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DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Ref: **Expediente No. 01.000.287**
Solicitud de Patente de Invención titulada: "COMPUESTOS ANTIBIOTICOS DE AZALIDA".
Solicitante: PFIZER PRODUCTS INC

RESPUESTA AL OFICIO No. 14620 NOTIFICADO POR FIJACIÓN EN LISTA No. 455, DE FECHA 21 DE DICIEMBRE DE 2006.
(REQUERIMIENTO ARTÍCULO 46)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 46 de la Decisión 486:

1. Presento copia completa del siguiente documento exigido por el Examinador en el examen de búsqueda de anterioridades, según lo previsto en el Artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina:

DJOKIC S ET AL: "ERYTHROMYCIN SERIES. PART 11. RING EXPANSION OF ERYTHROMYCIN A OXIME BY THE BECKMANN REARRANGEMENT" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1,CHEMICAL SOCIETY. LETCHWORTH,GB, no. 11, 1986, pages 1881-1890, XP002077691 ISSN: 1472-7781

Atentamente,

CARLOS R. OLARTE
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Anexo: Artículo mencionado.

Erythromycin Series. Part 11.[1] Ring Expansion of Erythromycin A Oxime by the Beckmann Rearrangement

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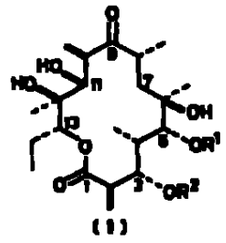
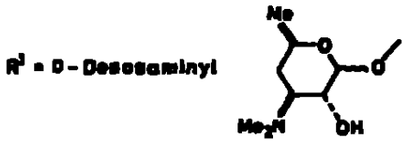
The synthesis of 10-dihydro-10-deoxo-11-azaerythromycin A (11) by the Beckmann rearrangement of erythromycin A oxime (2) and reduction of the imino ether so obtained (5) is described. The structure elucidation of the new ring-expanded semisynthetic erythromycins (5) and (11) has been established on the basis of their analytical and spectral data and acid-catalysed degradation into the aglycones (7) and (13), respectively. Finally, the complete structure of ring-expanded erythronolides (7) and (13) has been determined by *X*-ray crystallography.

Erythromycin A (1)[2–4] is a macrolide antibiotic characterised by a 14-membered lactone ring, erythronolide A,[5,6] with a 9-oxo group. In efforts to modify its biological and/or pharmacodynamic properties numerous derivatives of (1) have been prepared, including 9-amino derivatives.[7] Of the nucleophiles

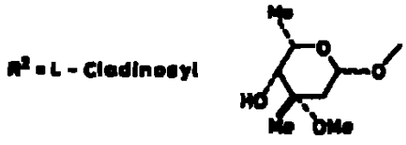


(1)

Erythromycin A



R^1 = D-Desosaminyl



R^2 = L-Cladinosyl

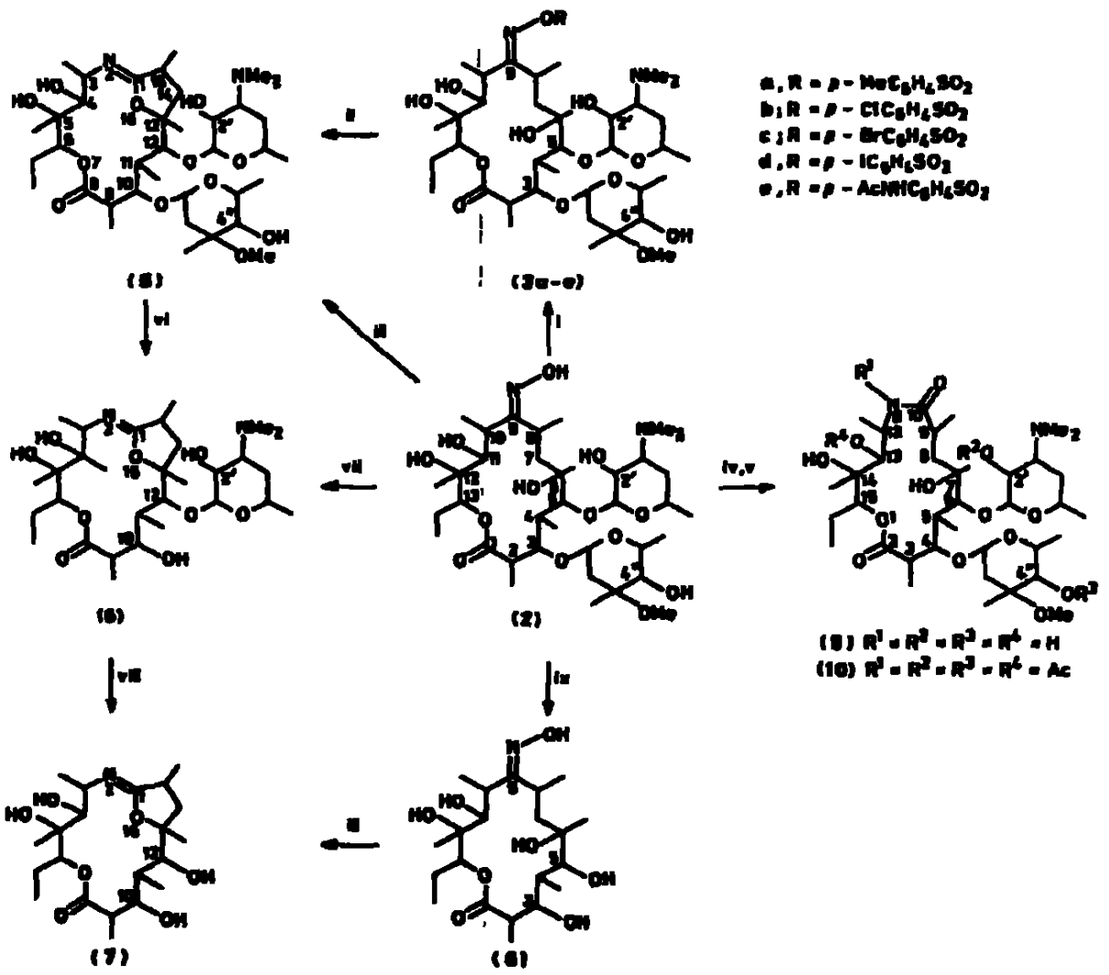
with low steric requirements which were allowed to react at the 9-carbonyl centre of (1), hydroxylamine was the most interesting[8,9] in that it yielded erythromycin A oxime, a substrate with potential for further modification of the aglycone ring. On the basis of its configurational analysis it was suggested that the *E*-isomer (2) predominated in the product.[7] To develop a method for the efficient introduction of the nitrogen atom into the 14-membered ring we studied the Beckmann rearrangement of 9-oxime (2) and conversion of the product (5) so obtained into a secondary amine (11).[10] Such erythromycin derivatives are the first of their kind in the literature.

