 1029.

Ejemplo 32

9-Deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(2-(trifluorometil)fenil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,08 g (0,591 mmol) de 2-(trifluorometil)fenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(2-(trifluorometil)fenil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 1033.

Ejemplo 33

9-Deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(3-fenilpropil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,10 g (0,591 mmol) de 3-fenilpropilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar

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la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(3-fenilpropil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 1022.

Ejemplo 34

9-Deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(β-feniletil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,10 g (0,591 mmol) de β-feniletilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(β-feniletil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 1008.

Ejemplo 35

9-Deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-etoxicarbonilmetil-carbamoil]-γ-aminopropil]-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,10 g (0,591 mmol) de etoxicarbonilmetilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-etoxicarbonilmetil-carbamoil]-γ-aminopropil]-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 974.

Ejemplo 36

9-Deoxo-9-dihidro-9a-N-{N'-(β-cianoetil)-N'-(1-(1-naftil)etil)carbamoil-γ-aminopropil}-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,11 g (0,591 mmol) de 1-(1-naftil)etilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar

la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-{N'-(β-cianoetil)-N'-(1-(1-naftil)etil)carbamoil-γ-aminopropil}-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 1042.

Ejemplo 37

9-Deoxo-9-dihidro-9a-N-{N'-(β-cianoetil)-N'-(3,4,5-trimetoxifenil)carbamoil-γ-aminopropil}-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,12 g (0,591 mmol) de 3,4,5-trimetoxifenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-{N'-(β-cianoetil)-N'-(3,4,5-trimetoxifenil)carbamoil-γ-aminopropil}-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 1053.

Ejemplo 38

9-Deoxo-9-dihidro-9a-N-{N'-(β-cianoetil)-N'-(2-naftil)carbamoil-γ-aminopropil}-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,11 g (0,591 mmol) de 2-naftilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-{N'-(β-cianoetil)-N'-(2-naftil)carbamoil-γ-aminopropil}-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 1014.

Ejemplo 39

9-Deoxo-9-dihidro-9a-N-{N'-(β-cianoetil)-N'-(2,4-dicloro fenil)carbamoil-γ-aminopropil}-9a-aza-9a-homoeritromicina A

Una mezcla de 0,5 g (0,591 mmol) de 9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-γ-aminopropil]-9a-aza-9a-homoeritromicina A y 0,11 g (0,591 mmol) de 2-naftilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el

sistema solvente metilencloruro : metanol : amoníaco = 90 : 9 : 1,5, 9-deoxo-9-dihidro-9a-N-{N'-(β-cianoetil)-N'-(2,4-diclorofenil)carbamoil-γ-aminopropil}-9a-aza-9a-homoeritromicina A pura.

MS(ES+)m/z = 1033.

Ejemplo 40

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-isopropilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,06 g (0,728 mmol) de isopropilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-isopropilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 771.

Ejemplo 41

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'(1-naftil)carbamoil-γ-aminopropil]-9a-aza-9a-

homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,12 g (0,728 mmol) de 1-naftilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'(1-naftil)carbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 855.

Ejemplo 42**5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-benzilcarbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A**

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,10 g (0,728 mmol) de benzilisocianato en 10 ml de tolueno seco se agitó 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro :

metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-benzilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 819.

Ejemplo 43

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-benziltiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,11 g (0,728 mmol) de benzilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-benziltiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 835.

Ejemplo 44

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(1-naftil)tiocarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,14 g (0,728 mmol) de 1-naftilisotiocianato en 10 ml de tolueno seco se agitó 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-(1-naftil)tiocarbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 855.

Ejemplo 45

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-(2-(trifluorometil)fenil)carbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,14 g (0,728 mmol) de 2-(trifluorometil)fenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-

(2-(trifluorometil)fenil)carbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 873.

Ejemplo 46

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(S-cianoetil)-N'-(3-fenilpropil)tio carbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,13 g (0,728 mmol) de 3-fenilpropilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(S-cianoetil)-N'-(3-fenilpropil)tiocarbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 863.

Ejemplo 47

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(S-cianoetil)-N'-(S-feniletil)tio carbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-

deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,12 g (0,728 mmol) de β -feniletilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-(β -feniletil)tiocarbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = .

Ejemplo 48

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-(etoxi-carbonilmetil carbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,09 g (0,728 mmol) de β -feniletilisotiocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-

(etoxi-carbonilmetilcarbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 815.

