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(71) Applicant *(for all designated States except US)*: PLIVA, FARMACEUTSKA, KEMIJSKA, PREHRAMBENA I KOZMETIČKA INDUSTRIJA, DIONIČKO DRUŠTVO [HR/HR]; Ulica grada Vukovara 49, HR–10000 Zagreb (HR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LAZAREVSKI, Gorjana [HR/HR]; Barutanski jarak 18, HR–10000 Zagreb (HR). KOBREHEL, Gabrijela [HR/HR]; Trg Ivana Kukuljevića 3, HR–10000 Zagreb (HR). KELNERIĆ, Željko [HR/HR]; Mašićeva 12, HR–10000 Zagreb (HR).

(74) Common Representative: PLIVA d.d.; Pravni Poslovi, Vesna Vasiljevic, Ulica grada Vukovara 49, HR–10000 Zagreb (HR).

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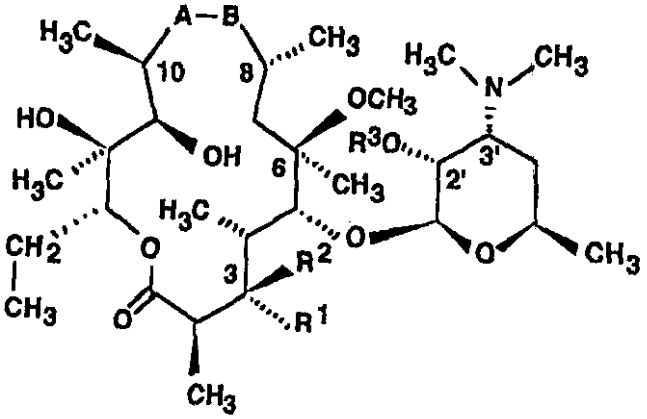
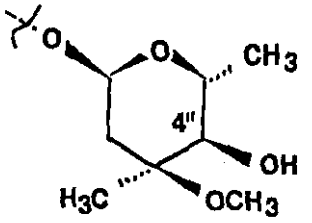
(54) Title: 15–MEMBERED LACTAMS KETOLIDES WITH ANTIBACTERIAL ACTIVITY

(57) Abstract

The present invention relates to the new 15–membered ketoazalides from the class of 6–*O*–methyl–8a–aza–8a–homo– and 6–*O*–methyl–9a–aza–9a–homoerythromycin A with general formula (I), wherein A represents NH group and B at the same time represents C=O group, or A represents C=O group and B at the same time represents NH group, R^1 represents OH group, L–cladinosyl group of formula (II) or together with R^2 represents ketone, R^2 represents hydrogen or together with R^1 represents ketone, R^3 represents hydrogen or C_1–C_4alkanoyl group, to intermediates and a process for their preparation, to their pharmaceutically acceptable addition salts with inorganic or organic acids, to the process for the preparation of pharmaceutical compositions, as well as to the use of pharmaceutical compositions for treating bacterial infections.



(I)



(II)

15-MEMBERED LACTAMS KETOLIDES WITH ANTIBACTERIAL ACTIVITY

Technical Problem

The present invention relates to new compounds of erythromycin A macrolide antibiotics class. Especially, it relates to new 15-membered ketoazalides of the class of 6-*O*-methyl-8a-aza-8a-homo- and 6-*O*-methyl-9a-aza-9a-homoerythromycin A, to intermediates and a process for their preparation, to their pharmaceutically acceptable addition salts with inorganic and organic acids, to a process for the preparation of pharmaceutical compositions as well as to the use of pharmaceutical compositions in the treatment of bacterial infections.

Prior Art

Erythromycin A is a macrolide antibiotic, whose structure is characterized by a 14-membered lactone ring having C-9 ketone and two sugars, L-cladinose and D-desosamine, which are glycosidically bound at C-3 and C-5 positions to the aglycone part of the molecule (McGuire: Antibiot. Chemother., 1952, 2: 281). For more than 40 years erythromycin A has been considered to be a safe and active antimicrobial agent for treating respiratory and genital infections caused by gram-positive bacteria of the strains like *Legionella, Mycoplasma, Chlamidia* and *Helicobacter.* The observed changes in bioavailability after the application of oral preparations, gastric intolerance in many patients and the loss of activity in an acidic medium are the main disadvantages of the therapeutical use of erythromycin A. The spirocyclization of aglycone ring is successfully inhibited by the chemical transformation of C-9 ketone or of hydroxyl groups at C-6 and/or C-12 position. Thus e.g. by oximation of C-9 ketone of erythromycin A with hydroxylamine hydrochloride, Beckmann's rearrangement of the obtained 9(*E*)-oxime and reduction of the thus formed 6,9-imino ether (6-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 6,9-cyclic imino ether), there was obtained 9-deoxo-9a-aza-9a-homoerythromycin A, the first semisynthetic macrolide

having a 15-membered azalactone ring (Kobrehel G. et al., US Pat. 4,328,334, 5/1982). By reductive methylation of the newly introduced endocyclic 9a-amino group according to Eschweiler-Clark process, 9-deoxo-9a-methyl-9a-aza-9a-homo-erythromycin A (AZITHROMYCIN), a prototype of a new azalide antibiotics class was synthesized (Kobrehel G. et al., BE 892 357, 7/1982). In addition to the broad antimicrobial spectrum including gram-negative bacteria, azithromycin is also characterized by a long biological half-time, a specific transport mechanism to the site of application and a short therapy period. Azithromycin is able to penetrate and to accumulate within human phagocyte cells, which results in an improved action upon intracellular pathogenic microorganisms of the strains *Legionella, Chlamydia* and *Helicobacter.*

Further, it is known that C-6/C-12 spirocyclization of erythromycin A is also inhibited by *O*-methylation of C-6 hydroxyl group of aglycone ring (Watanabe Y. et al., US Pat. 4,331,803, 5/1982). By reaction of erythromycin A with benzyloxycarbonyl chloride followed by methylation of the obtained 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-derivative, elimination of the protecting groups and 3'-*N*-methylation, 6-*O*-methyl-erythromycin A (CLARITHROMYCIN) (Morimoto S. et al., J.Antibiotics 1984, 37, 187) is formed. If compared to erythromycin A, clarithromycin is considerably more stable in acidic medium and shows an increased *in vitro* activity against gram-positive bacterial strains (Kirst H.A. et al, Antimicrobial Agents and Chemother., 1989, 1419).

New investigations on 14-membered macrolides have led to a new type of macrolide antibiotics, namely ketolides, characterized by 3-keto group instead of neutral sugar L-cladinose, the latter being well-known for its instability even in a weakly acidic medium (Agouridas C. et al., EP 596802 A1, 5/1994, Le Martret O., FR 2697524 A1, 5/94). Ketolides exibit significantly improved *in vitro* activity against MLS (macrolide, lincosamide and streptogramine B) induced by resistant organisms (Jamjian C., Antimicrob. Agents Chemother., 1997, 41, 485).

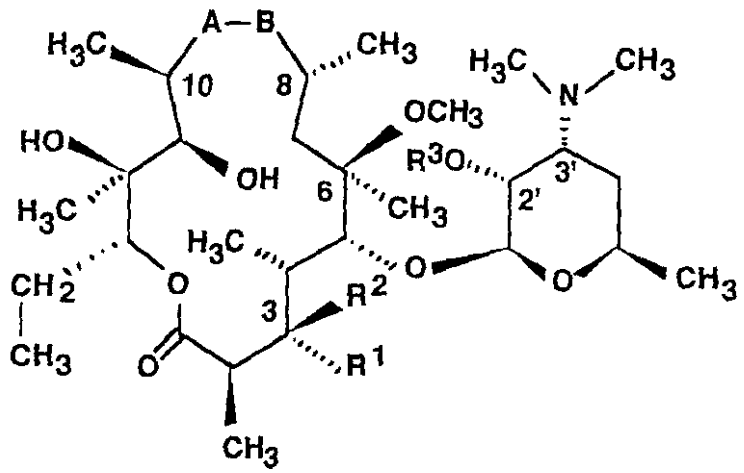
According to the known and established prior art, 15-membered ketoazalides from the class of 6-*O*-methyl-8a-aza-8a-homo- and 6-*O*-methyl-9a-aza-9a-homoerythromycin

A and their pharmaceutically acceptable addition salts with organic or inorganic acids, methods and intermediates for their preparation as well as methods for the preparation of pharmaceutical preparations and the use thereof have hitherto not been described.

The object of the present invention is represented by Beckmann's rearrangement of 9(*E*)- and 9(*Z*)-oxime of 6-*O*-methylerythromycin A, hydrolysis of cladinose in thus obtained 8a- and 9a-lactams, protection of hydroxyl groups in 2'-position of desosamine, oxidation of the 3-hydroxyl group and removal of protecting groups, whereby new, hitherto not described 15-membered ketoazalides from the class of 6-*O*-methyl-8a-aza-8a-homo- and 6-*O*-methyl-9a-aza-9a-homoerythromycin A are obtained.

Technical Solution

New 15-membered ketoazalides from the class of 6-*O*-methyl-8a-aza-8a-homo- and 6-*O*-methyl-9a-aza-9a-homoerythromycin A with the general formula (I)



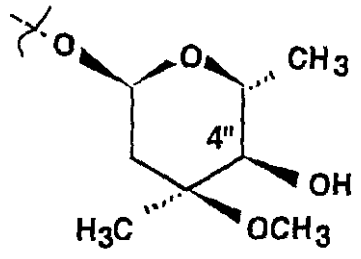
(I)

wherein

A represents NH group and B at the same time represents C=O group, or

A represents C=O group and B at the same time represents NH group,

R^1 represents OH group, L-cladinosyl group of the formula (II)



(II)

or together with R^2 represents ketone,

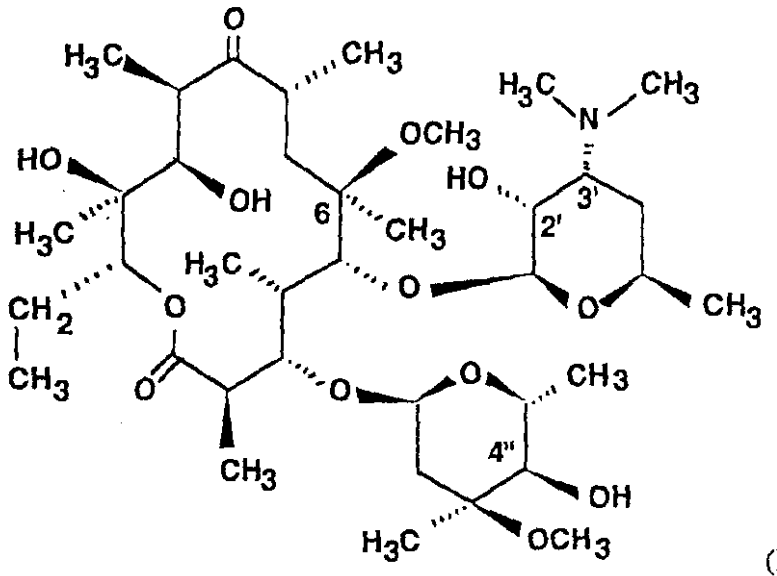
R^2 represents hydrogen or together with R^1 represents ketone,

R^3 represents hydrogen or C_1-C_4 alkanoyl group,

and their pharmaceutically acceptable addition salts with inorganic or organic acids are obtained as follows.

Step 1:

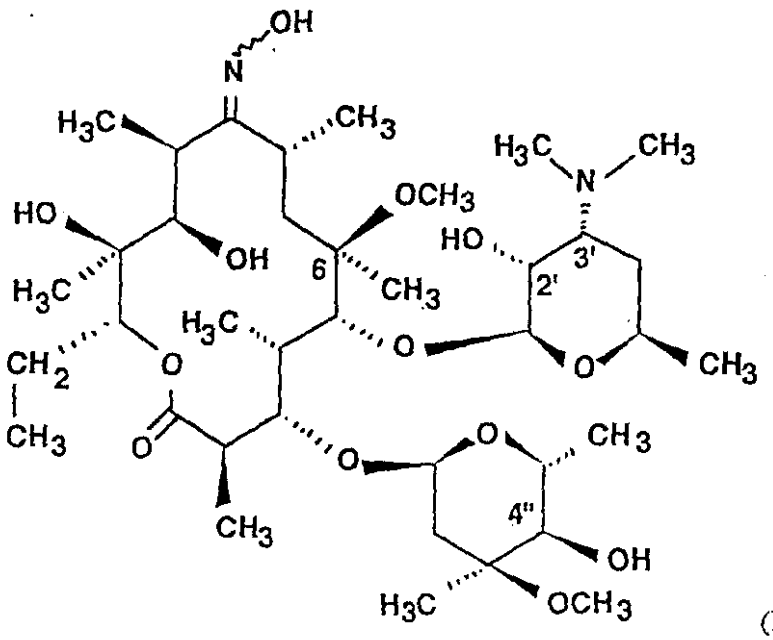
The first step of the invention includes oximation of C-9 ketone of 6-*O*-methylerythromycin A (clarithromycin) of the formula (III)



(III)

into the corresponding oxime. The conversion of ketone into oxime is a well-known reaction usually performed with hydroxylamine hydrochloride in the presence of

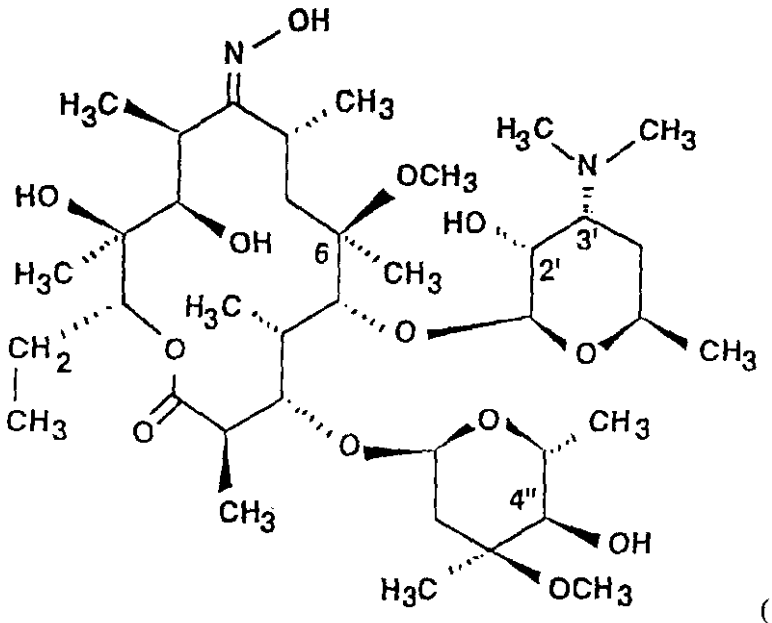
appropriate inorganic or organic bases in a suitable protic or aprotic solvent. Hydroxylamine hydrochloride is used in a 1 to 15-equimolar excess, preferably in a 10-equimolar excess with regard to clarithromycin. As suitable bases alkali hydroxides, carbonates, hydrogen carbonates and acetates are used whereas as solvents C_1-C_3 alcohols are used. The preferred base is sodium carbonate or sodium acetate and the preferred solvent is methanol. In general, the reaction is performed at a temperature from 0 to 80°C, preferably at 65°C, within 2 hours to a few days, but mainly it is accomplished within 8 to 20 hours. The treatment is performed in the usual manner, e.g. by evaporation of the solvent under vacuum, addition of a mixture of water and organic solvent followed by extraction in an alkaline medium, preferably at pH 8.0-10.0. As solvents for the extraction of the product methylene chloride, chloroform, ethyl acetate, diethylether and toluene are used, with chloroform being the preferred one. The product is isolated by the separation of the organic layer and evaporation of the solvent, which yields a mixture of 6-*O*-methylerythromycin A 9(*E*)- and 9(*Z*)-oxime of the formula (IV)



(IV)

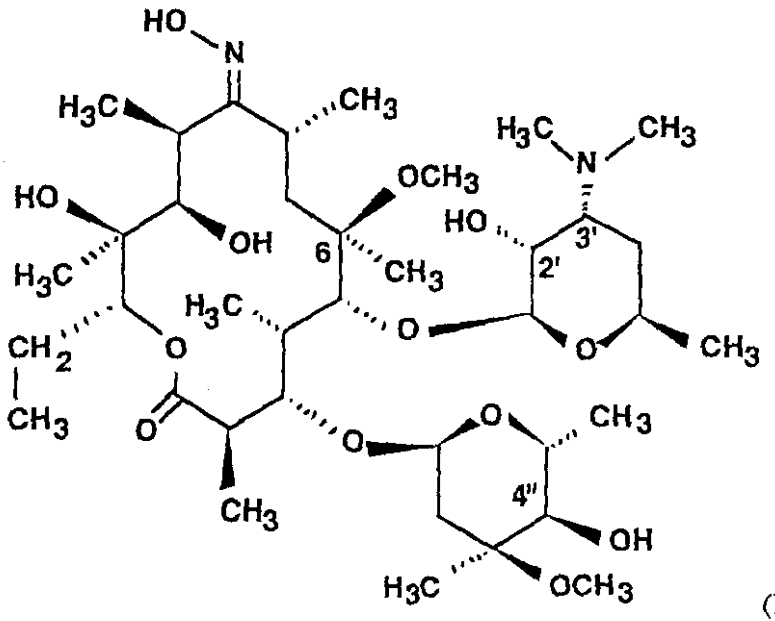
in a ratio of about 1:1. If necessary, the separation of the isomers is performed by chromatography on a silica gel column by using the system methylene chloride-methanol-ammonium hydroxide 90:9:1.5, which yields a chromatographically

homogeneous 6-*O*-methyl-erythromycin A 9(*E*)-oxime with Rf 0.446 of the formula (IVa)



(IVa)

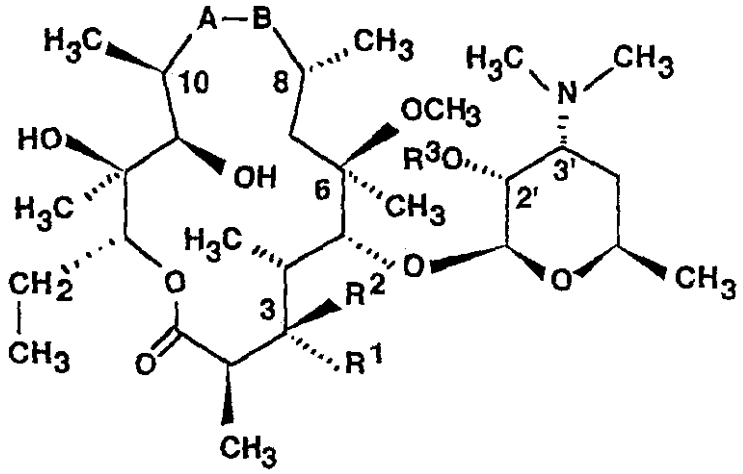
and chromatographically homogeneous 6-*O*-methylerythromycin A 9(*Z*)-oxime with Rf 0.355 of the formula (IVb)



(IVb)

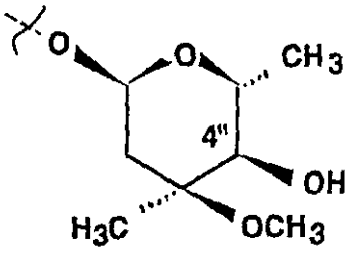
Step 2:

Conversion of 6-*O*-methyl-erythromycin A 9(*E*)-oxime of formula (IVa) into 6-*O*-methyl-9a-aza-9a-homoerythromycin A of the general formula (I)



(I)

wherein A represents NH group, B at the same time represents C=O group, R^1 represents L-cladinosyl group of the formula (II)



(II)

R^2 and R^3 are the same and represent hydrogen,

is performed by the reaction of Beckmann's rearrangement (see "Comprehensive Organic Chemistry", I.O. Sutherland (Ed.), Pergamon Press, New York, 1979, Vol. 2, 398-400 and 967-968). In general, Beckmann's rearrangement of ketoxime leads to carboxamide or, in the case of cyclic systems, to lactams. The rearrangement mechanism includes a preliminary conversion of oxime hydroxyl into a better leaving group, which in a second reaction step is cleaved off under a simultaneous migration of the carbon atom in the *anti*-position with regard to the leaving group. In an aqueous

medium as an intermediate a nitrilium ion is formed, which reacts with water yielding an appropriate amide.