Results and Discussion

It is well known that *O*-arylsulphonyloximes, especially *p*-tosyl compounds, are very suitable precursors in the Beckmann rearrangement of ketoximes.[11] By the reaction of the 9-oxime (2) with *para*-substituted arene sulphonyl chlorides in dry acetone in the presence of sodium hydrogen carbonate, a series of new erythromycin A 9-*O*-arylsulphonyloximes (3a—e) was prepared (Scheme 1).

The structure of these compounds was assigned from their spectroscopic properties. In particular, the i.r. spectrum of (3a) (Table 1) revealed new bands at 1 680 (C=N) and 1 600, 810, and 680 cm^{-1} (*p*-Ph). The ^1H n.m.r. spectrum displayed signals at δ 2.35 (s, 3 H, *p*-Me), 3.36 (s, 3 H, OMe), and 7.36 (q, 4 H, *p*-Ph). Apart from a typical chemical shift for dimethylamino protons of (1) (lit.,[12] 2.29 p.p.m.), (3a) showed a signal at δ 2.83 (s, 6 H) which corresponded to the *N*-methyl hydrogens of the protonated dimethylamine;[13] this indicated formation of the hydrochloric salt of (3a). Further characterization of (3a) was achieved by potentiometric titration which showed 4.07% (requires 3.77%) ionic bonded chlorine.

Surprisingly, Beckmann rearrangement of 9-*O*-arylsulphonyloximes (3a—e) carried out by a literature[14,15] method for related systems gave none of the expected lactam (9). Instead, it afforded the new compound (5) (erythromycin A imino ether) in 70—87% yield. This structure was confirmed by spectroscopic analysis. The i.r. spectrum of (5) showed strong absorption at 1 725 associated with the C-8 lactone carbonyl stretching and a new carbon–nitrogen (C=N) vibration at 1 705 cm^{-1}. The mass spectrum of (5) showed a peak at *m/z* 730, arising from loss of water from M^+ of the lactam (9) (Table 2) whilst the fragmentation pattern showed peaks at *m/z* 572 and 556, accounting for removal of cladinose with or without the glycosidic oxygen atom. The aglycone fragment devoid of both sugars gave rise to peaks at *m/z* 414 and 382. The fragments at *m/z* 174 and 158 indicated the presence of desosamine.[16] The ^{13}C n.m.r. spectrum displayed two singlets in a ^1H decoupling experiment (off-resonance decoupled, o.r.d.): at 178.8 [lit.,[17] 175.5 p.p.m. for (1)] arising from the C-8 lactone and at 163.9 p.p.m. for the imino C-1 carbon adjacent to the additional nitrogen atom of the aglycone ring. Comparison of the chemical shifts for the



Scheme 1. *Reagents*: i, *p*-substituted benzenesulphonyl chloride, dry Me_2CO, $NaHCO_3$, ii, CH_2Cl_2, 2M-HCl; iii, TsCl, Me_2CO–H_2O, $NaHCO_3$, iv, TsCl, Et_2O, pyridine; v, Ac_2O, pyridine; vi, 1% HCl in MeOH; vii, PCl_5, $CHCl_3$, viii, 2M-HCl, $CHCl_3$, reflux; ix, *cf.* Ref. 6

Table 1 Physical properties and analytical data of erythromycin A 9-*O*-arylsulphonyloximes (3a–e)

Compound (Formula)	Yield (%)	M.p. (°C)	$[\alpha]_D^{25}$ (°)[a]	ν_{max}/cm^{-1}[b]	Cl^-[c] Found (%) (Required)
(3a) ($C_{44}H_{74}N_2O_{15}S$·HCl)	84.5	137—138	−29.9	1 730 (C=O), 1 680 (C=N), 1 600, 810, 680 (*p*-Ph)	4.07 (3.77)
(3b) ($C_{43}H_{71}ClN_2O_{15}S$·HCl)	67.8	137—141	−23.7	1 730 (C=O), 1 680 (C=N), 1 590, 805, 645 (*p*-Ph)	3.85 (3.69)
(3c) ($C_{43}H_{71}BrN_2O_{15}S$·HCl)	90.6	146—148	−27.2	1 730 (C=O), 1 680 (C=N), 1 578, 740, 630 (*p*-Ph)	3.80 (3.53)
(3d) ($C_{43}H_{71}IN_2O_{15}S$·HCl)	85.6	143—151	−31.5	1 735 (C=O), 1 680 (C=N), 1 575, 1 000, 735 (*p*-Ph)	3.67 (3.37)
(3e) ($C_{45}H_{74}N_3O_{16}S$·HCl)	90.0	162—165	−40.3	1 730 (C=O), 1 680 (C=N), 1 595, 835, 715 (*p*-Ph), 1 530 (AcNH)	3.92 (3.61)

[a] *c* = 1 in methylene chloride. [b] I.r. spectra were taken in KBr. [c] Potentiometric titration using $AgNO_3$.