Ejemplo 49

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-(2-naftil)carbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida A y 0,12 g (0,728 mmol) de β -naftilisocianato en 10 ml de tolueno seco se agitó 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-(2-naftil)carbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 855.

Ejemplo 50

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β -cianoetil)-N'-[1-(1-naftil)etilcarbamoil- γ -aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ -aminopropil)-9a-aza-homoeritronolida

A y 0,15 g (0,728 mmol) de 1-(1-naftil)etilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-[1-(1-naftil)etilcarbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 883.

Ejemplo 51

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(3,4,5-trimetoxifenil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A

Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,14 g (0,728 mmol) de 3,4,5-trimetoxifenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(3,4,5-trimetoxifenil)carbamoil-γ-aminopropil]-9a-aza-9a-

homoeritronolida A pura.

MS(ES+)m/z = 895.

Ejemplo 52

5-O-Desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(2,4-diclorofenil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A

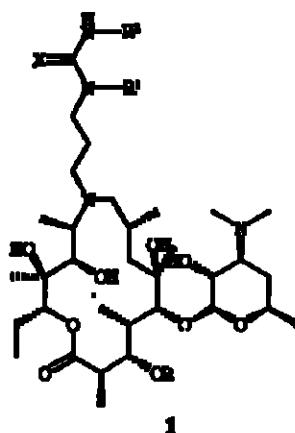
Una mezcla de 0,5 g (0,728 mmol) de 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-(γ-aminopropil)-9a-aza-homoeritronolida A y 0,14 g (0,728 mmol) de 2,4-diclorofenilisocianato en 10 ml de tolueno seco se agitó durante 30 minutos a la temperatura ambiente para completar la reacción. Los cristales del producto crudo se filtraron, obteniéndose por cromatografía en columna de gel de sílice usando el sistema solvente metilencloruro : metanol : amoníaco = 90 : 20 : 1,5, 5-O-desosaminil-9-deoxo-9-dihidro-9a-N-[N'-(β-cianoetil)-N'-(2,4-diclorofenil)carbamoil-γ-aminopropil]-9a-aza-9a-homoeritronolida A pura.

MS(ES+)m/z = 874.

REIVINDICACIONES

1. Derivados N" sustituidos 9a-N-(N'-carbamoil-γ-aminopropil), 9a-N-(N'-tiocarbamoil-γ-aminopropil), 9a-N-[N'-(β-cianoetil)-N'-carbamoil-γ-aminopropil] y 9a-N-[N'-(β-cianoetil)-N'-tiocarbamoil-γ-aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-

deoxo-9-dihidro-9a-aza-9a-homoeritronolida A, nuevos antibióticos macrólidos semisintéticos de la serie de azalidas de fórmula general 1,



donde R representa H o una parte cladinósilo, R^1 representa H o una parte β -cianoetilo, R^2 representa un grupo isopropilo, 1-naftilo, 2-naftilo, bencilo, 2-(trifluorometil)fenilo, 3-fenilpropilo, β -feniletilo, etoxycarbonil-metilo, 1-(1-naftil)etilo, 3,4,5-trimetoxifenilo y 2,4-diclorofenilo, y X representa O y S, y sus sales de adición aceptables con ácidos inorgánicos u orgánicos.

2. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo y R^1 representa H, R^2 representa un grupo isopropilo y X es O.

3. Sustancia de acuerdo con la reivindicación 1,

caracterizada porque R representa un grupo cladinósilo, R¹ representa H, y R² representa un grupo 1-naftilo y X es O.

4. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo, R¹ representa H, y R² representa un grupo 2-naftilo y X es O.

5. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo, R¹ representa H, y R² representa un grupo benzilo y X es O.

6. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo, R¹ representa H, y R² representa un grupo 2-(trifluorometil)fenilo y X es O.

7. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo, R¹ representa H, y R² representa un grupo 3-fenilpropilo y X es S.

8. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo, R¹ representa H, y R² representa un grupo β-feniletilo y X es S.

9. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo, R¹ representa H, y R² representa un grupo etoxicarbonilmetilo y X es O.

10. Sustancia de acuerdo con la reivindicación 1,

caracterizada porque R representa un grupo cladinósilo y R^1 representa H, R^2 representa un grupo 1-(1-naftil)etilo y X es O.

11. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo y R^1 representa H, R^2 representa un grupo 3,4,5-trimetoxifenilo y X es O.

12. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo y R^1 representa H, R^2 representa un grupo 2,4-diclorofenilo y X es O.

13. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo y R^1 representa H, R^2 representa un grupo benzilo y X es S.

14. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo y R^1 representa H, R^2 representa un grupo 1-naftilo y X es S.

15. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo, R^1 representa un grupo β -cianoetilo, R^2 representa un grupo isopropilo y X es O.

16. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinósilo, R^1 representa un grupo β -cianoetilo, R^2 representa un grupo 1-

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naftilo y X es O.

17. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo 2-naftilo y X es O.

18. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo benzilo y X es O.

19. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo 2-(trifluorometil)fenilo y X es O.

20. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo 3-fenilpropilo y X es S.

21. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo β-feniletilo y X es S.

22. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo

etoxicarbonilmetilo y X es O.

23. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo 1-(1-naftil)etilo y X es O.

24. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo 3,4,5-trimetoxifenilo y X es O.

25. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo 2,4-diclorofenilo y X es O.

26. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo benzilo y X es S.

27. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa un grupo cladinosilo, R¹ representa un grupo β-cianoetilo, R² representa un grupo 1-naftilo y X es S.

28. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo isopropilo y X es O.

29. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo 1-naftilo y X es O.

30. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo 2-naftilo y X es O.

31. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo benzilo y X es O.

32. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo 2-(trifluorometil)fenilo y X es O.

33. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo 3-fenilpropilo y X es S.

34. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo 8-feniletilo y X es S.

35. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo etoxycarbonilmetilo y X es O.

36. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo 1-(1-naftil)etilo y X es O.

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37. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo 3,4,5-trimetoxifenilo y X es O.

38. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo 2,4-diclorofenilo y X es O.

39. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo benzilo y X es S.

40. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R y R¹ representan H, R² representa un grupo 1-naftilo y X es S.

41. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R¹ representa β-cianoetilo, R² representa un grupo isopropilo y X es O.

42. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R¹ representa β-cianoetilo, R² representa un grupo 1-naftilo y X es O.

43. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R¹ representa β-cianoetilo, R² representa un grupo 2-naftilo y X es O.

44. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R¹ representa β-cianoetilo, R² representa un grupo benzilo y X es O.

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45. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R^1 representa β -cianoetilo, R^2 representa un grupo 2-(trifluorometil)fenilo y X es O.

46. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R^1 representa β -cianoetilo, R^2 representa un grupo 3-fenilpropilo y X es S.

47. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R^1 representa β -cianoetilo, R^2 representa un grupo β -feniletilo y X es O.

48. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R^1 representa β -cianoetilo, R^2 representa un grupo etoxicarbonilmetilo y X es O.

49. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R^1 representa β -cianoetilo, R^2 representa un grupo 1-(1-naftil)etilo y X es O.

50. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R^1 representa β -cianoetilo, R^2 representa un grupo 3,4,5-trimetoxifenilo y X es O.

51. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R^1 representa β -

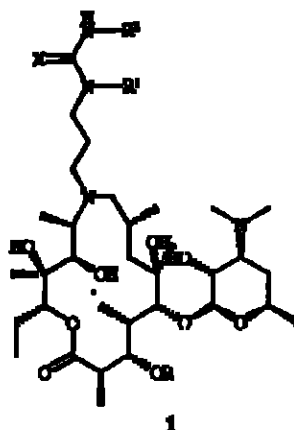
cianoetilo, R^2 representa un grupo 2,4-diclorofenilo y X es O.

52. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R^1 representa β -cianoetilo, R^2 representa un grupo benzilo y X es S.

53. Sustancia de acuerdo con la reivindicación 1, caracterizada porque R representa H, R^1 representa β -cianoetilo, R^2 representa un grupo 1-naftilo y X es S.