The reaction of Beckmann's rearrangement is performed under acidic, neutral and basic conditions. Common acidic reagents catalyzing the rearrangement include conc. sulfuric acid, polyphosphoric acid, tionyl chloride, phosphoric pentachloride, sulfur dioxide and formic acid. Due to the sensibility of macrolide molecule in an acidic medium and especially due to the ease of cleavage of neutral sugar L-cladinose, these reagents are not suitable for the rearrangement of oxime of the formula (IVa) into 6-*O*-methyl-9a-aza-9a-homoerythromycin A of the general formula (I), wherein A, B, R^1, R^2, and R^3 have the above-mentioned meanings. Preferably, Beckmann's rearrangement of oxime (IVa) is performed by initial *O*-sulfonation of oxime hydroxyl with alkylsulfonyl halides, arilsulfonyl halides or arilsulfonyl anhydrides. Intermediate oxime sulfonate is isolated or, usually, the rearrangement into the desired product is performed *in situ*. Generally, sulfonation and rearrangement are performed in the presence of organic or inorganic bases.

The preferred sulfonation reagents catalyzing the rearrangement of oxime (IVa) include methansulfonyl chloride, benzenesulfonyl chloride, 4-acetylamidosulfonyl chloride, p-toluenesulfonyl chloride, anhydrides of benzenesulfonic and p-toluene-sulfonic acid. The reaction is performed in the presence of inorganic bases such as sodium hydrogen carbonate or potassium carbonate or in presence of organic bases such as pyridine, 4-dimethylaminopyridine, triethylamine and *N,N*-diisopropyl- amine. Suitable solvents include aqueous mixtures such as acetone-water mixture and dioxan-water mixture, and organic solvents such as methylene chloride, chloroform, ethyl acetate, diethyl ether, tetrahydrofuran, toluene, acetonitrile and pyridine. Generally, the reaction is performed by the use of 1-3 equimolar excess of the sulfonation reagent and with the same or greater equimolar amount of the base at a temperature from -20 to 50°C. Pyridine is often used as the solvent and as the base at the same time. Preferably, Beckmann's rearrangement of oxime (IVa) is performed in an acetone-water mixture with a double equimolar excess of p-toluensulfochloride and sodium hydrogen carbonate. If necessary, the product is purified by chromatography on a

silica gel column by the use of the solvent system methylene chloride-methanol-ammonium hydroxide 90:9:1.5, yielding a chromatographically homogeneous 6-*O*-methyl-9a-aza-9a-homoerythromycin A.

Beckmann's rearrangement of 6-*O*-methylerythromycin A 9(*Z*)-oxime of the formula (IVb) into 6-*O*-methyl-8a-aza-8a-homoerythromycin A of the general formula (I), wherein A represents C=O group, B at the same time represents NH group, R^1 represents L-cladinosyl group of the formula (II), and R^2 and R^3 are the same and represent hydrogen, is performed in analogous manner as with 9(*E*)-oxime (IVa).

Step 3:

6-*O*-methyl-9a-aza-9a-homoerythromycin A or 6-*O*-methyl-8a-aza-8a-homoerythromycin A of Step 2 of the general formula (I), wherein A, B, R^1, R^2 and R^3 have the above-mentioned meanings, are subjected, if appropriate, to the action of strong acids, preferably 0.25-1.5 N hydrochloric acid, at room temperature within 10-30 hours, yielding 3-*O*-decladinosyl-3-oxy-derivatives of 6-*O*-methyl-9a-aza-9a-homoerythromycin A or 6-*O*-methyl-8a-aza-8a-homoerythromycin A of the general formula (I), wherein A represents NH group and B at the same time represents C=O group, or A represents C=O group and B at the same time represent NH group, R^1 represents OH group, and R^2 and R^3 are the same and represent hydrogen.

Step 4:

3-*O*-decladinosyl-3-oxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A or 6-*O*-methyl-8a-aza-8a-homoerythromycin A of Step 3 of the general formula (I), wherein A, B, R^1, R^2 and R^3 have the above-mentioned meanings, are subjected, if appropriate, to the reaction of selective acylation of hydroxyl group at 2'-position of desosamine. Acylation is performed by the use of anhydrides of carboxylic acids having up to 4 carbon atoms, preferably with acetic acid anhydride, in the presence of inorganic or organic bases in an inert organic solvent at a temperature from 0 to 30°C yielding 3-decladinosyl-3-oxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A 2'-*O*-acetate or 3-decladinosyl-3-oxy-6-*O*-methyl-8a-aza-8a-homoerythromycin A 2'-*O*-acetate of the general formula (I), wherein A represents NH group and B at the same time represents

C=O group, or A represents C=O group and B at the same time represent NH group, R^1 represents OH group, R^2 is hydrogen and R^3 is acetyl. As appropriate bases sodium hydrogen carbonate, sodium carbonate, potassium carbonate, triethylamine, pyridine, tributylamine, preferably sodium hydrogen carbonate are used. As a suitable inert solvent methylene chloride, dichloro ethane, acetone, pyridine, ethyl acetate, tetrahydrofuran, preferably methylene chloride are used.

Step 5:

3-decladinosyl-3-oxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A-2' *O*-acetate or 3-decladinosyl-3-oxy-6-*O*-methyl-8a-aza-8a-homoerythromycin A-2' *O*-acetate of Step 4 of the general formula (I), wherein A, B, R^1, R^2 and R^3 have the above-mentioned meanings, are subjected, if appropriate, to an oxidation of the hydroxyl group at C-3 position of aglycone ring according to the modified Moffat-Pfitzner process with *N,N*-dimethylaminopropyl-ethyl-carbodiimide in the presence of dimethylsulfoxide and pyridinium trifluoroacetate as a catalyst, in an inert organic solvent, preferably in methylene chloride, at a temperature from 10°C to room temperature, yielding 3-decladinosyl-3-oxo-6-*O*-methyl-9a-aza-9a-homoerythromycin A 2'-*O*-acetate or 3-decladinosyl-3-oxo-6-*O*-methyl-8a-aza-8a-homoerythromycin A 2'-*O*-acetate of the general formula (I), wherein A represents NH group and B at the same time represents C=O group, or A represents C=O group and B at the same time represents NH group, R^1 and R^2 together represent ketone and R^3 represents acetyl group.

Step 6:

3-decladinosyl-3-oxo-6-*O*-methyl-9a-aza-9a-homoerythromycin A 2'-*O*-acetate or 3-decladinosyl-3-oxo-6-*O*-methyl-8a-aza-8a-homoerythromycin A 2'-*O*-acetate of Step 5 of the general formula (I), wherein A, B, R^1, R^2 and R^3 have the above-mentioned meanings, are then subjected to solvolysis in lower alcohols, preferably in methanol, at a temperature from room temperature to the reflux temperature of the solvent, yielding 3-decladinosyl-3-oxo-6-*O*-methyl-9a-aza-9a-homoerythromycin A or 3-decladinosyl-3-oxo-6-*O*-methyl-8a-aza-8a-homoerythromycin A of the general formula (I), wherein A represents NH group and B at the same time represents C=O

group, or A represents C=O group and B at the same time represent NH group, R^1 and R^2 together represent ketone and R^3 represents hydrogen.

Pharmaceutically acceptable addition salts, which are also an object of the present invention are obtained by the reaction of new compounds from the class of 6-*O*-methyl-8a-aza-8a-homoerythromycin A and 6-*O*-methyl-9a-aza-9a-homoerythromycin A of the general formula (I), wherein A, B, R^1, R^2 and R^3 have the above-mentioned meanings, with at least equimolar amount of an appropriate inorganic or organic acid such as hydrochloric, hydroiodic, sulfuric, phosphoric, acetic, propionic, trifluoroacetic, maleic, citric, stearic, succinic, ethylsuccinic, methanesulfonic, benzenesulfonic, p-toluenesulfonic and laurylsulfonic acids in a solvent inert to the reaction. The addition salts are isolated by filtration if they are insoluble in a solvent inert to the reaction, by precipitation with a non-solvent or by evaporation of the solvent, mostly by method of lyophilization.

Antibacterial *in vitro* action of the new compounds of the general formula (I), wherein A, B, R^1, R^2 and R^3 have the above-mentioned meanings, and of their pharmaceutically acceptable addition salts with inorganic or organic acids was determined on a series of standard test microorganisms and clinical isolates by microdilution process according to the protocol NCCLS (The National Commitee for Clinical Laboratory Standards, Document M7-A2, Vol. 10, No. 8, 1990 and Document M11-A2, Vol. 10, 15,1991). The control of the laboratory process was performed by means of control strain *Staphyloccocus aureus* ATTC 29213 (The American Type Culture Collection) according to protocol NCCLS (Document M7-A2, Table 3, M100-S4).

The antibacterial *in vitro* action on a series of standard test microorganisms for 6-*O*-methyl-8a-aza-8a-homoerythromycin A from Example 3 in comparison with azithromycin, erythromycin and clarithromycin is represented in Table 1.

Table 1: Antibacterial *in vitro* action (MIC, mg/l) of 6-*O*-methyl-8a-aza-8a-homo-erythromycin A (Example 3) in comparison with azithromycin (Az), erythromycin (Er) and clarithromycin (Cl)

Test microorganism	**Az**	**Er**	**Cl**	**Example 3**
Listeria monocytogenes ATCC 7644	<0.125	<0.125	<0.125	<0.125
Staphylococcus aureus ATCC 25923	0.5	0.25	0.5	0.5
Staphylococcus epidermidis ATCC 12228	1.0	0.25	0.25	0.5
Enterococcus faecalis ATCC 35550	0.5	1.0	0.25	1.0
Streptococcus pneumoniae ATCC 6305	<0.125	<0.125	<0.125	<0.125
Streptococcus pyogenes ATCC 19615	<0.125	<0.125	<0.125	<0.125
Clostridium perfringens ATCC 13124	0.125	0.5	0.125	0.25
Moraxella catarrhalis ATCC 25238	<0.125	<0.125	<0.125	<0.125
Campylobacter fetus ATCC 19438	<0.125	<0.125	<0.125	<0.125
Campylobacter jejuni ATCC 33291	<0.125	<0.125	<0.125	<0.125
Citroobacter freundii ATCC 8090	4.0	64.0	64.0	16.0
Escherichia coli ATCC 25922	2.0	32.0	32.0	8.0
Proteus mirabilis ATCC 12453	64.0	>128.0	128.0	32.0
Proteus mirabilis ATCC 43071	64.0	>128.0	>128.0	32.0
Salmonella choleraesuis ATCC 13076	2.0	64.0	32.0	8.0
Shigella flexneri ATCC 12022	1.0	32.0	32.0	4.0
Yersinia enterocolitica ATCC 9610	1.0	16.0	16.0	4.0
Haemophilus influenzae ATCC 49247	0.5	2.0	4.0	1.0
Haemophilus influenzae ATCC 49766	1.0	4.0	8.0	1.0
Pseudomonas aeruginosa ATCC 25619	64.0	>128.0	>128.0	32.0

The process is illustrated by the following Examples, which do not limit the scope of the invention in any way.

Example 1

Preparation of 6-*O*-methylerythromycin A 9(*E*)- and 9(*Z*)-oxime

Method A

6-*O*-methylerythromycin A (2.0 g, 0.003 mole) in methanol (100 ml) was heated to the reflux temperature, hydroxylamine hydrochloride (2.0 g, 0.03 mole) and sodium carbonate (0.2 g, 0.002 mole) were added and it was heated under reflux while stirring for 3 hours. Then repeatedly the same amounts of hydroxylamine hydrochloride and sodium carbonate were added and it was heated under reflux for further 6 hours. Methanol was evaporated at reduced pressure and then water (200 ml) and chloroform (100 ml) were added, pH was adjusted to 9.8, the layers were separeted and the aqueous layer was extracted twice more with chloroform. The combined organic extracts were dried over potassium carbonate, filtered and evaporated at reduced pressure, yielding 2.0 g of a mixture of the title products. By chromatography on silica gel column using the system methylene chloride-methanol-conc. ammonium hydroxide 90:9:1.5, 0.63 g of chromatographically homogeneous 6-*O*-methyl-erythromycin A 9(*E*)-oxime with Rf 0.446 and 0.61 g of chromatographically homo-geneous 6-*O*-methylerythromycin A 9(*Z*)-oxime with Rf 0.355 were obtained.

9(E)-oxime:

Rf 0.418, ethylacetate-(n-hexane)-diethylamine, 100:100:20

IR (KBr) cm^{-1}: 3449, 2974, 2939, 2832, 2788, 1735, 1638, 1459, 1379, 1348, 1169, 1112, 1054, 1012, 957, 835, 755.

^1H NMR (300 MHz, $CDCl_3$) δ: 5.11 (H-13), 4.95 (H-1"), 4.45 (H-1'), 4.03 (H-5"), 3.77 (H-8), 3.76 ((H-3), 3.75 (H-11), 3.66 (H-5), 3.48 (H-5'), 3.33 (3"-OCH_3), 3.24 (H-2'), 3.10 (6-OCH_3), 3.03 (H-4"), 2.89 (H-2), 2.57 (H-10), 2.45 (H-3'), 2.37 (H-2"a), 2.31 /3'-$N(CH_3)_2$/, 1.93 (H-4), 1.93 (H-14a), 1.68 (H-4'a), 1.58 (H-2"b), 1.53 (H-7a), 1.48 (6-CH_3), 1.46 (H-14b), 1.31 (5"-CH_3), 1.25 (3"-CH_3), 1.23 (5'-CH_3), 1.20 (2-CH_3), 1.13 (10-CH_3), 1.13 (12-CH_3), 1.08 (4-CH_3), 1.00 (8-CH_3), 0.86 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.5 (C-1), 169.2 (C-9), 102.5 (C-1'), 95.7 (C-1"), 80.2 (C-5), 78.4 (C-6), 78.0 (C-3), 77.8 (C-4"), 76.5 (C-13), 73.8 (C-12), 72.4 (C-3"), 71.1 (C-2'), 70.0 (C-11), 68.2 (C-5'), 65.2 (C-5"), 64.9 (C-3'), 50.8 (6-OCH_3), 49.1 (3"-OCH_3), 44.7 (C-2), 40.1 /3'-$N(CH_3)_2$/, 38.7 (C-4), 37.0 (C-7), 34.6 (C-2"), 32.3 (C-10), 29.4 (C-4'), 24.9 (C-8), 21.1 (5'-CH_3), 21.0 (3"-CH_3), 20.8 (C-14), 19.6 (6-CH_3), 18.3 (5"-CH_3), 18.2 (8-CH_3), 15.7 (12-CH_3), 15.6 (2-CH_3), 14.6 (10-CH_3), 10.2 (15-CH_3), 8.8 (4-CH_3).

9(Z)-oxime:

Rf 0.300, ethylacetate-(n-hexane)-diethylamine, 100:100:20

IR (KBr) cm^{-1}: 3433, 2973, 2939, 2832, 1733, 1638, 1459, 1379, 1348, 1286, 1169, 1114, 1054, 1011, 958, 892, 755.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.07 (H-13), 4.93 (H-1"), 4.43 (H-1'), 4.03 (H-5"), 3.98 (H-11), 3.77 (H-3), 3.62 (H-5), 3.48 (H-5'), 3.33 (3"-OCH_3), 3.21 (H-2'), 3.09 (6-OCH_3), 3.06 (H-4"), 2.88 (H-2), 2.74 (H-8), 2.65 (H-10), 2.45 (H-3'), 2.36 (H-2"a), 2.30/3'-$N(CH_3)_2$/, 1.96 (H-4), 1.94 (H-14a), 1.76 (H-14b), 1.67 (H-4'a), 1.59 (H-2"b), 1.58 (H-7a), 1.47 (H-7b), 1.38 (6-CH_3), 1.32 (10-CH_3), 1.31 (5"-CH_3), 1.25 (3"-CH_3), 1.24 (5'-CH_3), 1.19 (2-CH_3), 1.14 (12-CH_3), 1.07 (4-CH_3), 1.06 (8-CH_3), 0.84 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.0 (C-1), 167.4 (C-9), 102.7 (C-1'), 96.0 (C-1"), 80.4 (C-5), 78.7 (C-6), 78.5 (C-3), 77.8 (C-4"), 76.9 (C-13), 74.7 (C-12), 72.6 (C-3"), 70.9 (C-2'), 70.3 (C-11), 68.4 (C-5'), 65.5 (C-5"), 65.3 (C-3'), 50.0 (6-OCH_3), 49.3 (3"-OCH_3), 45.0 (C-2), 41.0 /3'-$N(CH_3)_2$/, 38.9 (C-4), 37.0 (C-7), 35.6 (C-8), 34.7 (C-2"), 34.1 (C-10), 28.9 (C-4'), 21.3 (3"-CH_3), 21.2 (5'-CH_3), 21.1 (C-14), 19.7 (6-CH_3), 19.6 (8-CH_3), 18.5 (5"-CH_3), 16.4 (12-CH_3), 15.7 (2-CH_3), 10.7 (10-CH_3), 10.4 (15-CH_3), 9.8 (15-CH_3).