Table 2. The mass spectral fragmentation patterns of some new erythromycins with the expanded aglycone ring in comparison with erythromycin A oxime (2)

	m/z (%)		
Fragment	(2)	(5)	(9)
M^+	748 (0.10)	730 (0.90)	748 (0.08)
$M^+ - Me$	733 (0.03)	715 (0.25)	
$M^+ - H_2O$	730 (0.03)	712 (0.13)	730 (0.12)
$M^+ - EtCHO$	690 (0.05)		689 (1.30)
$M^+ - Me - EtCHO$		657 (0.70)	675 (0.50)
$M^+ -$ cladinose	590 (0.44)	572 (0.40)	590 (4.70)
$M^+ -$ cladinose $- O$	574 (0.33)	556 (2.30)	574 (0.70)
$M^+ -$ cladinose $-$ desosamine	432 (0.65)	414 (3.60)	432 (1.90)
$M^+ -$ cladinose $- O -$ desosamine	416 (0.89)	398 (8.40)	416 (1.50)
$M^+ - EtCHO -$ cladinose $-$ desosamine		356 (1.90)	374 (0.80)
$M^+ - EtCHO -$ cladinose $- O -$ desosamine	358 (0.23)	340 (1.10)	358 (1.00)
$C_8H_{16}NO_2$(desosamine + O)	174 (2.12)	174 (17.0)	174 (3.40)
$C_8H_{16}NO_2$(desosamine)	158 (100)	158 (100)	158 (100)

corresponding atoms in compounds (5) and (2) (Table 3) showed that introduction of a nitrogen atom into the ring in the former compound resulted in an upfield shift of −6.6 p.p.m. for the 9-oxime carbon and a downfield shift of 27.4 p.p.m. for the C-10 signal. The downfield chemical shift of +12.2 p.p.m. for the C-6 signal of (2) compared with the corresponding C-13 chemical shift of (5) suggested the additional change in the aglycone structure, *e.g.* formation of an internal imino ether, similar to that described for 8,9-anhydroerythromycin A 6,9-hemiacetal.[18,19] Selective cleavage of cladinose from (5) with hydrogen chloride in methanol provided the 12-*O*-desosaminyl derivative (6). The same compound was also obtained by Beckmann rearrangement of the oxime (2) with phosphorus pentachloride. Further acid hydrolysis of (6) removed desosamine to give the aglycone (7). An identical product was obtained in an alternative synthesis from the oxime (2), proceeding *via* erythronolide A oxime (8), according to the method of LeMahieu *et al.*[6] and subsequent Beckmann rearrangement of this.

The structure of the aglycone (7) was proved by *X*-ray structural analysis. The perspective view of the molecular structure is given in the Figure computed from the final atomic

Table 3. ^{13}C N.m.r absorption of erythromycin A (1), erythromycin A oxime (2), and some new ring-expanded erythromycins (5), (7), (9), (11), and (13)

	δ/p.p.m.[a–c]					
(1)[d]	(2)	(5)	(7)	(9)	(11)	(13)
175.5, s, C-1	175.1, s, C-1	178.1, s, C-8	175.1, s, C-8	179.6, s, C-2	178.5, s, C-2	176.8, s, C-2
44.8, d, C-2	44.5, d, C-2	43.3, d, C-9	43.2, d, C-9	43.1, d, C-3	43.3, d, C-3	41.8, d, C-3
80.0, d, C-3	79.4, d, C-3	76.1, d, C-10	76.9, d, C-10	78.0, d, C-4	78.1, d, C-4	80.4, d, C-4
39.4, d, C-4	38.9, d, C-4	42.6, d, C-11	35.4, d, C-11	39.7, d, C-5	42.1, d, C-5	34.7, d, C-5
83.6, d, C-5	82.3, d, C-5	78.0, d, C-12	79.8, d, C-12	81.3, d, C-6	83.4, d, C-6	83.7, d, C-6
74.8, s, C-6	73.0, s, C-6	87.7, s, C-13	85.6, s, C-13	86.0, s, C-7	73.7, s, C-7	73.5, s, C-7
38.5, t, C-7	37.7, t, C-7	37.1, t, C-14	36.3, t, C-14	38.0, t, C-8	42.2, t, C-8	39.8, t, C-8
44.8, d, C-8	32.5, d, C-8	35.1, d, C-15	34.4, d, C-15	34.2, d, C-9	29.9, d, C-9	29.2, d, C-9
221.1, s, C-9	170.5, s, C-9	163.7, s, C-1	161.5, s, C-1	174.6, s, C-10	57.3, t, C-10	56.8, t, C-10
38.2, d, C-10	25.2, d, C-10	52.3, d, C-3	52.5, d, C-3	47.9, d, C-12	56.7, d, C-12	58.3, d, C-12
68.7, d, C-11	70.9, d, C-11	72.6, d, C-4	71.9, d, C-4	72.8, d, C-13	73.2, d, C-13	74.1, d, C-13
74.8, s, C-12	74.1, s, C-12	74.9, s, C-5	74.6, s, C-5	74.0, s, C-14	73.8, s, C-14	73.4, s, C-14
77.0, d, C-13	76.5, d, C-13	77.1, d, C-6	78.6, d, C-6	76.1, d, C-15	77.2, d, C-15	77.4, d, C-13
18.5, 2-Me	16.5, 2-Me	16.0, 9-Me	16.4, 9-Me	18.0, 3-Me	15.0, 3-Me	16.1, 3-Me
9.1, 4-Me	9.1, 4-Me	9.2, 11-Me	7.1, 11-Me	11.0, 5-Me	9.2, 5-Me	7.3, 5-Me
20.8, 6-Me	26.9, 6-Me	23.7, 13-Me	26.4, 13-Me	25.1, 7-Me	27.4, 7-Me	26.0, 7-Me
16.2, 8-Me	14.4, 8-Me	13.5, 15-Me	14.4, 15-Me	12.2, 9-Me	14.0, 9-Me	13.7, 9-Me
12.0, 10-Me	18.6, 10-Me	18.2, 3-Me	18.2, 3-Me	19.0, 12-Me	21.9, 12-Me	21.1, 12-Me
16.0, 12-Me	16.1, 12-Me	17.4, 5-Me	16.9, 5-Me	15.2, 14-Me	16.2, 14-Me	15.8, 14-Me
21.3, 13-CH_2	20.9, 13-CH_2	21.4, 6-CH_2	21.1, 6-CH_2	22.2, 15-CH_2	21.1, 15-CH_2	20.8, 15-CH_2
10.5, 13-Me	10.6, 13-Me	11.1, 6-Me	10.8, 6-Me	11.1, 15-Me	11.2, 15-Me	10.8, 15-Me
103.1, d, C-1′	102.4, d, C-1′	102.6, d, C-1′		103.1, d, C-1′	103.9, d, C-1′	
70.9, d, C-2′	70.9, d, C-2′	70.5, d, C-2′		70.8, d, C-2′	70.9, d, C-2′	
65.3, d, C-3′	65.1, d, C-3′	65.5, d, C-3′		65.4, d, C-3′	65.5, d, C-3′	
28.7, t, C-4′	29.0, t, C-4′	28.4, t, C-4′		29.3, t, C-4′	28.8, t, C-4′	
68.8, d, C-5′	67.9, d, C-5′	68.7, d, C-5′		69.2, d, C-5′	68.7, d, C-5′	
21.3, 5′-Me	21.2, 5′-Me	21.3, 5′-Me		21.2, 5′-Me	21.4, 5′-Me	
40.3, 3′-NMe_2	40.2, 3′-NMe_2	40.3, 3′-NMe_2		40.4, 3′-NMe_2	40.3, 3′-NMe_2	
96.2, d, C-1″	96.1, d, C-1″	94.5, d, C-1″		95.0, d, C-1″	94.9, d, C-1″	
35.0, t, C-2″	35.2, t, C-2″	34.6, t, C-2″		35.2, t, C-2″	34.8, t, C-2″	
72.5, s, C-3″	72.7, s, C-3″	72.9, s, C-3″		72.8, s, C-3″	72.9, s, C-3″	
77.9, d, C-4″	77.8, d, C-4″	77.9, d, C-4″		77.9, d, C-4″	77.9, d, C-4″	
65.4, d, C-5″	65.3, d, C-5″	65.8, d, C-5″		65.6, d, C-5″	65.7, d, C-5″	
21.3, 3″-Me	21.4, 3″-Me	21.6, 3″-Me		21.6, 3″-Me	21.6, 3″-Me	
18.3, 5″-Me	18.6, 5″-Me	18.3, 5″-Me		18.5, 5″-Me	18.3, 5″-Me	
49.4, 3″-OMe	49.2, 3″-OMe	49.4, 3″-OMe		49.4, 3″-OMe	49.4, 3″-OMe	