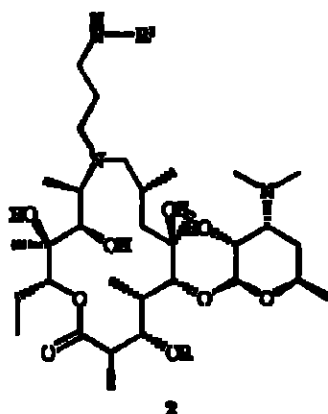
54. Procedimiento para la preparación de derivados N^o sustituidos 9a-N-(N'-carbamoil- γ -aminopropil), 9a-N-(N'-tiocarbamoil- γ -aminopropil), 9a-N-[N'-(β -cianoetil)-N'-carbamoil- γ -aminopropil] y 9a-N-[N'-(β -cianoetil)-N'-tiocarbamoil- γ -aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A de fórmula general 1,

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donde R representa H o una parte cladinósilo, R¹ representa H o una parte β-cianoetilo, R² representa un grupo isopropilo, 1-naftilo, 2-naftilo, bencilo, 2-(trifluorometil)fenilo, 3-fenilpropilo, β-feniletilo, etoxycarbonil-metilo, 1-(1-naftil)etilo, 3,4,5-trimetoxifenilo y 2,4-diclorofenilo, y X representa O y S, caracterizado porque los derivados 9a-N-(γ-aminopropil) y 9a-N-[N'-(β-cianoetil)-γ-aminopropil] de 9-deoxo-9-dihidro-9a-aza-9a-homoeritromicina A y 5-O-desosaminil-9-deoxo-9-dihidro-9a-aza-9a-homoeritronolida A de fórmula 2,

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donde R representa H y un grupo cladinosilo y R¹ representa H y un grupo β-cianoetilo, se hace reaccionar con isocianatos o isotiocianatos de fórmula general 3,



donde R² representa un grupo isopropilo, 1-naftilo, 2-naftilo, bencilo, 2-(trifluorometil)fenilo, 3-fenilpropilo, β-feniletilo, etoxycarbonil-metilo, 1-(1-naftil)etilo, 3,4,5-trimetoxifenilo y 2,4-diclorofenilo, y X representa O y S, en tolueno, xileno u otros solventes apróticos, a una temperatura comprendida entre 0°C y 110°C, y luego, de ser apropiado, a una reacción con ácidos inorgánicos u orgánicos.

55. Composiciones farmacéuticas que comprenden un

vehículo farmacéuticamente aceptable y una cantidad antibacterialmente efectiva de las sustancias de acuerdo con la reivindicación 1.

56. Uso de una sustancia de acuerdo con cualquiera de las reivindicaciones 1 a 51 en el tratamiento de infecciones bacterianas.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO

Folios: 110

RECIBO OFICIAL DE CAJA : 05 - 46,088
FECHA : JUNIO 21 DE 2005

Radicacion : 05067476 00000000
Fecha (HCB): 2005-07-08 17:15:17
Tracito : 011 PAT-DETECT 370 FASE HACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	030-00110-6	40117916	21/06/2005	62,639,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRANITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL :	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

060 14809-841-001-9

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	☒
- Indicación de que se solicita la concesión de una patente.	()	☒
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	☒
- Descripción de la invención.	()	☒
- Dibujos de ser estos pertinentes.	()	☒
- Comprobante de Pago de las tasas establecidas.	()	☒
COMPLETA ()	INCOMPLETA ()	()
DISEÑO INDUSTRIAL ()		-
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica del esquema de trazado.	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:

Fecha:

SUPERINDUSTRIA Y COMERCIO

Radicación: 65867476 65868358

Folios: 118

Fecha (HRS): 8/25-07-08 17:15:17

Trámite : 811 PCT-PATENT 378 FASE MACI 411 PRESENTAC

Dependencia: ES20 DIVISION DE NUEVAS CREATIVIDADES

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO

REFERENCIA	Radicación No.	5 67476
	Solicitud internacional	HR/2003/000062
	Fecha inicio fase nacional	12/07/2005
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	8911

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. De la figura característica enviar arte final en tamaño 12 x 12 por duplicado.
2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.
3. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.
4. Debe aclarar el nombre del solicitante, por cuanto la publicación internacional difiere del petitorio presentado en fase nacional.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

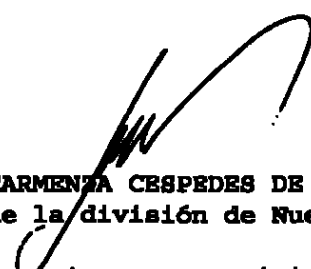
Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

Continua en la página siguiente...

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

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Radicación No.:5 67476



ALIX CARMENITA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha 30 SET. 2005
adpal