Method B

6-*O*-methylerythromycin A (10.8 g, 0.014 mole) in methanol (800 ml) was heated to the reflux temperature, then hydroxylamine hydrochloride (27.0 g, 0.388 mole) and anhydrous sodium acetate (15.0 g, 0.183 mole) were added to the reaction solution in

4 portions within 10 hours and it was heated under reflux while stirring for further 8 hours. Methanol was evaporated at reduced pressure, water (1500 ml) and methylene chloride (200 ml) were added, and it was extracted by gradient extraction at pH 5.0 and 9.8. The combined organic extracts at pH 9.8 were dried over potassium carbonate, filtered and evaporated at reduced pressure, yielding 9.5 g of a mixture of the title products. By chromatography on a silica gel column using the system methylene chloride-methanol-conc. ammonium hydroxide 90:9:1.5, chromatographically homogeneous 6-*O*-methylerythromycin A 9(*E*)-oxime and 6-*O*-methylerythromycin A 9(*Z*)-oxime with physical-chemical constants identical to those of Method A were obtained.

Example 2

Beckmann's rearrangement of 6-*O*-methylerythromycin A 9(*E*)-oxime

6-*O*-methylerythromycin A 9(*E*)-oxime from Example 1 (4.0 g, 0.005 mole) was dissolved in acetone (130 ml) and the solution was cooled to 0-5°C. Subsequently, solutions of p-toluenesulfochloride (2.6 g, 0.01 mole) in acetone (40 ml) and sodium hydrogen carbonate (0.830 g, 0.01 mole) in water (130 ml) were dropwise added thereto within 1 hour under stirring. The reaction mixture was stirred at room temperature for 8 hours, acetone was evaporated at reduced pressure and to the aqueous solution chloroform (40 ml) was added, whereupon it was extracted by gradient extraction at pH 5.0 and 9.0. The combined organic extracts at pH 9.0 were evaporated, yielding 2.8 g of 6-*O*-methyl-9a-aza-9a-homoerythromycin A.

Rf 0.218, ethylacetate-(n-hexane)-diethylamine, 100:100:20

IR (KBr) cm^{-1}: 3449, 2974, 2939, 2834, 1734, 1706, 1659, 1534, 1459, 1379, 1274, 1169, 1111, 1053, 1011, 958.

^1H NMR (300 MHz, $CDCl_3$) δ: 6.12 (9a-CONH), 4.85 (H-1"), 4.68 (H-13), 4.45 (H-1'), 4.21 (H-3), 4.16 (H-10), 4.07 (H-5"), 3.75 (H-5), 3.49 (H-5'), 3.34 (3"-OCH_3), 3.32 (6-OCH_3), 3.22 (H-11), 3.20 (H-2'), 3.04 (H-4"), 2.83 (H-2), 2.43 (H-3'), 2.38 (H-2"a), 2.30 /3'-$N(CH_3)_2$/, 2.22 (H-8), 2.07 (H-7a), 1.87 (H-4), 1.87 (H-14a), 1.67 (H-4'a), 1.57 (H-2"b), 1.57 (H-14b), 1.36 (6-CH_3), 1.33 (H-7b), 1.32 (5"-CH_3), 1.25

(3"-CH_3), 1.24 (H-4'b), 1.23 (5'-CH_3), 1.23 (2-CH_3), 1.18 (12-CH_3), 1.16 (10-CH_3), 1.09 (8-CH_3), 1.02 (4-CH_3), 0.89 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.5 (C-1), 177.3 (C-9), 102.5 (C-1'), 94.9 (C-1"), 79.1 (C-6), 78.5 (C-5), 77.7 (C-4"), 77.7 (C-13), 75.9 (C-3), 73.9 (C-12), 72.5 (C-3"), 72.6 (C-11), 70.7 (C-2'), 68.2 (C-5'), 65.3 (C-5"), 65.1 (C-3'), 51.0 (6-OCH_3), 49.1 (3"-OCH_3), 45.1 (C-10), 44.5 (C-2), 41.3 (C-4), 40.0 /3'-$N(CH_3)_2$/, 39.6 (C-7), 35.4 (C-8), 34.4 (C-2"), 28.8 (C-4'), 21.1 (5'-CH_3), 21.0 (3"-CH_3), 20.3 (C-14), 20.2 (6-CH_3), 19.1 (8-CH_3), 18.1 (5"-CH_3), 15.9 (12-CH_3), 14.6 (2-CH_3), 13.4 (10-CH_3), 10.7 (15-CH_3), 8.7 (4-CH_3).

Example 3

Beckmann's rearrangement of 6-*O*-methylerythromycin A 9(*Z*)-oxime

6-*O*-methylerythromycin A 9(*Z*)-oxime from Example 1 (1.4 g, 0.002 mole) was dissolved in acetone (50 ml) and the solution was cooled to 0-5°C. Subsequently, solutions of p-toluenesulfochloride (1.84 g, 0.014 mole) in acetone (56 ml) and sodium hydrogen carbonate (1.16 g, 0.014 mole) in water (180 ml) were dropwise added thereto within 1 hour under stirring. The reaction mixture was stirred at room temperature for 2 hours, acetone was evaporated at reduced pressure and to the aqueous solution chloroform (70 ml) was added, whereupon it was extracted by gradient extraction at pH 5.0 and 9.0. The combined organic extracts at pH 9.0 were evaporated, yielding 0.80 g of product, which, if appropriate, was purified by chromatography on a silica gel column using the system methylene chloride-methanol-conc. ammonium hydroxide 90:9:1.5, yielding 6-*O*-methyl-8a-aza-8a-homo-erythromycin A with the following physical-chemical constants:

Rf 0.152, ethylacetate-(n-hexane)-diethylamine, 100:100:20

IR (KBr) cm^{-1}: 3442, 2974, 2938, 2833, 1736, 1648, 1535, 1459, 1379, 1284, 1169, 1110, 1055, 1013, 960, 902.

^1H NMR (300 MHz, $CDCl_3$) δ: 5.78 (8a-CONH), 5.02 (H-1"), 4.96 (H-13), 4.41 (H-1'), 4.19 (H-8), 4.02 (H-5"), 3.96 (H-3), 3.69 (H-5), 3.51 (H-11), 3.47 (H-5'), 3.32 (3"-

OCH_3), 3.18 (H-2'), 3.16 (6-OCH_3), 3.02 (H-4"), 2.68 (H-2), 2.44 (H-3'), 2.35 (H-2"a), 2.29 /3'-$N(CH_3)_2$/, 2.22 (H-10), 1.92 (H-4), 1.91 (H-14a), 1.68 (H-7a), 1.64 (H-4'a), 1.56 (H-2"b), 1.53 (H-7b), 1.47 (H-14b), 1.39 (6-CH_3), 1.29 (5"-CH_3), 1.24 (3"-CH_3), 1.23 (5'-CH_3), 1.20 (2-CH_3), 1.18 (10-CH_3), 1.13 (12-CH_3), 1.13 (8-CH_3), 1.07 (4-CH_3), 0.88 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.0 (C-1), 174.3 (C-9), 102.9 (C-1'), 95.1 (C-1"), 80.1 (C-5), 78.6 (C-6), 77.9 (C-4"), 77.2 (C-3), 76.7 (C-13), 74.0 (C-12), 72.6 (C-3"), 70.4 (C-2'), 70.1 (C-11), 68.7 (C-5'), 65.4 (C-3'), 65.2 (C-5"), 51.5 (6-OCH_3), 49.1 (3"-OCH_3), 45.4 (C-2), 42.6 (C-7), 42.1 (C-4), 41.8 (C-10), 40.6 (C-8), 40.0/3'-$N(CH_3)_2$/, 34.5 (C-2"), 28.3 (C-4'), 23.5 (6-CH_3), 21.3 (C-14), 21.2 (12-CH_3), 21.1 (5'-CH_3), 21.1 (3"-CH_3), 17.9 (5"-CH_3), 15.8 (8-CH_3), 14.8 (2-CH_3), 10.8 (15-CH_3), 9.2 (10-CH_3), 9.1 (4-CH_3).

Example 4

3-decladinosyl-3-oxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A

The substance from Example 2 (1.5 g, 0.002 mole) was dissolved in 0.25 N hydrochloric acid (40 ml) and it was left to stand for 24 hours at room temperature. To the reaction mixture methylene chloride (30 ml) (pH 1.8) was added and the pH of the mixture was adjusted to 9.0 with conc. ammonia, the layers were separated and the aqueous layer was extracted twice more with methylene chloride (30 ml). The combined organic extracts were washed with a 10% aqueous solution of sodium hydrogen carbonate and water and then evaporated, yielding 1.3 g of a crude product, which, if appropriate, was purified by chromatography on a silica gel column using the system methylene chloride-methanol-conc. ammonium hydroxide 90:9:1.5. From 0.9 g of the crude product there were isolated 0.65 g of chromatographically homogeneous 3-decladinosyl-3-oxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A with the following physical-chemical constants:

Rf 0.152, ethylacetate-(n-hexane)-diethylamine, 100:100:20

IR (KBr) cm^{-1}: 3438, 2973, 2939, 2879, 2788, 1702, 1658, 1535, 1458, 1373, 1329, 1270, 1173, 1112, 1050, 985, 958, 937.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16 (9a-CONH), 4.63 (H-13), 3.81 (H-5), 4.45 (H-1'), 4.13 (H-10), 3.78 (H-3), 3.55 (H-5'), 3.30 (6-OCH_3), 3.25 (H-2'), 3.16 (H-11), 2.66 (H-2), 2.51 (H-3'), 2.39 (H-8), 2.26/3'-$N(CH_3)_2$/, 2.05 (H-4), 1.92 (H-14a), 1.84 (H-7a), 1.68 (H-4'a), 1.57 (H-14b), 1.43 (H-7b), 1.38 (6-CH_3), 1.33 (2-CH_3), 1.26 (5'-CH_3), 1.26 (H-4'b), 1.20 (10-CH_3), 1.12 (12-CH_3), 1.11 (8-CH_3), 1.01 (4-CH_3), 0.91 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.3 (C-1), 176.9 (C-9), 106.4 (C-1'), 88.1 (C-5), 79.1 (C-6), 78.7 (C-13), 78.0 (C-3), 73.8 (C-12), 73.9 (C-11), 70.2 (C-2'), 69.7 (C-5'), 65.4 (C-3'), 49.9 (6-OCH_3), 45.6 (C-10), 43.9 (C-2), 40.8 (C-7), 39.9/3'-$N(CH_3)_2$, 35.6 (C-4), 32.8 (C-8), 27.8 (C-4'), 20.9 (5'-CH_3), 20.5 (C-14), 18.3 (6-CH_3), 17.4 (8-CH_3), 15.8 (12-CH_3), 15.9 (2-CH_3), 14.8 (10-CH_3), 10.7 (15-CH_3), 7.5 (4-CH_3).

Example 5

3-decladinosyl-3-oxy-6-*O*-methyl-8a-aza-8a-homoerythromycin A

From the substance (1.5 g, 0.002 mole) of Example 3 there were obtained, according to the process described in Example 4, 1.2 g of a crude product, which, if appropriate, was purified by chromatography on a silica gel column using the system methylene chloride-methanol-conc. ammonium hydroxide 90:9:1.5, yielding chromatographically homogeneous 3-decladinosyl-3-oxy-6-*O*-methyl-8a-aza-8a-homoerythromycin A with the following physical-chemical constants:

Rf 0.195, chloroform-methanol-conc. ammonium hydroxide, 6:1:0.1

IR (KBr) cm^{-1}: 3438, 2974, 2939, 2788, 1733, 1648, 1535, 1458, 1378, 1263, 1165, 1113, 1075, 1050, 985, 958, 937.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.58 (9a-CONH), 5.09 (H-13), 4.38 (H-1'), 3.76 (H-5), 3.92 (H-8), 3.80 (H-3), 2.64 (H-2), 3.54 (H-5'), 3.47 (H-11), 3.25 (H-2'), 2.11 (H-4), 3.12 (6-OCH_3), 2.48 (H-3'), 2.38 (H-10), 2.25/3'-$N(CH_3)_2$/, 1.94 (H-14a), 2.11 (H-7a), 1.66 (H-4'a), 1.51 (H-7b), 1.50 (H-14b), 1.31 (2-CH_3), 1.39 (6-CH_3), 1.12 (4-CH_3), 1.26 (5'-CH_3), 1.26 (H-4'b), 1.20 (10-CH_3), 1.25 (8-CH_3), 1.13 (12-CH_3), 0.88 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.0 (C-1), 174.4 (C-9), 106.1 (C-1'), 89.6 (C-5), 77.3 (C-6), 75.8 (C-13), 78.3 (C-3), 74.3 (C-12), 70.3 (C-11), 69.9 (C-2'), 69.4 (C-5'), 64.9 (C-3'), 49.7 (6-OCH_3), 42.1 (C-10), 43.8 (C-2), 41.7 (C-7), 39.9/3'-$N(CH_3)_2$/, 35.2 (C-4), 42.4 (C-8), 27.4 (C-4'), 22.3 (5'-CH_3), 20.9 (C-14), 20.4 (6-CH_3), 20.5 (8-CH_3), 15.7 (12-CH_3), 15.2 (2-CH_3), 9.5 (10-CH_3), 10.1 (15-CH_3), 7.50 (4-CH_3).

Example 6

3-decladinosyl-3-oxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A 2'-*O*-acetate

To a solution of 3-decladinosyl-3-oxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A (0.750 g, 0.0012 mole) from Example 4 in methylene chloride (25 ml), sodium hydrogen carbonate (0.440 g, 0.0052 mole) and acetic acid anhydride (0.128 ml, 0.0013 mole) were added and it was stirred for 3 hours at room temperature. To the reaction mixture a saturated solution of sodium hydrogen carbonate (30 ml) was added, the layers were separated and the aqueous portion was again extracted with methylene chloride (2 x 20 ml). The combined organic extracts were washed successively with a saturated solution of hydrogen carbonate and water and evaporated, yielding 0.750 g of a crude title product with the following physical-chemical constants:

Rf 0.403 chloroform-methanol-conc. ammonium hydroxide, 6:1:0.1

IR (KBr) cm^{-1}: 3455, 2974, 2940, 2880, 2787, 1748, 1702, 1658, 1540, 1459, 1376, 1239, 1173, 1112, 1061, 986, 958, 937, 904.

Example 7

3-decladinosyl-3-oxy-6-*O*-methyl-8a-aza-8a-homoerythromycin A 2'-*O*-acetate

To a solution of 3-decladinosyl-3-oxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A (1.5 g, 0.0024 mole) from Example 5 in methylene chloride (40 ml), sodium hydrogen carbonate (0.88 g, 0.01 mole) and acetic acid anhydride (0.250 ml, 0.0025 mole) were added and then, according to the process described in Example 6, there were obtained 1.4 g of the title product with the following physical-chemical constants:

Rf 0.423, chloroform-methanol-conc. ammonium hydroxide, 6:1:0.1
IR (KBr) cm^{-1}: 3394, 2972, 2939, 2784, 1736, 1649, 1542, 1459, 1376, 1262, 1165, 1085, 1059, 986, 958, 904.

Example 8

3-decladinosyl-3-oxo-6-*O*-methyl-9a-aza-9a-homoerythromycin A

To a solution of 3-decladinosyl-3-oxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A 2'-*O*-acetate (0.760 g, 0.0012 mole) from Example 6 in methylene chloride (15 ml), dimethyl sulfoxide (1.27 ml) and *N,N*-dimethylaminopropyl-ethyl-carbodiimid (1.335 g, 0.007 mole) were added. The reaction mixture was cooled to 15°C and then, under stirring and maintaining this temperature, a solution of pyridinium trifluoroacetate (1.37 g, 0.007 mole) in methylene chloride (5 ml) was gradually added dropwise within 30 minutes. The temperature of the reaction mixture was gradually increased to room temperature, the stirring was continued for further 3 hours and then the reaction was ceased by the addition of a saturated solution of NaCl (20 ml) and methylene chloride (20 ml). After alkalizing the reaction mixture to pH 9.5 with 2N NaOH, it was extracted with CH_2Cl_2, the organic exstracts were successively washed with a saturated solution of NaCl, $NaHCO_3$ and water and then dried over K_2CO_3. After filtration and evaporation of methylene chloride at reduced pressure, 0.800 g of an oily residue were obtained. The oily residue was subjected to the methanolysis (30 ml of methanol) within 24 hours at room temperature. Methanol was evaporated at reduced pressure and the obtained residue (0.625g) was purified by low-pressure chromatography on a silica gel column using the solvent system dichloromethane-methanol-conc. ammonium hydroxide 90:9:0.5. By evaporation of the combined extracts with Rf 0.235, there was obtained a chromatographically homogeneous title product with the following physical-chemical constants:

Rf 0.235, methylene chloride-methanol-conc. ammonium hydroxide 90:9:0.5
IR (KBr) cm^{-1}: 3438, 2975, 2939, 2878, 2787, 1744, 1655, 1530, 1458, 1380, 1340, 1304, 1169, 1111, 1075, 1051, 986, 959, 940.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6,63 (9a-CONH), 4.64 (H-13), 4.49 (H-5), 4.41 (H-1'), 4.20 (H-10), 3.90 (H-2), 3.64 (H-5'), 3.34 (H-11), 3.20 (H-2'), 3.07 (6-OCH_3), 3.02 (H-4), 2.51 (H-3'), 2.30 (H-8), 2.27/3'-$N(CH_3)_2$/, 1.94 (H-14a), 1.94 (H-7a), 1.69 (H-4'a), 1.63 (H-14b), 1.42 (H-7b), 1.40 (2-CH_3), 1.30 (5'-CH_3), 1.29 (4-CH_3), 1.26 (6-CH_3), 1.25 (H-4'b), 1.22 (12-CH_3), 1,19 (10-CH_3), 1.10 (8-CH_3), 0.91 (15-CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8 (C-3), 177.3 (C-1), 173.8 (C-9), 102.6 (C-1'), 79.3 (C-13), 78.4 (C-6), 74.4 (C-5), 73.9 (C-12), 73.1 (C-11), 70.0 (C-2'), 69.1 (C-5'), 65.5 (C-3'), 50.1 (6-OCH_3), 49.0 (C-2), 46.2 (C-4), 45.3 (C-10), 40.3 (C-7), 40.0/3'-$N(CH_3)_2$/, 34.6 (C-8), 28.3 (C-4'), 21.0 (6-CH_3), 20.7 (C-14), 19.6 (5'-CH_3), 18.6 (8-CH_3), 15.9 (12-CH_3), 14.1 (2-CH_3), 13.9 (10-CH_3), 13.9 (4-CH_3), 10.7 (15-CH_3).