[a] ^{13}C N.m.r spectra were taken with JOEL 90 Q spectrometer at 22.35 MHz. [b] Solvent, $CDCl_3$ or $(CD_3)_2SO$ [compounds (2) and (7)]. [c] s = singlet, d = doublet, t = triplet. [d] *Tetrahedron Lett.*, 1975, 2383.

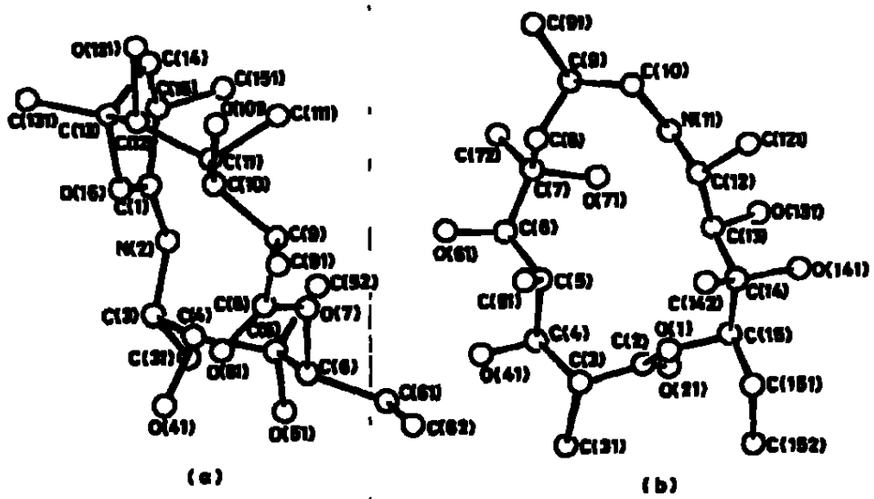


Figure. Perspective view of the structures of (a) aglycone (7), and (b) the cation of the HI salt of amine (13). Although the unit cell of (7) contains two crystallographically independent molecules since both have the same conformation only one is shown. Hydrogen atoms are omitted for clarity

Table 4. Atomic positional parameters with estimated standard deviations for $C_{21}H_{31}NO_7 \cdot 1.5H_2O$