Example 9

3-decladinosyl-3-oxo-6-*O*-methyl-8a-aza-8a-homoerythromycin A

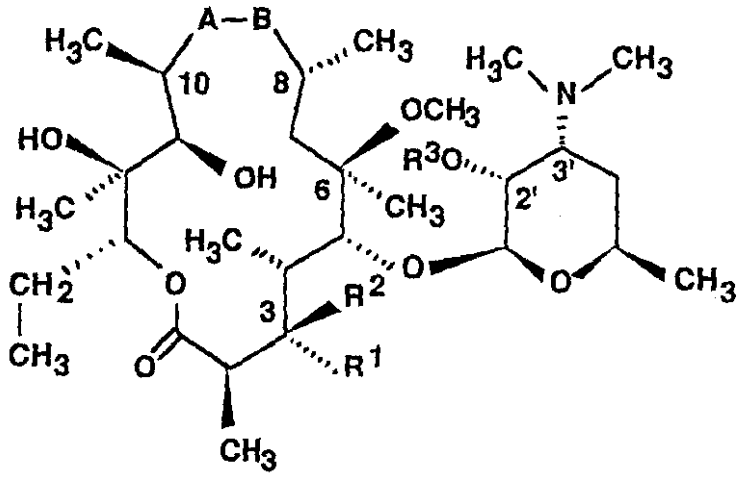
To a solution of 3-decladinosyl-3-oxy-6-*O*-methyl-8a-aza-8a-homoerythromycin A 2'-*O*-acetate (1.4 g, 0.0022 mole) from Example 7 in methylene chloride (30 ml), dimethyl sulfoxide (2.5 ml) and *N,N*-dimethylaminopropyl-ethyl-carbodiimid (2.7 g, 0.014 mole) were added. The reaction mixture was cooled to 15°C and, under stirring and maintaining this temperature, a solution of pyridinium trifluoroacetate (2.7 g, 0.014 mole) in methylene chloride (10 ml) was gradually added dropwise within 30 minutes. According to the process described in Example 8, there were obtained 1.1 g of the title product with the following physical-chemical constants:

IR (KBr) cm^{-1}: 3435, 2975, 2939, 2879, 2788, 1746, 1648, 1542, 1458, 1379, 1339, 1302, 1166, 1111, 1076, 1052, 989, 960, 918.
^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.89 (9a-CONH), 5.08 (H-13), 4.42 (H-1'), 4.27 (H-5), 4.03 (H-8), 3.78 (H-2), 3.60 (H-5'), 3.58 (H-11), 3.18 (H-2'), 3.05 (H-4), 2.91 (6-OCH_3), 2.49 (H-3'), 2.39 (H-10), 2.27/3'-$N(CH_3)_2$/, 1.96 (H-14a), 1.68 (H-7a), 1.68 (H-4'a), 1.50 (H-14b), 1.41 (2-CH_3), 1.32 (6-CH_3), 1.30 (4-CH_3), 1.25 (5'-CH_3), 1.23 (H-4'b), 1.20 (10-CH_3), 1.19 (8-CH_3), 1.17 (12-CH_3), 0.88 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.2 (C-3), 170.0 (C-9), 174.6 (C-1), 103.1 (C-1'), 78.2 (C-6), 77.9 (C-5), 77.5 (C-13), 74.1 (C-12), 70.6 (C-11), 70.0 (C-2'), 69.1 (C-5'), 65.5 (C-3'), 50.5 (6-OCH_3), 50.4 (C-2), 47.6 (C-4), 42.2 (C-10), 42.1 (C-7), 41.6 (C-8), 39.9/3'-$N(CH_3)_2$/, 28.0 (C-4'), 22.8 (8-CH_3), 21.2 (C-14), 20.8 (5'-CH_3), 20.1 (6-CH_3), 16.1 (12-CH_3), 15.4 (2-CH_3), 14.4 (4-CH_3), 10.5 (15-CH_3), 10.1 (10-CH_3).

Claims

1. Compound represented by the general formula (I)



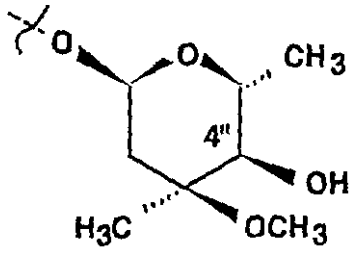
(I)

and its pharmaceutically acceptable addition salts with inorganic and organic acids, wherein

A represents NH group and B at the same time represents C=O group, or

A represents C=O group and B at the same time represent NH group,

R^1 represents OH group, L-cladinosyl group of the formula (II)



(II)

or together with R^2 represents ketone,

R^2 represents hydrogen or together with R^1 represents ketone,

R^3 represents hydrogen or C_1-C_4alkanoyl group.

2. Compound according to claim 1, characterized in that A represents NH group, B represents C=O group, R^1 represents L-cladinosyl group of the formula (II), R^2 and R^3 are the same and represent hydrogen.

3. Compound according to claim 1, characterized in that A represents C=O group, B represents NH group, R^1 represents L-cladinosyl group of the formula (II) and R^2 and R^3 are the same and represent hydrogen.

4. Compound according to claim 1, characterized in that A represents NH group, B represents C=O group, R^1 represents OH group and R^2 and R^3 are the same and represent hydrogen.

5. Compound according to claim 1, characterized in that A represents C=O group, B represents NH group, R^1 represents OH group and R^2 and R^3 are the same and represent hydrogen.

6. Compound according to claim 1, characterized in that A represents NH group, B represents C=O group, R^1 represents OH group, R^2 is hydrogen and R^3 represents C_1-C_4 alkanoyl group.

7. Compound according to claim 6, characterized in that R^3 represents acetyl group.

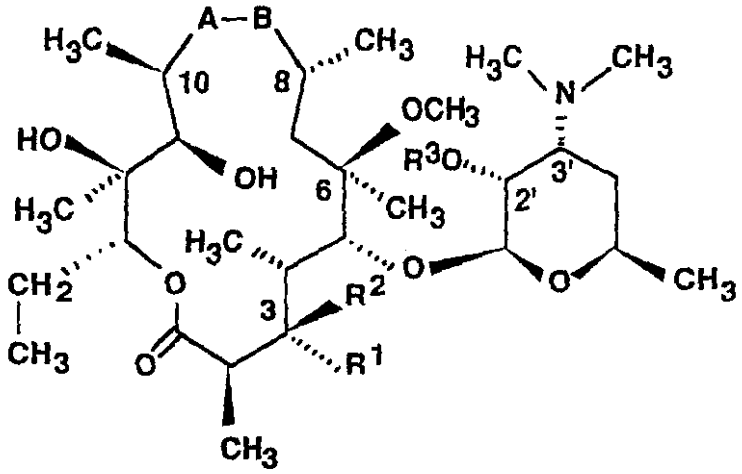
8. Compound according to claim 1, characterized in that A represents C=O group, B represents NH group, R^1 represents OH group, R^2 is hydrogen and R^3 represents C_1-C_4 alkanoyl group.

9. Compound according to claim 8, characterized in that R^3 represents acetyl group.

10. Compound according to claim 1, characterized in that A represents NH group, B represents C=O group, R^1 and R^2 together represent ketone and R^3 is hydrogen.

11. Compound according to claim 1, characterized in that A represents C=O group, B represents NH group, R^1 and R^2 together represent ketone and R^3 is hydrogen.

12. Process for the preparation of a compound of the general formula (I)



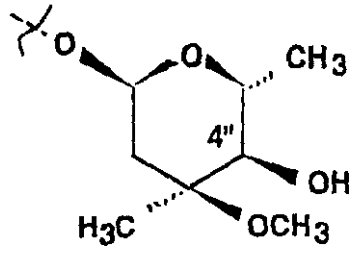
(I)

and its pharmaceutically acceptable addition salts with inorganic and organic acids, wherein

A represents NH group and B at the same time represents C=O group, or

A represents C=O group and B at the same time represents NH group,

R^1 represents OH group, L-cladinosyl group of the formula (II)



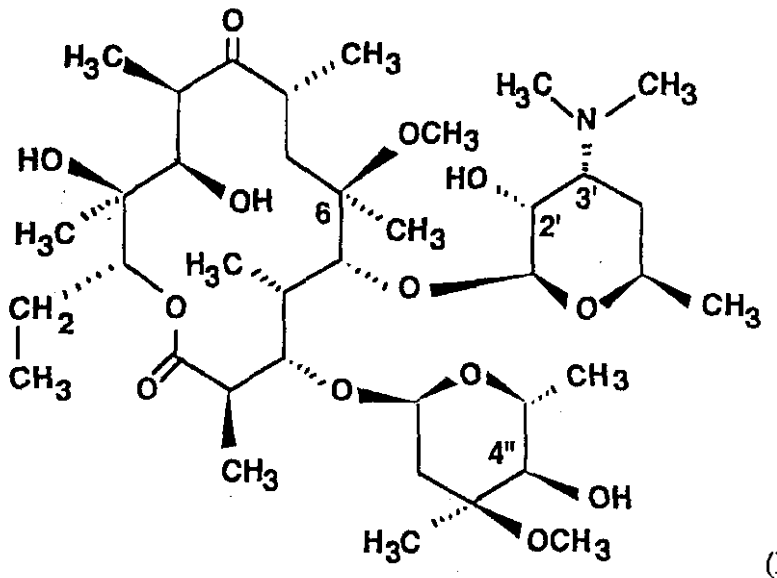
(II)

or together with R^2 represents ketone,

R^2 represents hydrogen or together with R^1 represents ketone,

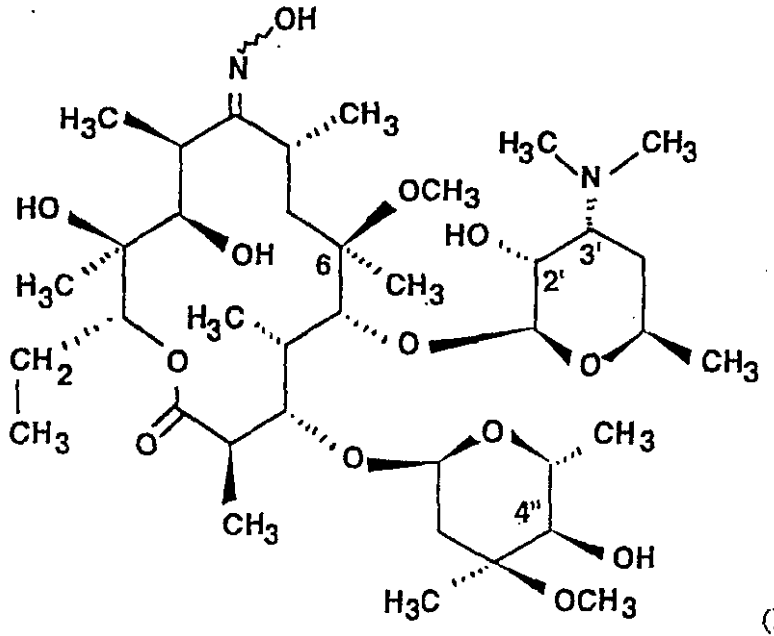
R^3 represents hydrogen or C_1-C_4alkanoyl group,

characterized in that 6-*O*-methylerythromycin A of the formula (III)



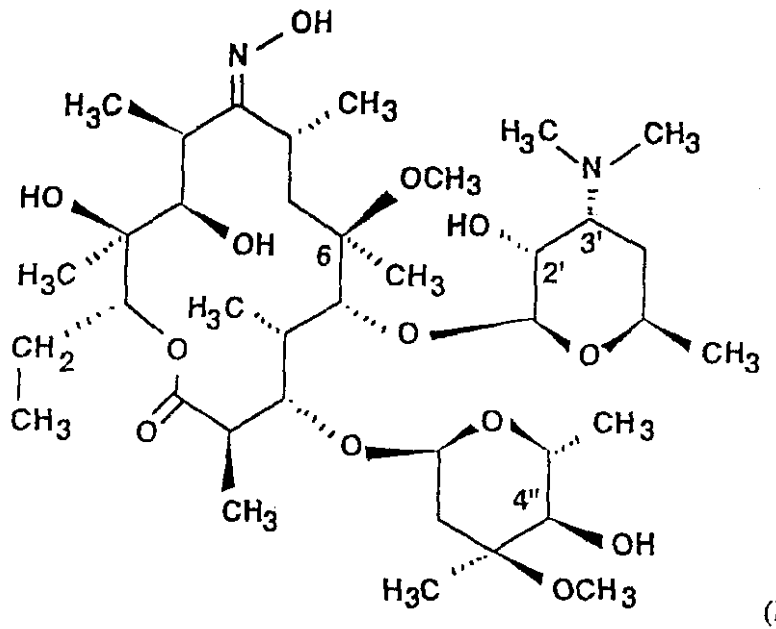
(III)

is subjected to a reaction with hydroxylamine hydrochloride in the presence of appropriate inorganic or organic bases, yielding a mixture of 6-*O*-methylerythromycin A 9(E)- and 9(Z)-oximes of the formula (IV)



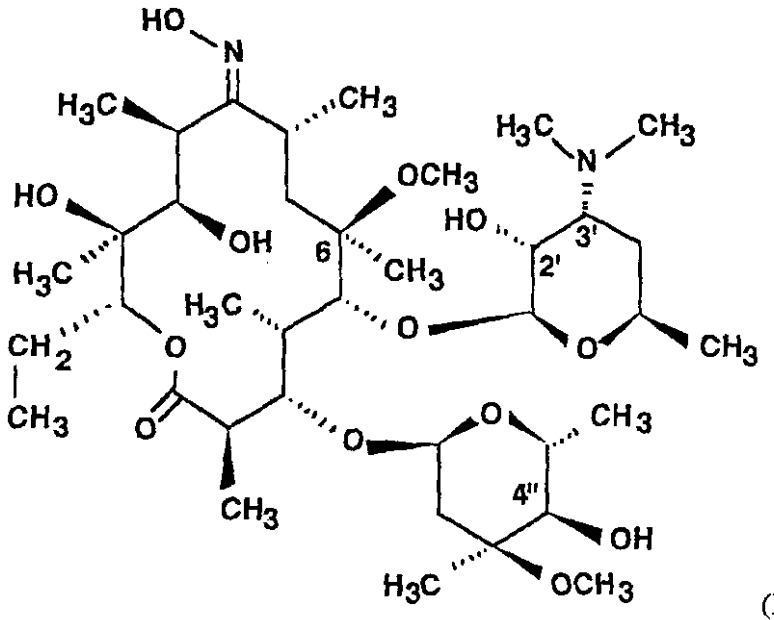
(IV)

which, if appropriate, is subjected to separation on a silica gel column using the system methylene chloride-methanol-conc. ammonium hydroxide 90:9:1.5, yielding chromatographically homogeneous 6-*O*-methyl-erythromycin A 9(*E*)-oxime with Rf 0.446 of the formula (IVa)



(IVa)

and chromatographically homogeneous 6-*O*-methylerythromycin A 9(*Z*)-oxime with Rf 0.355 of the formula (IVb)



(IVb)

and then to the reaction of Beckmann's rearrangement with arylsulfonyl halides, preferably with p-toluenesulfonyl chloride, in the presence of inorganic bases, preferably sodium hydrogen carbonate, in a solvent or solvent mixture inert to the reaction, preferably in a mixture of acetone-water, yielding in the case of 6-*O*-methyl-erythromycin A 9(*E*)-oxime of the formula (IVa) a compound of the general formula (I), wherein A represents NH group, B represents C=O group, R^1 represents L-cladinosyl group of the formula (II) and R^2 and R^3 are the same and represent hydrogen, or in the case of 6-*O*-methylerythromycin A 9(*Z*)-oxime of the formula (IVb) a compound of the general formula (I), wherein A represents C=O group, B represents NH group, R^1 represents L-cladinosyl group and R^2 and R^3 are the same and represent hydrogen,

which is then subjected to the action of diluted inorganic acids, preferably 0.25 N hydrochloric acid, at a room temperature, yielding a compound of the general formula (I), wherein A represents NH group and B at the same time represents C=O group, or A represents C=O group and B at the same time represents NH group, R^1 represents OH group and R^2 and R^3 are the same and represent hydrogen,

which is then subjected to the reaction of selective acylation with anhydrides of carboxylic acids with up to 4 carbon atoms, preferably with acetic acid anhydride in an inert organic solvent, preferably in methylene chloride, yielding a compound of general formula (I), wherein A represents NH group and B at the same time represents C=O group, or A represents C=O group and B at the same time represents NH group, R^1 is OH group, R^2 is hydrogen and R^3 is acetyl,

which is then subjected to oxidation with diimides, preferably with *N,N*-dimethylaminopropyl-ethyl-carbodiimide in the presence of dimethylsulfoxide and pyridinium trifluoroacetate as a catalyst in an inert organic solvent, preferably in methylene chloride, at a temperature from 10°C to room temperature, yielding a compound of the general formula (I), wherein A represents NH group and B at the same time represents C=O group, or A represents C=O group and B at the same time represents NH group, R^1 together with R^2 represents ketone and R^3 is acetyl group,

which is then subjected to the reaction of deacylation at 2'-position by solvolysis in lower alcohols, preferably in methanol at room temperature, yielding a compound of the general formula (I), wherein A represents NH group and B at the same time represents C=O group, or A represents C=O group and B at the same time represents NH group, R^1 together with R^2 represent ketone and R^3 is hydrogen,

which, if appropriate, is then subjected to the reaction with inorganic or organic acids, yielding their pharmaceutically acceptable addition salts.

13. Pharmaceutical composition useful for treating bacterial infections in humans and animals, which contains antibacterially effective amounts of a compound of the general formula (I) or of its pharmaceutically acceptable addition salts according to claim 1 in combination with a pharmaceutically acceptable carrier.

14. Method for treating bacterial infections in humans and animals, which comprises administering to a human or an animal, as required, antibacterially effective amounts of a compound of the general formula (I) or of its pharmaceutically acceptable

addition salts according to claim 1 in combination with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/HR 99/00004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H17/08 A61K31/70

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 6 C07H A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 549 040 A (MERCK & CO INC) 30 June 1993 (1993-06-30) example 4	1-14
Y	EP 0 507 595 A (MERCK & CO INC) 7 October 1992 (1992-10-07) abstract	1-14
Y	EP 0 596 802 A (ROUSSEL UCLAF) 11 May 1994 (1994-05-11) abstract	1-14
Y	EP 0 422 843 A (TAISHO PHARMA CO LTD) 17 April 1991 (1991-04-17) claim 1	1-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 1999	27/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scott, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HR 99/00004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	S.T.WADDELL ET AL.: "Synthesis and Antibacterial Activity of O-methyl Derivatives of Azalide Antibiotics : II. 6-OMe Derivatives via Clarithromycin." BIOORGANIC MEDICINAL CHEMITRY LETTERS, vol. 8, no. 11, June 1998 (1998-06), pages 1321-1326, XP004137197 page 1324, compound 17	1,2, 12-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HR 99/00004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0549040 A	30-06-1993	CA 2083762 A	21-06-1993
		JP 5255374 A	05-10-1993
		JP 6092434 B	16-11-1994
EP 0507595 A	07-10-1992	US 5202434 A	13-04-1993
		CA 2064985 A	06-10-1992
		JP 5239086 A	17-09-1993
EP 0596802 A	11-05-1994	FR 2697523 A	06-05-1994
		FR 2707088 A	06-01-1995
		AT 135706 T	15-04-1996
		AU 670329 B	11-07-1996
		AU 5047793 A	19-05-1994
		BR 9304481 A	21-06-1994
		CA 2102457 A	06-05-1994
		CN 1090581 A,B	10-08-1994
		DE 69301897 D	25-04-1996
		DK 596802 T	03-06-1996
		ES 2085130 T	16-05-1996
		GR 3019385 T	30-06-1996
		HU 66446 A	28-11-1994
		JP 6220082 A	09-08-1994
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		US 5614614 A	25-03-1997
EP 0422843 A	17-04-1991	AT 118503 T	15-03-1995
		CA 2027074 A	08-04-1991
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		DE 69016912 T	06-07-1995
		DK 422843 T	03-04-1995
		ES 2071036 T	16-06-1995
		JP 3204893 A	06-09-1991
		US 5302705 A	12-04-1994

INTERNATIONAL SEARCH REPORT

..ernational application No.
PCT/HR 99/ 00004

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 14
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

[19]中华人民共和国国家知识产权局

[51]Int. Cl[7]
C07H 17/08
A61K 31/70

[12]发明专利申请公开说明书

[21]申请号 99806356.8

[43]公开日 2001年6月27日

[11]公开号 CN 1301268A

[22]申请日 1999.4.2 [21]申请号 99806356.8
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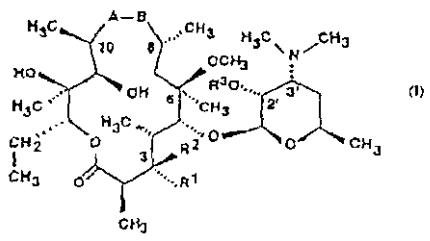
[32]1998.4.6 [33]HR [31]P980189A
[86]国际申请 PCT/HR99/00004 1999.4.2
[87]国际公布 WO99/51616 英 1999.10.14
[85]进入国家阶段日期 2000.11.17
[71]申请人 普利瓦药物工业公司
地址 克罗地亚萨格勒布
[72]发明人 G·拉扎莱夫斯基 G·科布莱海尔
Z·凯尔纳里克
[74]专利代理机构 中国国际贸易促进委员会专利商标事务所
代理人 周中琦

权利要求书6页 说明书20页 附图页数0页

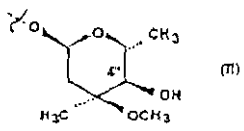
[54]发明名称 抗细菌活性的15元内酰胺类酮内酯

[57]摘要

本发明涉及具有通式(I)的来自6-O-甲基-8a-氮杂-8a-高-和6-O-甲基-9a-氮杂-9a-高红霉素A类的新型15元环酮氮杂内酯类,其中A代表NH基且B同时代表C=O基、或A代表C=O基且B同时代表NH基,R^1代表OH基、通式(II)的L-克拉定糖基或与R^2一起代表酮,R^2代表氢或与R^1一起代表酮;R^3代表氢或C_1-C_4的链烷酰基,本发明还涉及其制备的中间产物及方法、涉及其与无机或有机酸的药物上可接受的加成盐、涉及药物组合物的制备方法以及药物组合物用于治疗细菌感染的用途。



(I)

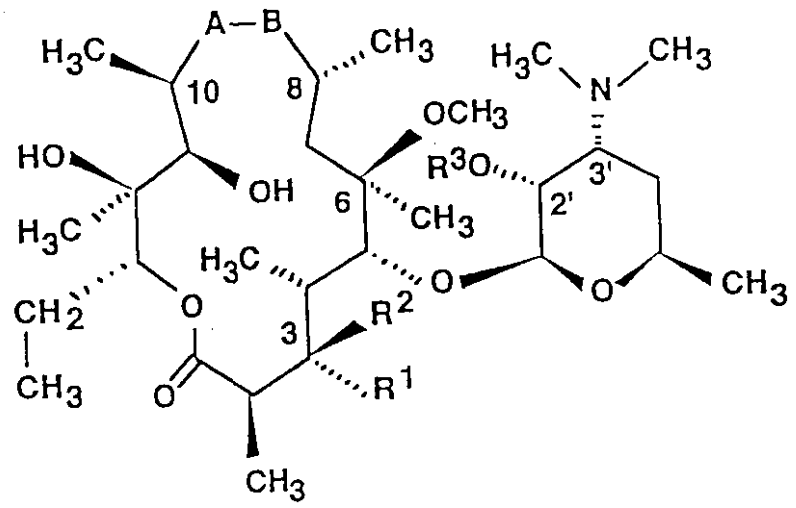


(II)

ISSN1008-4274

权 利 要 求 书

1. 通式（I）代表的化合物



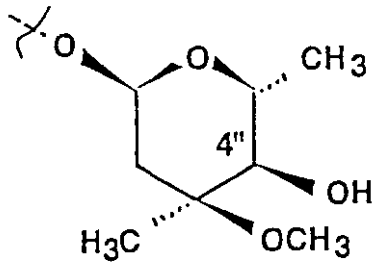
(I)

及其与无机和有机酸类的药物上可接受的加成盐，

其中 A 代表 NH 基且 B 同时代表 C=O 基；或

A 代表 C=O 基且 B 同时代表 NH 基；

R^1代表 OH 基、通式（II）的 L-克拉定糖基



(II)

或与 R^2一起代表酮；

R^2代表氢或与 R^1一起代表酮；

R^3代表氢或 C_1－C_4的链烷酰基。

2. 根据权利要求 1 的化合物，其特征在于 A 代表 NH 基，B 代表 C=O 基，R^1代表通式（II）的 L-克拉定糖基，R^2与 R^3相同并代表氢。

3. 根据权利要求 1 的化合物，其特征在于 A 代表 C=O 基，B 代表 NH 基，R^1 代表通式（II）的 L-克拉定糖基，R^2 与 R^3 相同并代表氢。

4. 根据权利要求 1 的化合物，其特征在于 A 代表 NH 基，B 代表 C=O 基，R^1 代表 OH 基且 R^2 与 R^3 相同并代表氢。

5. 根据权利要求 1 的化合物，其特征在于 A 代表 C=O 基，B 代表 NH 基，R^1 代表 OH 基且 R^2 与 R^3 相同并代表氢。

6. 根据权利要求 1 的化合物，其特征在于 A 代表 NH 基，B 代表 C=O 基，R^1 代表 OH 基，R^2 是氢且 R^3 代表 C_1-C_4 的链烷酰基。

7. 根据权利要求 6 的化合物，其特征在于 R^3 代表乙酰基。

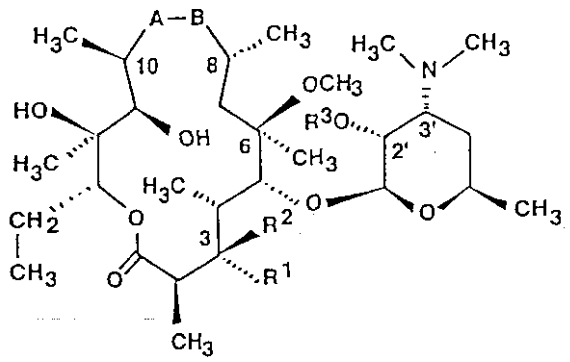
8. 根据权利要求 1 的化合物，其特征在于 A 代表 C=O 基，B 代表 NH 基，R^1 代表 OH 基，R^2 是氢且 R^3 代表 C_1-C_4 的链烷酰基。

9. 根据权利要求 8 的化合物，其特征在于 R^3 代表乙酰基。

10. 根据权利要求 1 的化合物，其特征在于 A 代表 NH 基，B 代表 C=O 基，R^1 和 R^2 一起代表酮氢且 R^3 是氢。

11. 根据权利要求 1 的化合物，其特征在于 A 代表 C=O 基，B 代表 NH 基，R^1 和 R^2 一起代表酮氢且 R^3 是氢。

12. 制备通式（I）化合物



(I)

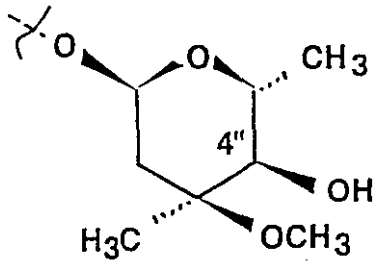
及其与无机和有机酸类的药物上可接受的加成盐的方法，

其中

A 代表 NH 基且 B 同时代表 C=O 基；或

A 代表 C=O 基且 B 同时代表 NH 基；

R^1 代表 OH 基、通式（II）的 L-克拉定糖基



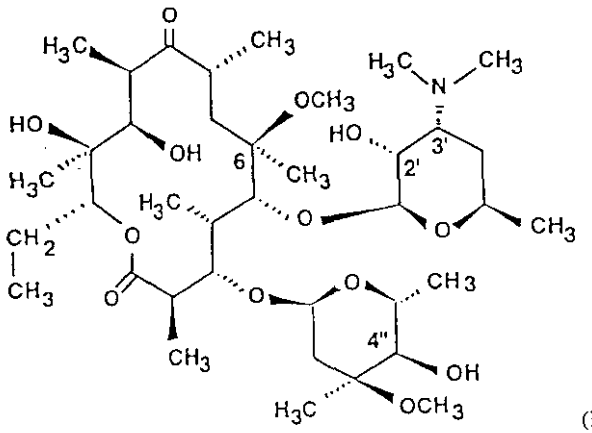
(II)

或与 R^2 一起代表酮；

R^2 代表氢或与 R^1 一起代表酮；

R^3 代表氢或 C_1 - C_4 的链烷酰基；

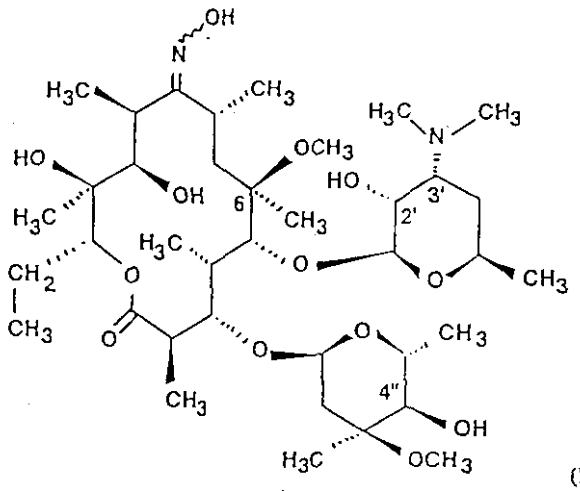
其特征在于使通式（III）的 6-O-甲基红霉素 A



(III)

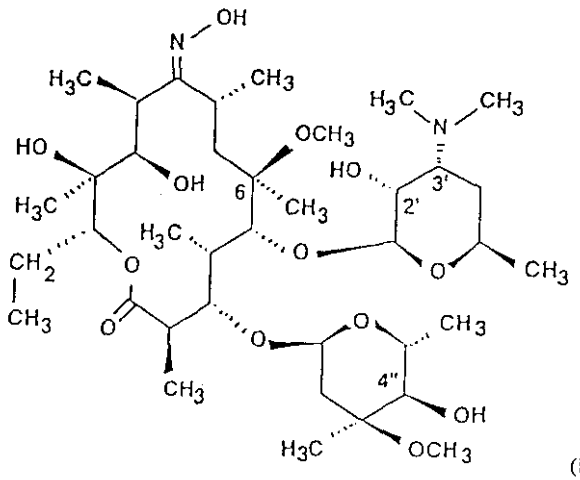
与盐酸羟基胺在有合适的无机或有机碱类的情况下进行反应，产生通

式（IV）的6-O-甲基红霉素A 9(E)-和9(Z)-肟类的混合物，



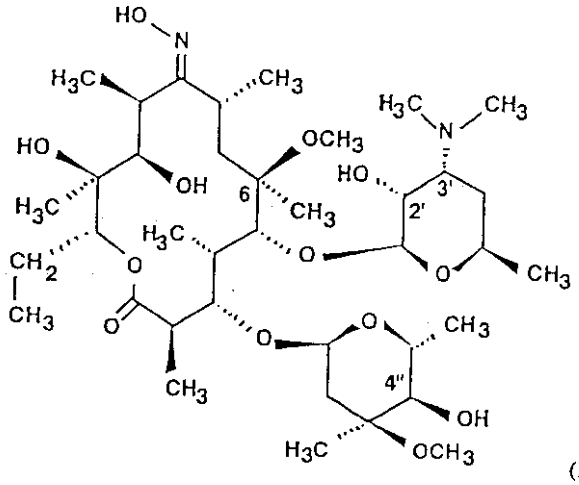
(IV)

如果合适，使用二氯甲烷-甲醇-浓氢氧化铵90: 9: 1.5的系统将上述混合物进行硅胶柱分离，产生色谱均相的具有Rf值为0.446的通式（IVa）的6-O-甲基红霉素A 9(E)-肟；



(IVa)

和色谱均相的具有Rf值为0.355的通式（IVb）的6-O-甲基红霉素A 9(Z)-肟；



(IVb)

且然后使上述产物与芳基磺酰卤类，优选与对甲苯磺酰氯在无机碱类，优选碳酸氢钠存在的情况下在溶剂或溶剂混合物，优选在丙酮-水的混合物中进行贝克曼重排反应，所述的溶剂或溶剂混合物对该反应来说是惰性的，就通式（IVa）的6-O-甲基红霉素A 9(E)-肟而言，产生通式（I）的化合物，其中A代表NH基，B代表C=O基，R^1代表L-克拉定糖基且R^2与R^3相同并代表氢；或就通式（IVb）的6-O-甲基红霉素A 9(Z)-肟而言，产生通式（I）的化合物，其中A代表C=O基，B代表NH基，R^1代表L-克拉定糖基，R^2与R^3相同并代表氢；

接着在室温下使上述产物与稀释的无机酸类，优选0.25N的盐酸发生作用，产生通式（I）的化合物，其中A代表NH基且B同时代表C=O基，或A代表C=O基且B同时代表NH基，R^1代表OH基且R^2与R^3相同并代表氢；

接下来使上述产物与带有至多达4个碳原子的羧酸酐类，优选与乙酸酐在惰性有机溶剂，优选在二氯甲烷中进行选择性酰化反应，产生通式（I）的化合物，其中A代表NH 基且B同时代表C=O基，或A代表C=O基且B同时代表NH基，R^1代表OH基，R^2是氢且R^3是乙酰基；

然后在10℃－室温下使上述产物与二酰亚胺类，优选与N,N-二甲氨基丙基-乙基-碳化二亚胺在有二甲亚砜和三氟乙酸吡啶鎓作为催化剂存在的情况下在惰性有机溶剂，优选在二氯甲烷中进行氧化反应，产生通式（I）的化合物，其中A代表NH 基且B同时代表C=O基，或

A 代表 C=O 基且 B 同时代表 NH 基，R^1 与 R^2 一起代表酮且 R^3 是乙酰基；

接着使上述产物在室温下在低级醇类，优选在甲醇中通过溶剂分解作用进行 2'-位上的脱酰反应，产生通式（I）的化合物，其中 A 代表 NH 基且 B 同时代表 C=O 基，或 A 代表 C=O 基且 B 同时代表 NH 基，R^1 与 R^2 一起代表酮且 R^3 是氢；

如果合适，接下来使上述产物与无机或有机酸类进行反应，产生其药物上可接受的加成盐。

13. 用于治疗人体和动物体中细菌感染的药物组合物，该组合物包括抗菌有效量的权利要求 1 的通式（I）的化合物或其药物上可接受的加成盐以及药物上可接受的载体。

14. 用于治疗人体和动物体中细菌感染的方法，该方法包括下列步骤：对人体或动物体根据需要给予抗菌有效量的权利要求 1 的通式（I）的化合物或其药物上可接受的加成盐以及药物上可接受的载体。