	Molecule (A)				Molecule (B)		
Atom	*x/a*	*y/b*	*z/c*	Atom	*x/a*	*y/b*	*z/c*
C( )	0.145(1)	1.070(1)	0.216(2)	C(1)	−0.453(1)	0.468(1)	−0.803(2)
N(2)	0.112(1)	1.036(1)	0.072(1)	N(2)	−0.478(1)	0.446(1)	−0.935(1)
C(3)	0.000(1)	1.009(1)	−0.020(1)	C(3)	−0.405(1)	0.475(1)	−1.017(2)
C(4)	−0.023(1)	0.871(1)	−0.005(1)	C(4)	−0.378(1)	0.613(1)	−0.996(1)
C(5)	0.032(1)	0.760(1)	−0.085(1)	C(5)	−0.472(1)	0.703(1)	−1.064(1)
C(6)	−0.001(1)	0.628(2)	−0.064(2)	C(6)	−0.427(1)	0.842(1)	−1.031(2)
O(7)	0.097(1)	0.615(1)	0.097(1)	O(7)	−0.402(1)	0.893(1)	−0.870(1)
C(8)	−0.004(1)	0.612(1)	0.185(1)	C(8)	−0.298(1)	0.922(1)	−0.789(2)
C(9)	0.045(1)	0.584(1)	0.338(1)	C(9)	−0.262(1)	0.983(2)	−0.626(2)
C(10)	0.084(1)	0.711(1)	0.453(1)	C(10)	−0.253(1)	0.880(2)	−0.528(2)
C(1)	0.145(1)	0.809(1)	0.415(1)	C(11)	−0.345(1)	0.789(2)	−0.554(1)
C('2)	0.134(1)	0.942(1)	0.513(1)	C(12)	−0.300(1)	0.675(2)	−0.472(2)
C(3)	0.154(1)	1.065(1)	0.460(2)	C(13)	−0.357(1)	0.541(2)	−0.547(2)
C('4)	0.270(1)	1.087(2)	0.467(2)	C(14)	−0.473(2)	0.538(2)	−0.564(2)
C('5)	0.256(1)	1.126(2)	0.316(2)	C(15)	−0.521(1)	0.438(2)	−0.710(2)
O(16)	0.090(1)	1.040(1)	0.297(1)	O(16)	−0.356(1)	0.522(1)	−0.705(1)
C('1)	0.001(0)	0.994(0)	−0.169(0)	C(31)	−0.490(0)	0.440(0)	−1.161(0)
O(41)	−0.142(1)	0.848(1)	−0.079(1)	O(41)	−0.296(1)	0.620(1)	−1.063(1)
O(51)	−0.014(1)	0.762(1)	−0.241(1)	O(51)	−0.505(1)	0.664(1)	−1.227(1)
C(52)	0.158(1)	0.771(2)	−0.031(2)	C(52)	−0.375(1)	0.701(2)	−1.019(2)
C(61)	0.031(1)	0.509(2)	−0.159(2)	C(61)	−0.517(1)	0.937(2)	−1.110(2)
C(62)	−0.009(2)	0.383(2)	−0.138(2)	C(62)	−0.466(2)	1.066(2)	−1.091(3)
O(81)	−0.099(1)	0.633(1)	0.151(1)	O(81)	−0.222(1)	0.901(1)	−0.838(1)
C(91)	0.002(1)	0.487(2)	0.379(2)	C(91)	−0.195(2)	1.088(2)	−0.582(2)
O(101)	0.136(1)	0.692(1)	0.600(1)	O(101)	−0.211(1)	0.948(2)	−0.381(2)
C(11)	0.262(1)	0.765(2)	0.424(2)	C(111)	−0.435(3)	0.868(3)	−0.512(3)
O(121)	0.209(1)	0.952(1)	0.665(1)	O(121)	−0.316(1)	0.705(1)	−0.325(1)
C(131)	0.106(1)	1.184(2)	0.536(2)	C(131)	−0.283(2)	0.440(2)	−0.477(2)
C(151)	0.353(2)	1.094(2)	0.258(2)	C(151)	−0.647(2)	0.458(2)	−0.785(2)
O(1w)	0.226(1)	0.156(1)	0.904(1)				
O(2w)	0.324(1)	0.349(1)	0.827(1)				
O(3w)	0.299(1)	0.508(1)	0.619(1)				

co-ordinates given in Table 4. In the structure there are two crystallographically independent molecules, (A) and (B), and three water molecules. The gross structure comprises a 15-membered ring with the furanoic ring significantly out of the plane of the rest of the molecule. The torsion angles C(11)–C(12)–C(13)–C(14) and C(3)–N(2)–C(1)–C(15) are −69 and −176°, and −64 and −178° in the molecules (A) and (B), respectively. The majority of the interatomic distances and

Table 5. Bond lengths (Å) and bond angles (°) with estimated standard deviations for $C_{21}H_{37}O_{12}N\cdot 1.5H_2O$

	Molecule (A)	Molecule (B)		Molecule (A)	Molecule (B)
C(1)–N(2)	1.29(2)	1.18(2)	C(8)–O(81)	1.18(2)	1.22(2)
C(1)–C(15)	1.52(2)	1.54(3)	C(9)–C(10)	1.54(1)	1.53(3)
C(1)–O(16)	1.31(2)	1.37(2)	C(9)–C(91)	1.54(3)	1.51(3)
N(2)–C(3)	1.48(2)	1.50(2)	C(10)–C(11)	1.52(2)	1.52(3)
C(3)–C(4)	1.56(2)	1.49(2)	C(10)–O(101)	1.40(1)	1.38(2)
C(3)–C(31)	1.42(1)	1.45(1)	C(11)–C(12)	1.56(1)	1.54(3)
C(4)–C(5)	1.54(2)	1.54(2)	C(11)–C(111)	1.53(2)	1.51(4)
C(4)–O(41)	1.48(2)	1.43(2)	C(12)–C(13)	1.56(2)	1.57(3)
C(5)–C(6)	1.56(3)	1.56(2)	C(12)–O(121)	1.45(1)	1.47(2)
C(5)–O(51)	1.43(1)	1.46(1)	C(13)–C(14)	1.51(2)	1.46(3)
C(5)–C(52)	1.54(2)	1.54(2)	C(13)–O(16)	1.49(2)	1.50(2)
C(6)–O(7)	1.51(2)	1.47(2)	C(13)–C(131)	1.53(2)	1.49(3)
C(6)–C(61)	1.52(3)	1.58(2)	C(14)–C(15)	1.54(3)	1.52(2)
O(7)–C(8)	1.34(2)	1.33(2)	C(15)–C(151)	1.53(3)	1.56(3)
C(8)–C(9)	1.52(1)	1.53(3)	C(61)–C(62)	1.52(3)	1.51(3)
N(2)–C(1)–C(15)	123(1)	126(1)	C(8)–C(9)–C(91)	108(1)	106(2)
N(2)–C(1)–O(16)	126(1)	126(1)	C(10)–C(9)–C(91)	111(1)	114(2)
C(15)–C(1)–O(16)	110(1)	108(1)	C(9)–C(10)–C(11)	112(1)	115(2)
C(1)–N(2)–C(3)	121(1)	123(1)	C(9)–C(10)–O(101)	113(1)	108(2)
N(2)–C(3)–C(4)	114(1)	116(1)	C(11)–C(10)–O(101)	111(1)	113(2)
N(2)–C(3)–C(31)	103(1)	92(1)	C(10)–C(11)–C(12)	108(1)	110(1)
C(4)–C(3)–C(31)	104(1)	107(1)	C(10)–C(11)–C(111)	112(1)	107(2)
C(3)–C(4)–C(5)	116(1)	117(1)	C(12)–C(11)–C(111)	116(1)	117(2)
C(3)–C(4)–O(41)	107(1)	108(1)	C(11)–C(12)–C(13)	118(1)	117(1)
C(5)–C(4)–O(41)	105(1)	106(1)	C(11)–C(12)–O(121)	111(1)	109(1)
C(4)–C(5)–C(6)	110(1)	109(1)	C(13)–C(12)–O(121)	105(1)	104(1)
C(4)–C(5)–O(51)	106(1)	107(1)	C(12)–C(13)–C(14)	117(1)	117(2)
C(4)–C(5)–C(52)	113(1)	116(1)	C(12)–C(13)–O(16)	103(1)	104(1)
C(6)–C(5)–O(51)	106(1)	105(1)	C(12)–C(13)–C(131)	111(1)	108(2)
C(6)–C(5)–C(52)	110(1)	112(1)	C(14)–C(13)–O(16)	105(1)	104(2)
O(51)–C(5)–C(52)	111(1)	108(1)	C(14)–C(13)–C(131)	112(1)	114(2)
C(5)–C(6)–O(7)	108(1)	108(1)	O(16)–C(13)–C(131)	109(1)	106(2)
C(5)–C(6)–C(61)	116(1)	112(1)	C(13)–C(14)–C(15)	104(1)	105(2)
O(7)–C(6)–C(61)	106(1)	104(1)	C(1)–C(15)–C(14)	103(1)	101(2)
C(6)–O(7)–C(8)	119(1)	118(1)	C(1)–C(15)–C(151)	110(2)	113(2)
O(7)–C(8)–C(9)	112(1)	114(1)	C(14)–C(15)–C(151)	116(2)	113(2)
O(7)–C(8)–O(81)	125(1)	124(1)	C(1)–O(16)–C(13)	112(1)	110(1)
C(9)–C(8)–O(81)	123(1)	123(1)	C(6)–C(61)–C(62)	113(2)	110(2)
C(8)–C(9)–C(10)	109(1)	111(1)			