说　明　书

抗细菌活性的 15 元内酰胺类酮内酯

技术领域

国际专利分类：A61K31/70，C07H17/08

技术难题

本发明涉及红霉素 A 大环内酯抗菌素类的新型化合物。特别地，本发明涉及 6-O-甲基-8a-氮杂-8a-高-和 6-O-甲基-9a-氮杂-9a-高红霉素 A（homoerythromycin）类的新型 15 元环酮氮杂内酯类（ketoazalides）、涉及其制备的中间产物及方法、涉及其与无机或有机酸的药物上可接受的加成盐、涉及药物组合物的制备方法以及药物组合物用于治疗细菌感染的用途。

现有技术

红霉素是一种大环内酯抗菌素，其结构特征在于带有 C-9 酮和两种糖，L-克拉定糖和 D-德糖胺的 14 元内酯环，其中所述的糖在 C-3 和 C-5 位上以糖苷方式结合到所述分子的糖苷配基部分（McGuire：《抗菌素化疗法》（Antibiot. Chemother.）1952，2：281）。40 多年来一直认为红霉素 A 是治疗由象军团菌属、支原体属、衣原体属和螺杆菌属这样菌株的革兰氏阳性菌引起的呼吸道和生殖器感染的安全而有效的抗菌剂。在使用口服制剂后所观察到的生物利用度的改变、许多患者中的胃部产生不耐受性和在酸性介质中的活性缺失是使用红霉素 A 疗法中的主要缺陷。糖苷配基环的螺环化成功地被 C-9 酮或 C-6 和/或 C-12 位上的羟基的化学转化所抑制。因此，例如通过使红霉素 A 中的 C-9 酮与盐酸羟基胺发生肟化反应、使所得的 9(E)-肟发生贝克曼重排并还原由此形成的 6,9-亚氨醚（6-脱氧代-9-脱氧代-9a-氮杂-9a-高红霉素 A 6,9-环亚氨醚），获得 9-脱氧代-9a-氮杂-9a-高红霉

素 A，它是第一种半合成的带有 15 元氮杂内酯环的大环内酯（Kobrehel G.等，美国专利 4,328,334, 5/1982）。通过使按照埃谢韦勒-克莱克反应将新引入的桥环 9a-氨基还原性甲基化来合成 9-脱氧代-9a-甲基-9a-氮杂-9a-高红霉素 A（阿齐红霉素），它是一种新型氮杂内酯（azalide）抗菌素类的原型（Kobrehel G.等，BE 892 357, 7/1982）。除具有包括抗革兰氏阴性菌在内的广抗菌谱外，阿齐红霉素的特征还在于具有较长的生物半衰期、输送到施用部位的特异性机制和较短的治疗期。阿齐红霉素能够透入并蓄积在人体吞噬细胞内，从而导致对军团菌属、衣原体属和螺杆菌属菌株的胞内致病微生物起改进作用。

此外，公知红霉素 A 的 C-6/C-12 螺环化还受到糖苷配基环中的 C-6 羟基的 O-甲基化的抑制（Watanabe Y.等，美国专利 4,331,803, 5/1982）。通过使红霉素 A 与苄氧基羰基氯反应、随后使所得的 2'-O,3'-N-双(苄氧基羰基)-衍生物甲基化、消除保护基和 3'-N-甲基化而形成 6-O-甲基-红霉素 A（甲红霉素-克拉霉素）（Morimoto S.等《抗菌素杂志》（J. Antibiotics）1984, 37, 187）。如果与红霉素 A 比较，那么甲红霉素-克拉霉素在酸性介质中明显更为稳定并在体外表现出对革兰氏阳性菌菌株的活性增加（Kirst H. A.等《抗菌剂和化疗法》（Antimicrobial Agents and Chemother. ）1989, 1419）。

对 14 元大环内酯类的新近研究已经产生了新型大环内酯抗菌素即酮内酯类（ketolides），其特征在于 3-酮基取代了中性糖 L-克拉定糖，众所周知后者甚至在弱酸性介质中也具有不稳定性（Agouridas C.等，EP 596802 A1, 5/1994; Le Martret O., FR 2697524 A1, 5/94）。酮内酯类在体外表现出抗由抗性生物体诱发的 MLS（大环内酯、林肯酰胺和链阳菌素 B）的显著增强的活性（Jamjian C. 《抗菌剂化疗》（Antimicrob. Agents Chemother. ）1997, 41, 485）。

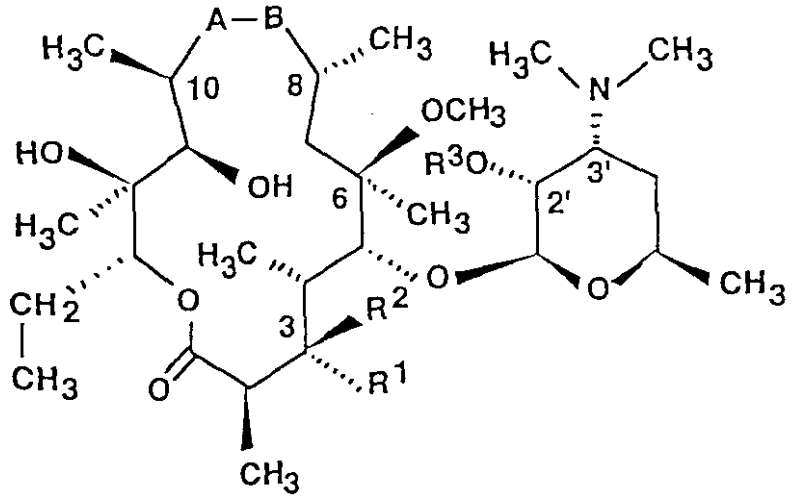
根据公知和确定的现有技术，迄今为止还没有描述过来自 6-O-甲基-8a-氮杂-8a-高-和 6-O-甲基-9a-氮杂-9a-高红霉素 A 类的 15 元环酮氮杂内酯类及其与无机或有机酸的药物上可接受的加成盐、其制备

方法及其中间产物以及药物组合物的制备方法及其用途。

本发明的目的以下列步骤为代表：使 6-O-甲基红霉素 A 的 9(E)-和 9(Z)-肟发生贝克曼重排、在由此获得的 8a-和 9a-内酰胺类中水解克拉定糖、保护德糖胺中 2'-位上的羟基、氧化 3-羟基并除去保护基，由此获得迄今为止还没有描述过的来自 6-O-甲基-8a-氮杂-8a-高-和 6-O-甲基-9a-氮杂-9a-高红霉素 A 类的新型 15 元环酮氮杂内酯类。

技术方案

按照如下步骤获得来自具有通式（I）的 6-O-甲基-8a-氮杂-8a-高-和 6-O-甲基-9a-氮杂-9a-高红霉素 A 类的新型 15 元环酮氮杂内酯类（ketoazalides）及其与无机和有机酸类的药物上可接受的加成盐：

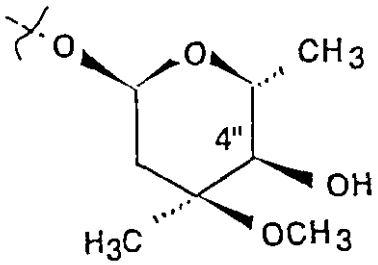


(I)

其中 A 代表 NH 基且 B 同时代表 C=O 基；或

A 代表 C=O 基且 B 同时代表 NH 基；

R^1 代表 OH 基、通式（II）的 L-克拉定糖基



(II)

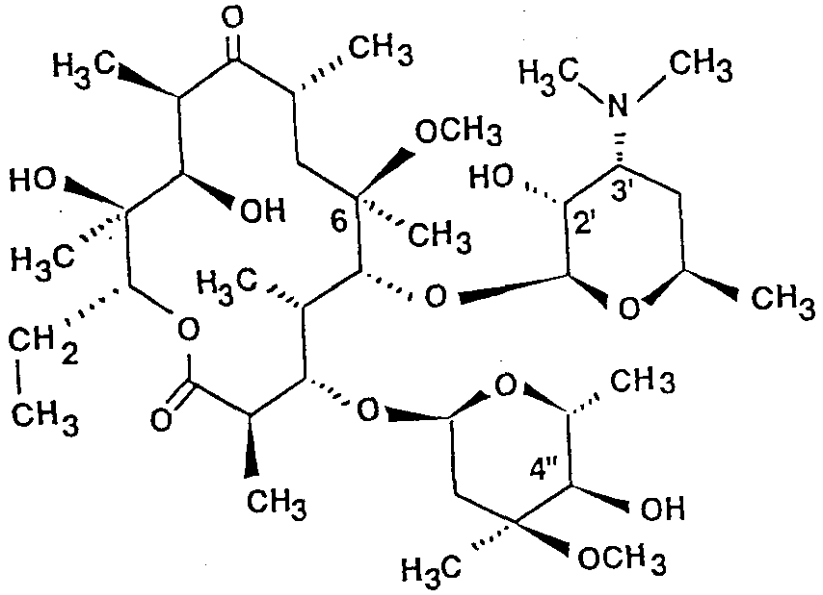
或与 R^2 一起代表酮；

R^2代表氢或与R^1一起代表酮;

R^3代表氢或C_1-C_4的链烷酰基;

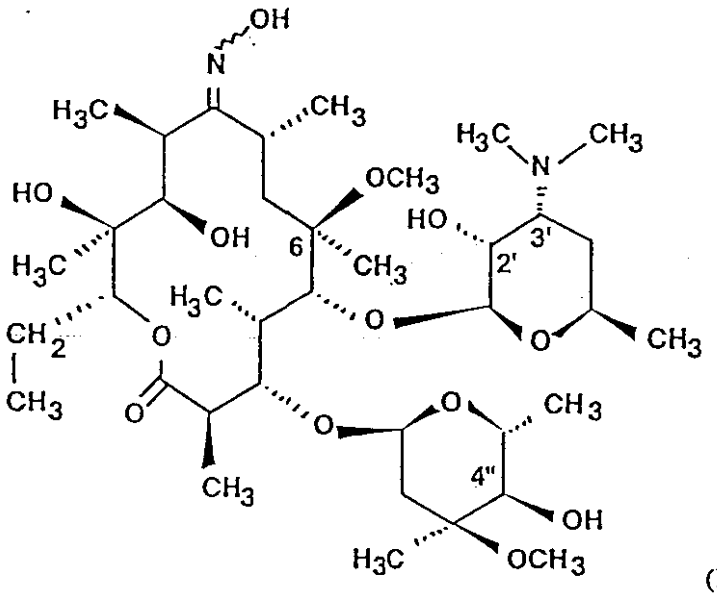
步骤 1:

本发明的第一步包括将通式（III）



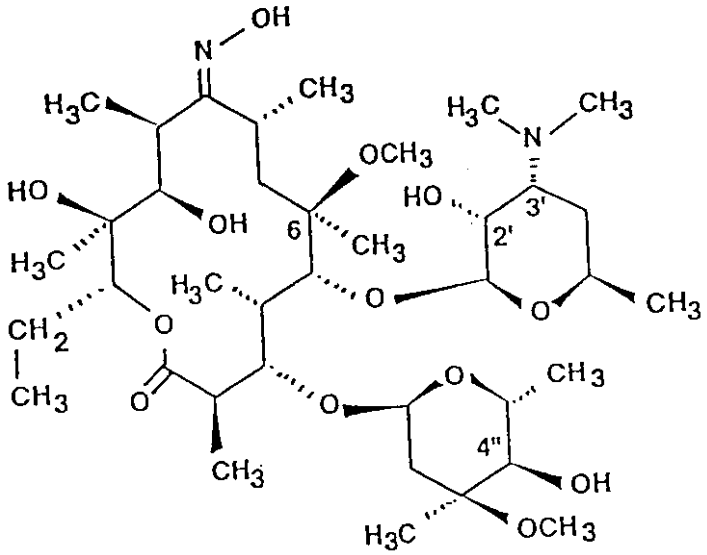
(III)

的 6-O-甲基红霉素 A(甲红霉素-克拉霉素)的 C-9 酮肟化成相应的肟。酮转化成肟是众所周知的反应，该反应通常用盐酸羟基胺在有合适的无机或有机碱类存在的情况下在合适的质子溶剂或非质子传递溶剂中进行。相对于甲红霉素-克拉霉素而言，以 1-15 等摩尔过量、优选以 10-等摩尔过量使用盐酸羟基胺。将碱金属氢氧化物、碳酸盐；碳酸氢盐和乙酸盐作为合适的碱类使用，而将 C_1-C_3的醇类作为溶剂使用。优选的碱是碳酸钠或乙酸钠且优选的溶剂是甲醇。一般来说，该反应在 0-80℃的温度下、优选在 65℃下进行 2 小时至几天，但基本上在 8-20 小时内完成。按照常规方式进行处理，例如通过在真空中蒸发溶剂；添加水与有机溶剂的混合物；随后在碱介质中、优选在 pH 8.0-10.0 下萃取。将二氯甲烷、氯仿、乙酸乙酯、乙醚和甲苯用作产物的萃取溶剂，氯仿是优选的萃取溶剂。通过分离有机层并蒸发溶剂来分离产物，从而产生约 1: 1 比例的通式（IV）



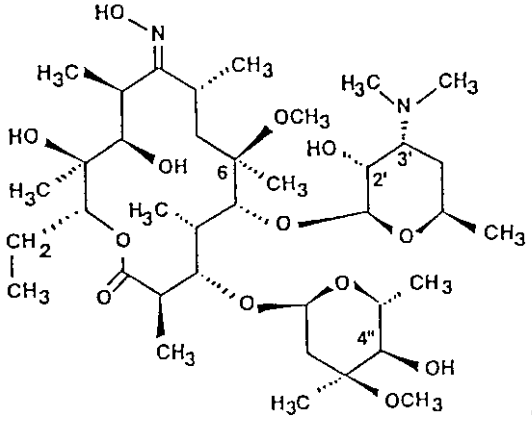
(IV)

的 6-O-甲基红霉素 A9(E)-和 9(Z)-肟的混合物。如果必要，通过使用二氯甲烷-甲醇-氢氧化铵 90: 9: 1.5 系统的硅胶柱层析来进行异构体的分离，从而产生色谱均相的具有 Rf 值为 0.446 的通式(IVa)的 6-O-甲基红霉素 A 9(E)-肟;



(IVa)

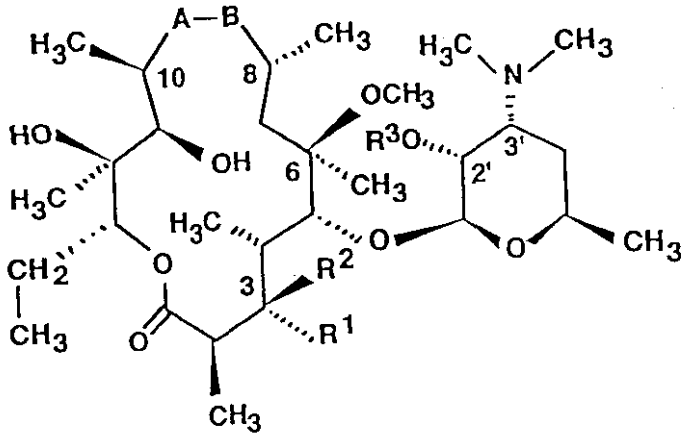
和色谱均相的具有 Rf 值为 0.355 的通式（ IVb）的 6-O-甲基红霉素 A 9(Z)-肟。



(IVb)

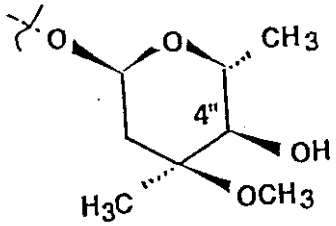
步骤 2:

通过贝克曼重排反应（参见“综合有机化学”，I. O. Sutherland（编辑），Pergamon Press，New York，1979，第 2 卷，398-400 和 967-968）而将通式（IVa）的 6-O-甲基红霉素 A 9(E)-肟转化成通式（I）的 6-O-甲基-红霉素 A，



(I)

其中 A 代表 NH 基；B 同时代表 C=O 基；R^1代表通式（II）的 L-克拉定糖基；



(II)

R^2和 R^3相同并代表氢。一般来说，酮肟的贝克曼重排产生甲酰胺或就环系而言产生内酰胺类。这种重排的机理包括肟羟基预转化成更好的离去基团，它在第二个反应步骤相对于离去基团反位的碳原子的同时迁移下被裂解。在水性介质中形成腈鎓离子作为中间产物，它与水反应生成一种合适的酰胺。

贝克曼重排反应在酸性、中性和碱性条件下进行。催化重排的常用酸性试剂包括浓硫酸、多磷酸、tionyl chloride、五氯化磷、二氧化硫和甲酸。由于大环内酯分子在酸性介质中的敏感性且特别是由于中性糖 L-克拉定糖易发生裂解，所以这些试剂不适于将通式（IVa）的肟重排成通式（I）的 6-O-甲基-9a-氮杂-9a-高红霉素 A，其中 A、B、R^1、R^2和 R^3具有上述含义。优选的情况是，通过最初用烷基磺酰卤类、芳基磺酰卤类或芳基磺酰酐类使肟羟基 O-磺化来进行肟（IVa）

的贝克曼重排。分离中间产物肟磺酸酯或通常在原位进行重排成所需产物。一般来说，磺化和重排在有有机或无机碱类存在的情况下进行。

催化肟（IVa）重排的优选磺化试剂包括甲磺酰氯、苯磺酰氯、4-乙酰氨基磺酰氯、对甲苯磺酰氯、苯磺酸和对甲苯磺酸的酐类。该反应在有无机碱类诸如碳酸氢钠或碳酸钾存在的情况下或在有有机碱类诸如吡啶、4-二甲氨基吡啶、三乙胺和 N,N-二异丙基-胺存在的情况下进行。合适的溶剂包括含水混合物诸如丙酮-水混合物和二噁烷-水混合物以及有机溶剂诸如二氯甲烷、氯仿、乙酸乙酯、乙醚、四氢呋喃、甲苯、乙腈和吡啶。一般来说，通过使用 1 - 3 等摩尔过量的磺化试剂并使用相同或更大等摩尔量的碱在-20 到 50℃的温度下进行该反应。通常将吡啶用作溶剂并同时用作碱。优选的情况是，肟（IVa）的贝克曼重排在丙酮-水混合物中使用双倍等摩尔过量的对甲苯磺酰氯和碳酸氢钠来进行。如果必要，通过使用二氯甲烷-甲醇-氢氧化铵 90: 9: 1.5 溶剂系统的硅胶柱层析来纯化产物，从而产生色谱均相的 6-O-甲基-9a-氮杂-9a-高红霉素 A。

按照与 9(E)-肟（IVa）类似的方式来进行式（IV_b）的 6-O-甲基红霉素 A 9(Z)-肟转化成通式（I）的 6-O-甲基-8a-氮杂-8a-高红霉素 A 的贝克曼重排，其中 A 代表 C=O 基，B 同时代表 NH 基；R^1代表通式（II）的 L-克拉定糖基；且 R^2和 R^3相同并代表氢。

步骤 3:

如果合适，使步骤 2 中通式（I）的 6-O-甲基-9a-氮杂-9a-高红霉素 A 或 6-O-甲基-8a-氮杂-8a-高红霉素 A 与强酸类、优选 0.25-1.5N 的盐酸在室温下的 10 - 30 小时内发生作用，其中 A、B、R^1、R^2和 R^3具有上述含义，从而产生通式（I）的 6-O-甲基-9a-氮杂-9a-高红霉素 A 或 6-O-甲基-8a-氮杂-8a-高红霉素 A 的 3-O-脱克拉定糖基-3-氧-衍生物，其中 A 代表 NH 基且 B 同时代表 C=O 基；或 A 代表 C=O 基且 B 同时代表 NH 基；R^1代表 OH 基；且 R^2和 R^3相同并代表氢。

步骤 4:

如果合适，使步骤 3 中通式（I）的 3-O-脱克拉定糖基-3-氧-6-O-甲基-9a-氮杂-9a-高红霉素 A 或 6-O-甲基-8a-氮杂-8a-高红霉素 A 与德糖胺中 2'-位上的羟基发生选择性酰化反应，其中 A、B、R^1、R^2 和 R^3 具有上述含义。在 0 - 30℃的温度下，通过使用带有多达 4 个碳原子的羧酸的酐类、优选使用乙酸酐在有无机或有机碱类存在的情况下在惰性有机溶剂中进行酰化反应，产生通式（I）的 3-脱克拉定糖基-3-氧-6-O-甲基-9a-氮杂-9a-高红霉素 A 2'-O-乙酸酯或 3-脱克拉定糖基-3-氧-6-O-甲基-8a-氮杂-8a-高红霉素 A 2'-O-乙酸酯，其中 A 代表 NH 基且 B 同时代表 C=O 基；或 A 代表 C=O 基且 B 同时代表 NH 基；R^1 代表 OH 基；R^2 是氢且 R^3 是乙酰基。将碳酸氢钠、碳酸钠、碳酸钾、三乙胺、吡啶、三丁胺用作合适的碱类，优选使用碳酸氢钠。将二氯甲烷、二氯乙烷、丙酮、吡啶、乙酸乙酯、四氢呋喃用作合适的惰性溶剂，优选使用二氯甲烷。

步骤 5:

如果合适，在 10℃ - 室温的温度下，按照改进的 Moffat-Pfitzner 方法，在有二甲亚砜和三氟乙酸吡啶鎓作为催化剂存在的情况下使步骤 4 中通式（I）的 3-脱克拉定糖基-3-氧-6-O-甲基-9a-氮杂-9a-高红霉素 A-2'O-乙酸酯或 3-脱克拉定糖基-3-氧-6-O-甲基-8a-氮杂-8a-高红霉素 A-2'O-乙酸酯与 N,N-二甲氨基丙基-乙基-碳化二亚胺在惰性有机溶剂、优选在二氯甲烷中进行糖苷配基环 C-3 位上羟基的氧化反应，其中 A、B、R^1、R^2 和 R^3 具有上述含义，产生通式（I）的 3-脱克拉定糖基-3-氧代-6-O-甲基-9a-氮杂-9a-高红霉素 A 2'-O-乙酸酯或 3-脱克拉定糖基-3-氧代-6-O-甲基-8a-氮杂-8a-高红霉素 A 2'-O-乙酸酯，其中 A 代表 NH 基且 B 同时代表 C=O 基；或 A 代表 C=O 基且 B 同时代表 NH 基；R^1 和 R^2 一起代表酮且 R^3 代表乙酰基。

步骤 6:

接下来使步骤 5 中通式（I）的 3-脱克拉定糖基-3-氧代-6-O-甲基-9a-氮杂-9a-高红霉素 A 2'-O-乙酸酯或 3-脱克拉定糖基-3-氧-6-O-甲基-8a-氮杂-8a-高红霉素 A 2'-O-乙酸酯在低级醇类、优选在甲醇中在室温至溶剂的回流温度下进行溶剂分解反应，其中 A、B、R^1、R^2和 R^3具有上述含义，产生通式(I)的 3-脱克拉定糖基-3-氧代-6-O-甲基-9a-氮杂-9a-高红霉素或 3-脱克拉定糖基-3-氧代-6-O-甲基-8a-氮杂-8a-高红霉素 A，其中 A 代表 NH 基且 B 同时代表 C=O 基；或 A 代表 C=O 基且 B 同时代表 NH 基；R^1和 R^2一起代表酮且 R^3代表氢。

通过使来自通式(I)的 6-O-甲基-8a-氮杂-8a-高红霉素 A 和 6-O-甲基-9a-氮杂-9a-高红霉素 A 类的新型化合物与至少等摩尔量的合适无机或有机酸诸如盐酸、氢碘酸、硫酸、磷酸、乙酸、丙酸、三氟乙酸、马来酸、柠檬酸、硬脂酸、琥珀酸、乙基琥珀酸、甲磺酸、苯磺酸、对甲苯磺酸和月桂基磺酸类在对反应来说是惰性的溶剂中进行反应来获得也属于本发明目的的药物上可接受的加成盐，其中 A、B、R^1、R^2和 R^3具有上述含义。如果加成盐在对反应来说是惰性的溶剂中是不溶的，那么通过过滤来分离所述的加成盐，在其它情况中通过用非溶剂沉淀或通过蒸发溶剂、多数情况下通过冻干法来分离加成盐。

通过根据 NCCLS 方案（临床实验室标准国家委员会，文件 M7-A2，第 10 卷，第 8 期，1990 和文件 M11-A2，第 10 卷，15，1991）的微量稀释法测定通式（I）的新型化合物（其中 A、B、R^1、R^2和 R^3具有上述含义）及其药物上可接受的与无机或有机酸类的加成盐对一系列标准测试微生物和临床分离物的体外抗菌作用。按照 NCCLS 方案（文件 M7-A2，表 3，M100-S4）、借助于对照菌株金黄色葡萄球菌 ATTC 29213（美国典型培养物保藏中心）来进行实验室方法的对照。

将来自实施例 3 的 6-O-甲基-8a-氮杂-8a-高红霉素 A 与阿齐红霉素、红霉素和甲红霉素-克拉霉素比较的对一系列标准测试微生物的体外抗菌作用列在表 1 中。

表 1: 6-O-甲基-8a-氮杂-8a-高红霉素 A（实施例 3）的体外抗菌作用与阿齐红霉素（Az）、红霉素（Er）和甲红霉素-克拉霉素（Cl）的比较

测试微生物	Az	Er	Cl	实施例 3
单核细胞增生利斯特氏菌 ATCC 7644	<0.125	<0.125	<0.125	<0.125
金黄色葡萄球菌 ATCC 25923	0.5	0.25	0.5	0.5
表皮葡萄球菌 ATCC 12228	1.0	0.25	0.25	0.5
粪肠球菌 ATCC 35550	0.5	1.0	0.25	1.0
肺炎链球菌 ATCC 6305	<0.125	<0.125	<0.125	<0.125
化脓链球菌 ATCC 19615	<0.125	<0.125	<0.125	<0.125
产气荚膜梭状芽孢杆菌 ATCC 13124	0.125	0.5	0.125	0.25
粘膜炎莫拉氏菌 ATCC 25238	<0.125	<0.125	<0.125	<0.125
胎儿弯曲杆菌 ATCC 19438	<0.125	<0.125	<0.125	<0.125
空肠弯曲杆菌 ATCC 33291	<0.125	<0.125	<0.125	<0.125
弗劳地氏柠檬酸杆菌 ATCC 8090	4.0	64.0	64.0	16.0
大肠杆菌 ATCC 25922	2.0	32.0	32.0	8.0
奇异变形菌 ATCC 12453	64.0	>128.0	>128.0	32.0
奇异变形菌 ATCC 43071	64.0	>128.0	>128.0	32.0
猪霍乱沙门氏菌 ATCC 13076	2.0	64.0	32.0	8.0
弗氏志贺氏菌 ATCC 12022	1.0	32.0	32.0	4.0
小肠结肠炎耶尔森氏菌 ATCC 9610	1.0	16.0	16.0	4.0
流感嗜血杆菌 ATCC 49247	0.5	2.0	4.0	1.0
流感嗜血杆菌 ATCC 49766	1.0	4.0	8.0	1.0
铜绿假单胞菌 ATCC 25619	64.0	>128.0	>128.0	32.0

通过下列实施例来举例说明本方法，它们不以任何方式来限定本发明的范围。

实施例 1

6-O-甲基红霉素 A9(E)-和 9(Z)-肟的制备

方法 A

将甲醇（100ml）中的 6-O-甲基红霉素 A（2.0g，0.003 摩尔）加热到回流温度，加入盐酸羟基胺（2.0g，0.03 摩尔）和碳酸钠（0.2g，0.002 摩尔）并在回流条件下加热该体系，同时搅拌 3 小时。然后再加入相同量的盐酸羟基胺和碳酸钠并在回流条件下将该体系进一步加热 6 小时。在减压条件下蒸发甲醇并加入水（200ml）和氯仿（100ml），将 pH 调元至 9.8，分离该层并再用氯仿将水层萃取两次。将合并的有机提取物用碳酸钾干燥、过滤并在减压下蒸发，得到 2.0g 的标题产物的混合物。通过使用二氯甲烷-甲醇-浓氢氧化铵 90: 9: 1.5 系统的硅胶柱层析来获得 0.63g 色谱均相的具有 Rf 值为 0.446 的 6-O-甲基红霉素 A9(E)-肟和 0.61g 色谱均相的具有 Rf 值为 0.355 的 6-O-甲基红霉素 A9(Z)-肟。

9(E)-肟:

Rf 0.418，乙酸乙酯-(正己烷)-二乙胺，100: 100: 20

IR (KBr) cm^{-1}: 3449, 2974, 2939, 2832, 2788, 1735, 1638, 1459, 1379, 1348, 1169, 1112, 1054, 1012, 957, 835, 755.

^1H NMR (300 MHz, $CDCl_3$) δ: 5.11 (H-13), 4.95 (H-1"), 4.45 (H-1'), 4.03 (H-5"), 3.77 (H-8), 3.76 ((H-3), 3.75 (H-11), 3.66 (H-5), 3.48 (H-5'), 3.33 (3"-OCH_3), 3.24 (H-2'), 3.10 (6-OCH_3), 3.03 (H-4"), 2.89 (H-2), 2.57 (H-10), 2.45 (H-3'), 2.37 (H-2"a), 2.31 /3'-$N(CH_3)_2$/, 1.93 (H-4), 1.93 (H-14a), 1.68 (H-4'a), 1.58 (H-2"b), 1.53 (H-7a), 1.48 (6-CH_3), 1.46 (H-14b), 1.31 (5"-CH_3), 1.25 (3"-CH_3), 1.23 (5'-CH_3), 1.20 (2-CH_3), 1.13 (10-CH_3), 1.13 (12-CH_3), 1.08 (4-CH_3), 1.00 (8-CH_3), 0.86 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.5 (C-1), 169.2 (C-9), 102.5 (C-1'), 95.7 (C-1"), 80.2 (C-5), 78.4 (C-6), 78.0 (C-3), 77.8 (C-4"), 76.5 (C-13), 73.8 (C-12), 72.4 (C-3"), 71.1 (C-2'), 70.0 (C-11), 68.2 (C-5'), 65.2 (C-5"), 64.9 (C-3'), 50.8 (6-OCH_3), 49.1 (3"-OCH_3), 44.7 (C-2), 40.1 /3'-$N(CH_3)_2$/, 38.7 (C-4), 37.0 (C-7), 34.6 (C-2"), 32.3 (C-10), 29.4 (C-4'), 24.9 (C-8), 21.1 (5'-CH_3), 21.0 (3"-CH_3), 20.8 (C-14), 19.6 (6-CH_3), 18.3 (5"-CH_3), 18.2 (8-CH_3), 15.7 (12-CH_3), 15.6 (2-CH_3), 14.6 (10-CH_3), 10.2 (15-CH_3), 8.8 (4-CH_3).

9(Z)-肟:

Rf 0.300, 乙酸乙酯-(正己烷)-二乙胺, 100: 100: 20

IR (KBr) cm^{-1}: 3433, 2973, 2939, 2832, 1733, 1638, 1459, 1379, 1348, 1286, 1169, 1114, 1054, 1011, 958, 892, 755.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.07 (H-13), 4.93 (H-1"), 4.43 (H-1'), 4.03 (H-5"), 3.98 (H-11), 3.77 (H-3), 3.62 (H-5), 3.48 (H-5'), 3.33 (3"-OCH_3), 3.21 (H-2'), 3.09 (6-OCH_3), 3.06 (H-4"), 2.88 (H-2), 2.74 (H-8), 2.65 (H-10), 2.45 (H-3'), 2.36 (H-2"a), 2.30/3'-$N(CH_3)_2$/, 1.96 (H-4), 1.94 (H-14a), 1.76 (H-14b), 1.67 (H-4'a), 1.59 (H-2"b), 1.58 (H-7a), 1.47 (H-7b), 1.38 (6-CH_3), 1.32 (10-CH_3), 1.31 (5"-CH_3), 1.25 (3"-CH_3), 1.24 (5'-CH_3), 1.19 (2-CH_3), 1.14 (12-CH_3), 1.07 (4-CH_3), 1.06 (8-CH_3), 0.84 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.0 (C-1), 167.4 (C-9), 102.7 (C-1'), 96.0 (C-1"), 80.4 (C-5), 78.7 (C-6), 78.5 (C-3), 77.8 (C-4"), 76.9 (C-13), 74.7 (C-12), 72.6 (C-3"), 70.9 (C-2'), 70.3 (C-11), 68.4 (C-5'), 65.5 (C-5"), 65.3 (C-3'), 50.0 (6-OCH_3), 49.3 (3"-OCH_3), 45.0 (C-2), 41.0 /3'-$N(CH_3)_2$/, 38.9 (C-4), 37.0 (C-7), 35.6 (C-8), 34.7 (C-2"), 34.1 (C-10), 28.9 (C-4'), 21.3 (3"-CH_3), 21.2 (5'-CH_3), 21.1 (C-14), 19.7 (6-CH_3), 19.6 (8-CH_3), 18.5 (5"-CH_3), 16.4 (12-CH_3), 15.7 (2-CH_3), 10.7 (10-CH_3), 10.4 (15-CH_3), 9.8 (15-CH_3).

方法 B

将甲醇（800ml）中的 6-O-甲基红霉素 A（10.8g，0.014 摩尔）加热到回流温度，然后将盐酸羟基胺（27.0g，0.388 摩尔）和无水乙酸钠（15.2g，0.183 摩尔）在 10 小时之内分 4 部分加入到反应溶液中并在回流条件下加热该体系，同时进一步搅拌 8 小时。在减压条件下蒸发甲醇、加入水（1500ml）和二氯甲烷（200ml）并通过在 pH 5.0 和 9.8 时的梯度萃取来萃取该反应体系。将 pH 为 9.8 的合并的有机提取物用碳酸钾干燥、过滤并在减压下蒸发，得到 9.5g 的标题产物的混合物。通过使用二氯甲烷-甲醇-浓氢氧化铵 90: 9: 1.5 系统的硅胶柱层析来获得色谱均相的 6-O-甲基红霉素 A9(E)-肟和 6-O-甲基红霉素 A9(Z)-肟，其理化常数与方法 A 中那些物质的理化常数相同。

实施例 2

6-O-甲基红霉素 A 9(E)-肟的贝克曼重排

将来自实施例 1 的 6-O-甲基红霉素 A 9(E)-肟（4.0g，0.005 摩尔）溶于丙酮（130ml）并将该溶液冷却至 0－5℃。随后，在搅拌下在 1 小时内向其中逐滴加入对甲苯磺酰氯（2.6g，0.01 摩尔）的丙酮（40ml）溶液和碳酸氢钠（0.830g，0.01 摩尔）的水（130ml）溶液。在室温下将该反应混合物搅拌 8 小时，在减压下蒸发丙酮并向该水溶液中加入氯仿（40ml），由此通过在 pH 5.0 和 9.0 时的梯度萃取来萃取该反应体系。蒸发 pH 9.0 时的合并的有机萃取物，从而得到 2.8g 的 6-O-甲基-9a-氮杂-9a-高红霉素 A。

Rf 0.218，乙酸乙酯-(正己烷)-二乙胺，100: 100: 20

IR (KBr) cm^{-1}: 3449, 2974, 2939, 2834, 1734, 1706, 1659, 1534, 1459, 1379, 1274, 1169, 1111, 1053, 1011, 958.

^1H NMR (300 MHz, $CDCl_3$) δ: 6.12 (9a-CONH), 4.85 (H-1"), 4.68 (H-13), 4.45 (H-

1'), 4.21 (H-3), 4.16 (H-10), 4.07 (H-5"), 3.75 (H-5), 3.49 (H-5'), 3.34 (3"-OCH_3), 3.32 (6-OCH_3), 3.22 (H-11), 3.20 (H-2'), 3.04 (H-4"), 2.83 (H-2), 2.43 (H-3'), 2.38 (H-2"a), 2.30 /3'-$N(CH_3)_2$/, 2.22 (H-8), 2.07 (H-7a), 1.87 (H-4), 1.87 (H-14a), 1.67 (H-4'a), 1.57 (H-2"b), 1.57 (H-14b), 1.36 (6-CH_3), 1.33 (H-7b), 1.32 (5"-CH_3), 1.25 (3"-CH_3), 1.24 (H-4'b), 1.23 (5'-CH_3), 1.23 (2-CH_3), 1.18 (12-CH_3), 1.16 (10-CH_3), 1.09 (8-CH_3), 1.02 (4-CH_3), 0.89 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.5 (C-1), 177.3 (C-9), 102.5 (C-1'), 94.9 (C-1"), 79.1 (C-6), 78.5 (C-5), 77.7 (C-4"), 77.7 (C-13), 75.9 (C-3), 73.9 (C-12), 72.5 (C-3"), 72.6 (C-11), 70.7 (C-2'), 68.2 (C-5'), 65.3 (C-5"), 65.1 (C-3'), 51.0 (6-OCH_3), 49.1 (3"-OCH_3), 45.1 (C-10), 44.5 (C-2), 41.3 (C-4), 40.0 /3'-$N(CH_3)_2$/, 39.6 (C-7), 35.4 (C-8), 34.4 (C-2"), 28.8 (C-4'), 21.1 (5'-CH_3), 21.0 (3"-CH_3), 20.3 (C-14), 20.2 (6-CH_3), 19.1 (8-CH_3), 18.1 (5"-CH_3), 15.9 (12-CH_3), 14.6 (2-CH_3), 13.4 (10-CH_3), 10.7 (15-CH_3), 8.7 (4-CH_3).