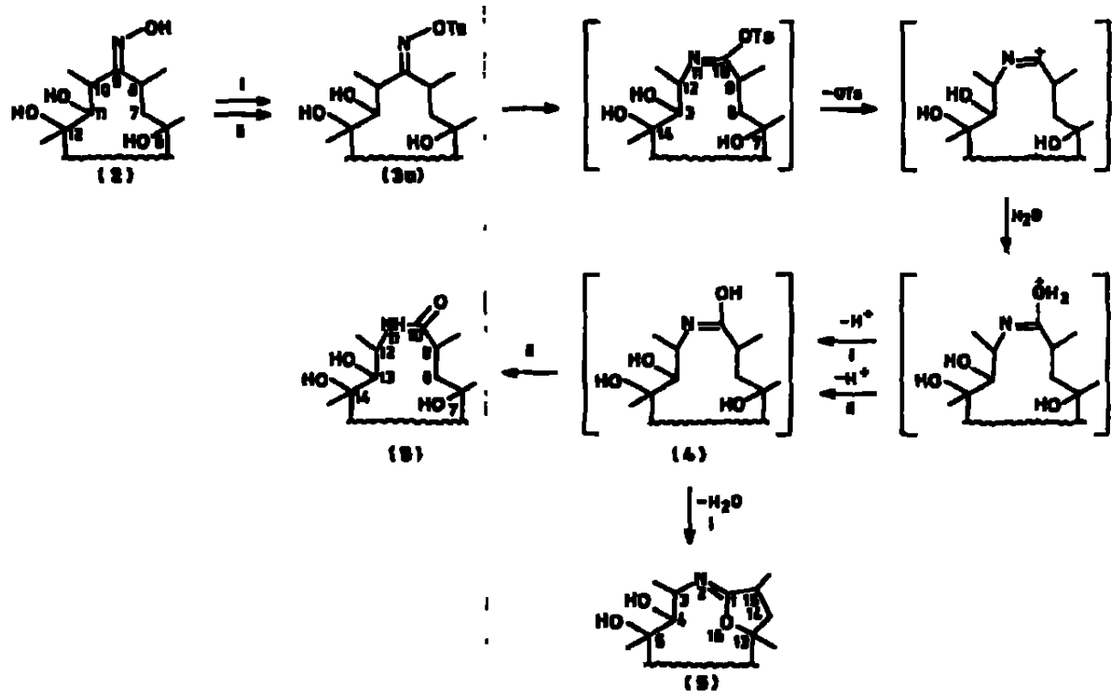
angles in the molecules (A) and (B) (Table 5) agree well with each other as well as with the known values found in the literature.[20,21]

All three water molecules [$H_2O(1w)$, $H_2O(2w)$, and $H_2O(3w)$], apart of being hydrogen bonded to each other at 2.88(2) and 2.79(2) Å participate also in the hydrogen bonding to -OH groups and N atoms from three different [one (B) and two (A)] aglycone molecules. These hydrogen bonds between N(2A)···O(1w), N(2B)···O(2w), O(51B)···O(3w), and O(101A)···O(3w) amount to 2.90(2), 2.90(2), 2.91(2), and 2.75(2) Å, respectively.

Beckmann rearrangement of erythromycin A oxime (2) with toluene-*p*-sulphonyl chloride (*p*-TsCl) gave in aqueous acetone the imino ether (5) (71.8% yield), identical with that obtained by the rearrangement of ester (3a—e). However, the rearrangement of (2) with *p*-TsCl in pyridine seems to give the erythromycin A lactam (9). Examination of the ^{13}C n.m.r spectrum of (9) showed a singlet lactam carbonyl at 174.6 p.p.m. (o.r.d.). The mass spectrum showed the molecular ion peak at *m/z* 748, which together with the fragmentation pattern correspond to the structure of the lactam (9). To give some further chemical evidence for the structural assignment of the lactam, (9) was acetylated with an excess of acetic anhydride in pyridine (72 h, 25 °C), since it is known that the 2'-, 4"-, and 11-hydroxyl groups of erythromycin are acylated under these conditions.[22,23] Acetylation of the lactam (9) produced a new product (10) which had four acetyl signals in its ^1H n.m.r spectrum and a molecular ion at *m/z* 916. The ^{13}C n.m.r showed in the carbonyl region six singlets (o.r.d.). Apart from the signals at 179.3 (C-O, lactone) and 174.7 p.p.m. (C-O, lactam), compound (10) exhibited four new signals at 171.9, 170.5, 169.9, and 169.2 p.p.m., these indicated that besides *O*-acylation at C-2', C-4", and C-13, *N*-acylation had also occurred at the 11-position.

To explain the formation of the imino ether (5) and lactam (9) in the Beckmann rearrangement of erythromycin A oxime (2), the mechanism outlined in Scheme 2 is suggested. Beckmann rearrangement generally involves conversion of the oxime hydroxy group into a better leaving group, followed by rearrangement and tautomerization.[24,25] Thus it was established that the lactim (4) may undergo two types of transformation depending on the solvent used: namely, isomerization (path ii) to yield the expected lactam (9), or elimination of water from the 7- and 10-hydroxyl groups (path i) to yield the unusual lactim ether (5). This result probably arises from the greater stability of (4) in aqueous acetone than in pyridine. Consequently, the rate of conversion of (4) into the lactam (9) is slowed. Since structure (4) is sterically well disposed for internal ether formation,[26] it is reasonable to suppose, that the elimination of water from (4) to give (5) will compete successfully with the isomerization of (4) into (9). In contrast, pyridine will favour rapid tautomerization of (4) into (9).

In order to prepare amino derivatives of the new macrocyclic



Scheme 2. *Reagents*: I, *p*-TsCl, Me_2CO–H_2O; II, *p*-TsCl, pyridine

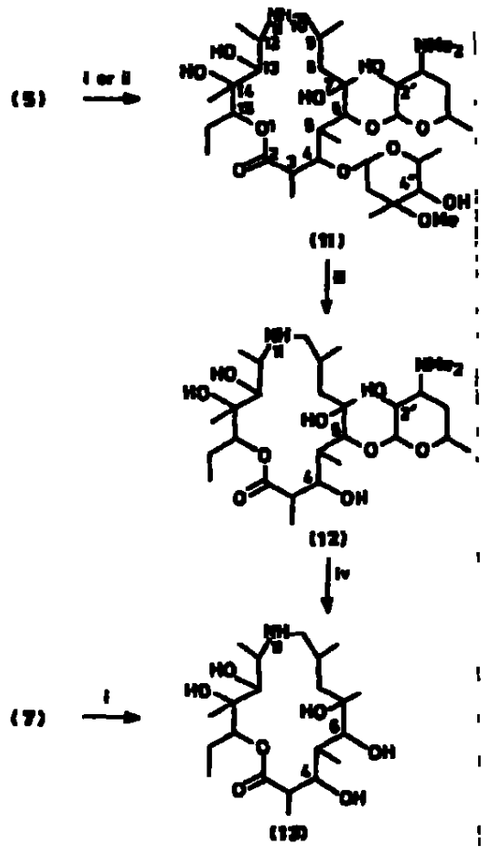
structure, the imino ethers (5) and (7) were subjected to reduction (see Scheme 3). Catalytic hydrogenation of the imino ether (5) in glacial acetic acid using platinum(IV) oxide gave in high yield (79.8%) compound (11); the i.r. spectrum of (11) lacked the amino band at 1 705 cm^{-1}, as well as a 1-imino carbon singlet (*o.f.d.*) at 163.9 p.p.m. in its ^{13}C n.m.r. spectrum. This spectrum also showed a new triplet at 57.3 p.p.m. suggesting the presence of a secondary amino group in the new 15-membered aglycone ring. The mass spectrum gave additional support to the structure proposed. An identical product, *i.e.* the 10-dihydro-10-deoxo-11-azaerythromycin A (11), was obtained by chemical reduction of the imino ether (5) with metal hydrides, *e.g.* sodium borohydride in methanol.

Glycosidic cleavage of (11) removed smoothly both sugars and yielded 10-dihydro-10-deoxo-11-azaerythronolide A (13) which exhibited the expected molecular ion at *m/z* 419 in the mass spectrum. The p*K* value of 8.3 (66% DMF) was consistent with the presence of the amino group in the ring. The same product (13) was obtained by the catalytic hydrogenation of the aglycone (7) with platinum(IV) oxide in glacial acetic acid. The final evidence for the structure of the amine (13) came from an *X*-ray analysis, but since it was impossible to obtain suitable crystals of amine (13) itself, its HI crystalline salt was prepared by treating the parent compound (13) with hydrogen iodide in dry acetone.

The structure of the amine (13) consists of $C_{21}H_{42}O_7N^+$ cations and I^- anions. A perspective view of the molecular structure is shown in the Figure obtained from the final atomic parameters given in Table 6. A general feature of the molecule is here again the 15-membered ring with bond lengths and angles similar to those found in the structure of the aglycone (7) and to the data known from previously published analogous structures.[20,21] All relevant bond lengths and angles are given

Table 6. Atomic positional parameters with estimated standard deviations for $C_{21}H_{42}INO_7$

Atom	*x/a*	*y/b*	*z/c*
I	0.136 1(1)	0.242 0(2)	0.151 7(2)
O(1)	0.038(1)	0.319(2)	0.592(1)
C(2)	0.028(1)	0.226(4)	0.495(2)
C(3)	0.022(1)	0.084(3)	0.489(3)
C(4)	0.075(1)	0.021(2)	0.461(2)
C(5)	0.127(1)	0.089(2)	0.518(2)
C(6)	0.175(1)	0.007(3)	0.449(2)
C(7)	0.225(1)	0.105(2)	0.449(2)
C(8)	0.251(1)	0.124(2)	0.558(3)
C(9)	0.295(1)	0.248(3)	0.569(3)
C(10)	0.278(1)	0.377(2)	0.628(2)
N(11)	0.230(1)	0.432(3)	0.570(2)
C(12)	0.188(1)	0.479(3)	0.651(3)
C(13)	0.134(1)	0.491(3)	0.589(2)
C(14)	0.088(1)	0.518(3)	0.681(3)
C(15)	0.037(1)	0.478(2)	0.593(2)
O(21)	0.020(1)	0.303(2)	0.403(2)
C(31)	−0.034(1)	0.029(2)	0.458(3)
O(41)	0.071(1)	−0.128(2)	0.473(2)
C(51)	0.130(1)	0.013(3)	0.650(2)
O(61)	0.192(1)	−0.133(2)	0.488(2)
O(71)	0.286(1)	0.246(2)	0.410(1)
C(72)	0.263(1)	0.053(3)	0.360(3)
C(91)	0.344(1)	0.184(3)	0.627(3)
C(121)	0.203(1)	0.623(4)	0.719(3)
O(131)	0.140(1)	0.601(2)	0.508(2)
O(141)	0.051(1)	0.668(3)	0.686(2)
C(142)	0.088(1)	0.428(4)	0.774(2)
C(151)	−0.015(2)	0.503(6)	0.650(10)
C(152)	−0.065(1)	0.466(4)	0.576(3)