实施例 3

6-O-甲基红霉素 A 9(Z)-肟的贝克曼重排

将来自实施例 1 的 6-O-甲基红霉素 A 9(Z)-肟（1.4g，0.002 摩尔）溶于丙酮（50ml）并将该溶液冷却至 0－5℃。随后在搅拌下在 1 小时内向其中逐滴加入对甲苯磺酰氯（1.84g，0.014 摩尔）的丙酮（56ml）溶液和碳酸氢钠（1.16g，0.014 摩尔）的水（180ml）溶液。在室温下将该反应混合物搅拌 2 小时，在减压下蒸发丙酮并向该水溶液中加入氯仿（70ml），由此通过在 pH 5.0 和 9.0 时的梯度萃取来萃取该反应体系。蒸发 pH 9.0 时的合并的有机萃取物，从而得到 0.80g 的产物，如果合适，通过使用二氯甲烷-甲醇-浓氢氧化铵 90: 9: 1.5 系统的硅胶柱层析来纯化该产物，得到 6-O-甲基-8a-氮杂-8a-高红霉素 A，它具有下列理化常数:

Rf 0.152, 乙酸乙酯-(正己烷)-二乙胺, 100: 100: 20

IR (KBr) cm^{-1}: 3442, 2974, 2938, 2833, 1736, 1648, 1535, 1459, 1379, 1284, 1169, 1110, 1055, 1013, 960, 902.

^1H NMR (300 MHz, $CDCl_3$) δ: 5.78 (8a-CONH), 5.02 (H-1"), 4.96 (H-13), 4.41 (H-1'), 4.19 (H-8), 4.02 (H-5"), 3.96 (H-3), 3.69 (H-5), 3.51 (H-11), 3.47 (H-5'), 3.32 (3"-OCH_3), 3.18 (H-2'), 3.16 (6-OCH_3), 3.02 (H-4"), 2.68 (H-2), 2.44 (H-3'), 2.35 (H-2"a), 2.29 /3'-$N(CH_3)_2$/, 2.22 (H-10), 1.92 (H-4), 1.91 (H-14a), 1.68 (H-7a), 1.64 (H-4'a), 1.56 (H-2"b), 1.53 (H-7b), 1.47 (H-14b), 1.39 (6-CH_3), 1.29 (5"-CH_3), 1.24 (3"-CH_3), 1.23 (5'-CH_3), 1.20 (2-CH_3), 1.18 (10-CH_3), 1.13 (12-CH_3), 1.13 (8-CH_3), 1.07 (4-CH_3), 0.88 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.0 (C-1), 174.3 (C-9), 102.9 (C-1'), 95.1 (C-1"), 80.1 (C-5), 78.6 (C-6), 77.9 (C-4"), 77.2 (C-3), 76.7 (C-13), 74.0 (C-12), 72.6 (C-3"), 70.4 (C-2'), 70.1 (C-11), 68.7 (C-5'), 65.4 (C-3'), 65.2 (C-5"), 51.5 (6-OCH_3), 49.1 (3"-OCH_3), 45.4 (C-2), 42.6 (C-7), 42.1 (C-4), 41.8 (C-10), 40.6 (C-8), 40.0/3'-$N(CH_3)_2$/, 34.5 (C-2"), 28.3 (C-4'), 23.5 (6-CH_3), 21.3 (C-14), 21.2 (12-CH_3), 21.1 (5'-CH_3), 21.1 (3"-CH_3), 17.9 (5"-CH_3), 15.8 (8-CH_3), 14.8 (2-CH_3), 10.8 (15-CH_3), 9.2 (10-CH_3), 9.1 (4-CH_3).

实施例 4

3-脱克拉定糖基-3-氧-6-O-甲基-9a-氮杂-9a-高红霉素 A

将来自实施例 2 的物质(1.5g, 0.002 摩尔)溶于 0.25N 盐酸(40ml)并在室温下将该溶于放置稳定 24 小时。向该反应混合物中加入二氯甲烷(30ml)(pH 1.8)并用浓氨水将该混合物的 pH 调元至 9.0, 分离该层并再用二氯甲烷(301)将水层萃取两次。将合并的有机萃取物用 10%的碳酸氢钠水溶液和水洗涤且然后蒸发, 得到 1.3g 的粗产物, 如果合适, 通过使用二氯甲烷-甲醇-浓氢氧化铵 90: 9: 1.5 系统的硅胶柱层析来纯化该产物。从 0.9g 的粗产物中分离出 0.65g 的色谱均相的

3-脱克拉定糖基-3-氧-6-O-甲基-9a-氮杂-9a-高红霉素 A，它具有下列理化常数:

Rf 0.152，乙酸乙酯-(正己烷)-二乙胺，100: 100: 20

IR (KBr) cm^{-1}: 3438, 2973, 2939, 2879, 2788, 1702, 1658, 1535, 1458, 1373, 1329, 1270, 1173, 1112, 1050, 985, 958, 937.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16 (9a-CONH), 4.63 (H-13), 3.81 (H-5), 4.45 (H-1'), 4.13 (H-10), 3.78 (H-3), 3.55 (H-5'), 3.30 (6-OCH_3), 3.25 (H-2'), 3.16 (H-11), 2.66 (H-2), 2.51 (H-3'), 2.39 (H-8), 2.26/3'-$N(CH_3)_2$/, 2.05 (H-4), 1.92 (H-14a), 1.84 (H-7a), 1.68 (H-4'a), 1.57 (H-14b), 1.43 (H-7b), 1.38 (6-CH_3), 1.33 (2-CH_3), 1.26 (5'-CH_3), 1.26 (H-4'b), 1.20 (10-CH_3), 1.12 (12-CH_3), 1.11 (8-CH_3), 1.01 (4-CH_3), 0.91 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.3 (C-1), 176.9 (C-9), 106.4 (C-1'), 88.1 (C-5), 79.1 (C-6), 78.7 (C-13), 78.0 (C-3), 73.8 (C-12), 73.9 (C-11), 70.2 (C-2'), 69.7 (C-5'), 65.4 (C-3'), 49.9 (6-OCH_3), 45.6 (C-10), 43.9 (C-2), 40.8 (C-7), 39.9/3'-$N(CH_3)_2$, 35.6 (C-4), 32.8 (C-8), 27.8 (C-4'), 20.9 (5'-CH_3), 20.5 (C-14), 18.3 (6-CH_3), 17.4 (8-CH_3), 15.8 (12-CH_3), 15.9 (2-CH_3), 14.8 (10-CH_3), 10.7 (15-CH_3), 7.5 (4-CH_3).

实施例 5

3-脱克拉定糖基-3-氧-6-O-甲基-8a-氮杂-8a-高红霉素 A

按照实施例 4 中所述的方法，从实施例 3 的物质（1.5g，0.002 摩尔）获得 1.2g 的粗产物，如果合适，通过使用二氯甲烷-甲醇-浓氢氧化铵 90: 9: 1.5 系统的硅胶柱层析来纯化该产物，得到色谱均相的 3-脱克拉定糖基-3-氧-6-O-甲基-8a-氮杂-8a-高红霉素 A，它具有下

列理化常数:

Rf 0.195, 氯仿-甲醇-氢氧化铵, 6: 1: 0.1

IR (KBr) cm^{-1}: 3438, 2974, 2939, 2788, 1733, 1648, 1535, 1458, 1378, 1263, 1165, 1113, 1075, 1050, 985, 958, 937.

^1H NMR (300 MHz, $CDCl_3$) δ: 5.58 (9a-CONH), 5.09 (H-13), 4.38 (H-1'), 3.76 (H-5), 3.92 (H-8), 3.80 (H-3), 2.64 (H-2), 3.54 (H-5'), 3.47 (H-11), 3.25 (H-2'), 2.11 (H-4), 3.12 (6-OCH_3), 2.48 (H-3'), 2.38 (H-10), 2.25/3'-$N(CH_3)_2$/, 1.94 (H-14a), 2.11 (H-7a), 1.66 (H-4'a), 1.51 (H-7b), 1.50 (H-14b), 1.31 (2-CH_3), 1.39 (6-CH_3), 1.12 (4-CH_3), 1.26 (5'-CH_3), 1.26 (H-4'b), 1.20 (10-CH_3), 1.25 (8-CH_3), 1.13 (12-CH_3), 0.88 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.0 (C-1), 174.4 (C-9), 106.1 (C-1'), 89.6 (C-5), 77.3 (C-6), 75.8 (C-13), 78.3 (C-3), 74.3 (C-12), 70.3 (C-11), 69.9 (C-2'), 69.4 (C-5'), 64.9 (C-3'), 49.7 (6-OCH_3), 42.1 (C-10), 43.8 (C-2), 41.7 (C-7), 39.9/3'-$N(CH_3)_2$/, 35.2 (C-4), 42.4 (C-8), 27.4 (C-4'), 22.3 (5'-CH_3), 20.9 (C-14), 20.4 (6-CH_3), 20.5 (8-CH_3), 15.7 (12-CH_3), 15.2 (2-CH_3), 9.5 (10-CH_3), 10.1 (15-CH_3), 7.50 (4-CH_3).

实施例 6

3-脱克拉定糖基-3-氧-6-O-甲基-9a-氮杂-9a-高红霉素 A 2'-O-乙酸酯

向来自实施例 4 的 3-脱克拉定糖基-3-氧-6-O-甲基-9a-氮杂-9a-高红霉素 A (0.750g, 0.0012 摩尔) 的二氯甲烷 (25ml) 溶液中加入碳酸氢钠 (0.440g, 0.0052 摩尔) 和乙酸酐 (0.128ml, 0.0013 摩尔) 并在室温下搅拌 3 小时。向该反应混合物中加入饱和碳酸氢钠溶液 (30ml), 分离该层并用二氯甲烷 (2 ×20ml) 再次提取含水部分。将合并的有机提取物依次用饱和碳酸氢钠溶液和水洗涤并蒸发, 得到

0.750g 的粗标题产物，它具有下列理化常数:

Rf 0.403, 氯仿-甲醇-浓氢氧化铵, 6: 1: 0.1

IR (KBr) cm^{-1}: 3455, 2974, 2940, 2880, 2787, 1748, 1702, 1658, 1540, 1459, 1376, 1239, 1173, 1112, 1061, 986, 958, 937, 904.

实施例 7

3-脱克拉定糖基-3-氧-6-0-甲基-8a-氮杂-8a-高红霉素 A 2'-0-乙酸酯

向来自实施例5的3-脱克拉定糖基-3-氧-6-0-甲基-9a-氮杂-9a-高红霉素 A（1.5g, 0.0024 摩尔）的二氯甲烷（40ml）溶液中加入碳酸氢钠（0.88g, 0.01 摩尔）和乙酸酐（0.250ml, 0.0025 摩尔）且然后按照实施例 6 中所述的方法获得 1.4g 的标题产物，它具有下列理化常数:

Rf 0.423, 氯仿-甲醇-浓氢氧化铵, 6: 1: 0.1

IR (KBr) cm^{-1}: 3394, 2972, 2939, 2784, 1736, 1649, 1542, 1459, 1376, 1262, 1165, 1085, 1059, 986, 958, 904.

实施例 8

3-脱克拉定糖基-3-氧代-6-0-甲基-9a-氮杂-9a-高红霉素 A

向来自实施例6的3-脱克拉定糖基-3-氧-6-0-甲基-9a-氮杂-9a-高红霉素 A 2'-0-乙酸酯（0.760g, 0.0012 摩尔）的二氯甲烷（15ml）溶液中加入二甲亚砜（1.27ml）和 N,N-二甲氨基丙基-乙基-碳化二亚胺（1.335g, 0.007 摩尔）。将该反应混合物冷却至 15℃且然后在不断搅拌和维持该温度的条件下在30分钟内逐滴逐步加入三氟乙酸吡啶鎓（1.37g, 0.007 摩尔）溶于二氯甲烷（5ml）所得到的溶液。将该反应混合物的温度逐步升高到室温，持续进一步搅拌 3 小时并通过加入饱和 NaCl 溶液（20ml）和二氯甲烷（20ml）来中止反应。在用 2N NaOH

将该反应混合物碱化至 pH 9.5 后，将其用 CH_2Cl_2 萃取，将有机萃取物依次用饱和 NaCl、$NaHCO_3$ 溶液和水洗涤且然后用 K_2CO_3 干燥。在过滤并在减压下蒸发二氯甲烷后，获得 0.800g 的油状残余物。在室温下和 24 小时内使该油状残余物进行甲醇分解（30ml 甲醇）。在减压下蒸发甲醇并通过使用二氯甲烷-甲醇-浓氢氧化铵 90: 9: 0.5 溶剂系统的低压硅胶柱层析来纯化获得残余物（0.625g）。通过蒸发具有 Rf 值为 0.235 的合并的萃取物来获得色谱均相的标题产物，它具有下列理化常数:

Rf 0.235，二氯甲烷-甲醇-浓氢氧化铵，90: 9: 0.5

IR (KBr) cm^{-1}: 3438, 2975, 2939, 2878, 2787, 1744, 1655, 1530, 1458, 1380, 1340, 1304, 1169, 1111, 1075, 1051, 986, 959, 940.

^1H NMR (300 MHz, $CDCl_3$) δ: 6,63 (9a-CONH), 4.64 (H-13), 4.49 (H-5), 4.41 (H-1'), 4.20 (H-10), 3.90 (H-2), 3.64 (H-5'), 3.34 (H-11), 3.20 (H-2'), 3.07 (6-OCH_3), 3.02 (H-4), 2.51 (H-3'), 2.30 (H-8), 2.27/3'-$N(CH_3)_2$/, 1.94 (H-14a), 1.94 (H-7a), 1.69 (H-4'a), 1.63 (H-14b), 1.42 (H-7b), 1.40 (2-CH_3), 1.30 (5'-CH_3), 1.29 (4-CH_3), 1.26 (6-CH_3), 1.25 (H-4'b), 1.22 (12-CH_3), 1,19 (10-CH_3), 1.10 (8-CH_3), 0.91 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8 (C-3), 177.3 (C-1), 173.8 (C-9), 102.6 (C-1'), 79.3 (C-13), 78.4 (C-6), 74.4 (C-5), 73.9 (C-12), 73.1 (C-11), 70.0 (C-2'), 69.1 (C-5'), 65.5 (C-3'), 50.1 (6-OCH_3), 49.0 (C-2), 46.2 (C-4), 45.3 (C-10), 40.3 (C-7), 40.0/3'-$N(CH_3)_2$/, 34.6 (C-8), 28.3 (C-4'), 21.0 (6-CH_3), 20.7 (C-14), 19.6 (5'-CH_3), 18.6 (8-CH_3), 15.9 (12-CH_3), 14.1 (2-CH_3), 13.9 (10-CH_3), 13.9 (4-CH_3), 10.7 (15-CH_3).

实施例 9

3-脱克拉定糖基-3-氧代-6-O-甲基-8a-氮杂-8a-高红霉素 A

向来自实施例 7 的 3-脱克拉定糖基-3-氧-6-O-甲基-8a-氮杂-8a-高红霉素 A 2'-O-乙酸酯（1.4g，0.0022 摩尔）的二氯甲烷（30ml）溶液中加入二甲亚砜（2.5ml）和 N,N-二甲氨基丙基-乙基-碳化二亚胺（2.7g，0.014 摩尔）。将该反应混合物冷却至 15℃且然后在不断搅

拌和维持该温度的条件下在 30 分钟内逐滴逐步加入三氟乙酸吡啶鎓（2.7g，0.014 摩尔）溶于二氯甲烷（10ml）所得到的溶液。按照实施例 8 中所述的方法获得 1.1g 的标题产物，它具有下列理化常数:

IR (KBr) cm^{-1}: 3435, 2975, 2939, 2879, 2788, 1746, 1648, 1542, 1458, 1379, 1339, 1302, 1166, 1111, 1076, 1052, 989, 960, 918.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.89 (9a-CONH), 5.08 (H-13), 4.42 (H-1'), 4.27 (H-5), 4.03 (H-8), 3.78 (H-2), 3.60 (H-5'), 3.58 (H-11), 3.18 (H-2'), 3.05 (H-4), 2.91 (6-OCH_3), 2.49 (H-3'), 2.39 (H-10), 2.27/3'-$N(CH_3)_2$/, 1.96 (H-14a), 1.68 (H-7a), 1.68 (H-4'a), 1.50 (H-14b), 1.41 (2-CH_3), 1.32 (6-CH_3), 1.30 (4-CH_3), 1.25 (5'-CH_3), 1.23 (H-4'b), 1.20 (10-CH_3), 1.19 (8-CH_3), 1.17 (12-CH_3), 0.88 (15-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.2 (C-3), 170.0 (C-9), 174.6 (C-1), 103.1 (C-1'), 78.2 (C-6), 77.9 (C-5), 77.5 (C-13), 74.1 (C-12), 70.6 (C-11), 70.0 (C-2'), 69.1 (C-5'), 65.5 (C-3'), 50.5 (6-OCH_3), 50.4 (C-2), 47.6 (C-4), 42.2 (C-10), 42.1 (C-7), 41.6 (C-8), 39.9/3'-$N(CH_3)_2$/, 28.0 (C-4'), 22.8 (8-CH_3), 21.2 (C-14), 20.8 (5'-CH_3), 20.1 (6-CH_3), 16.1 (12-CH_3), 15.4 (2-CH_3), 14.4 (4-CH_3), 10.5 (15-CH_3), 10.1 (10-CH_3).