Scheme 3. *Reagents*: i, PtO_2, HOAc; ii, $NaBH_4$, MeOH, iii, *cf.* Ref. 26; iv, *tert*-HCl, $CHCl_3$

Table 7. Bond lengths (Å) and bond angles (°) with estimated standard deviations for $C_{21}H_{43}NO_7$

O(1)–C(2)	1.41(4)	C(8)–C(9)	1.56(4)
O(1)–C(15)	1.45(3)	C(9)–C(10)	1.56(4)
C(2)–C(3)	1.44(5)	C(9)–C(91)	1.55(4)
C(2)–O(21)	1.26(4)	C(10)–N(11)	1.50(4)
C(3)–C(4)	1.44(4)	N(11)–C(12)	1.50(4)
C(3)–C(31)	1.40(4)	C(12)–C(13)	1.57(4)
C(4)–C(5)	1.52(3)	C(13)–C(131)	1.54(5)
C(4)–O(41)	1.43(3)	C(13)–C(14)	1.49(4)
C(5)–C(6)	1.57(3)	C(13)–O(131)	1.41(3)
C(5)–C(51)	1.48(4)	C(14)–C(15)	1.60(4)
C(6)–C(7)	1.50(3)	C(14)–O(141)	1.40(4)
C(6)–O(61)	1.47(3)	C(14)–C(142)	1.55(5)
C(7)–C(8)	1.52(4)	C(15)–C(151)	1.52(8)
C(7)–O(71)	1.48(3)	C(151)–C(152)	1.58(9)
C(7)–C(72)	1.47(4)		

C(2)–O(1)–C(15)	123(2)	C(7)–C(8)–C(9)	115(2)
O(1)–C(2)–C(3)	126(3)	C(8)–C(9)–C(10)	115(2)
O(1)–C(2)–O(21)	116(3)	C(8)–C(9)–C(91)	111(2)
O(21)–C(2)–C(3)	117(3)	C(91)–C(9)–C(10)	105(2)
C(2)–C(3)–C(4)	115(2)	C(9)–C(10)–N(11)	107(2)
C(2)–C(3)–C(31)	114(2)	C(10)–N(11)–C(12)	114(2)
C(31)–C(3)–C(4)	125(3)	N(11)–C(12)–C(13)	109(2)
C(3)–C(4)–C(5)	123(2)	N(11)–C(12)–C(121)	113(2)
C(3)–C(4)–O(41)	109(2)	C(121)–C(12)–C(13)	113(2)
O(41)–C(4)–C(5)	108(2)	C(12)–C(13)–C(14)	114(2)
C(4)–C(5)–C(6)	109(2)	C(12)–C(13)–O(131)	107(2)
C(4)–C(5)–C(51)	111(2)	O(131)–C(13)–C(14)	111(2)
C(51)–C(5)–C(6)	108(2)	C(13)–C(14)–C(15)	106(3)
C(5)–C(6)–C(7)	115(2)	C(13)–C(14)–O(141)	113(2)
C(5)–C(6)–O(61)	115(2)	C(13)–C(14)–C(142)	116(3)
O(61)–C(6)–C(7)	107(2)	O(141)–C(14)–C(15)	107(2)
C(6)–C(7)–C(8)	113(2)	O(141)–C(14)–C(142)	107(3)
C(6)–C(7)–O(71)	106(2)	C(142)–C(14)–C(15)	108(2)
C(6)–C(7)–C(72)	110(2)	C(14)–C(15)–O(1)	107(2)
O(71)–C(7)–C(8)	106(2)	C(14)–C(15)–C(151)	114(4)
O(71)–C(7)–C(72)	109(2)	C(151)–C(15)–O(1)	104(3)
C(72)–C(7)–C(8)	112(2)	C(15)–C(151)–C(152)	113(7)

m Table 7 There are no additional interactions between the aglycone rings except van der Waals contacts.

Experimental

All m.p.s were determined with a Fisher-Johns apparatus and are uncorrected. I.r. spectra (KBr pellets or $CHCl_3$) were taken on a Perkin-Elmer 257 G spectrometer. ^1H N.m.r. spectra were determined with a Varian A-60 spectrometer (solvents: $CDCl_3$, $(CD_3)_2SO$, CD_3N; $SiMe_4$ as internal reference). ^{13}C N.m.r. spectra were recorded with JOEL 90 Q spectrometer (with $SiMe_4$ as internal standard) and electron impact mass spectra with a CEC 21-110 C spectrometer at 70 eV. Characteristic frequencies only are reported; the spectra recorded were otherwise in agreement with the structure given.

T.l.c. was performed on Merck silica gel 60 F_{254} plates; the plates were initially examined under u.v. light and then detected with a mixture (3 100, w/v) of phenol–[ethanol–sulphuric acid (95 5, v/v)]. The following solvent systems were used: (A) 40 55 5 C_6H_6–$CHCl_3$–MeOH (saturated with NH_3 vapour); (B) 4 1 5 BuOH–HOAc–H_2O (upper layer); (C) 7 3 $CHCl_3$–MeOH; (D) 9 1 DMF–MeOH. The homogeneity of all compounds was tested by t.l.c. and their analytical data are listed in Table 8. Merck silica gel 60 (70—230 mesh) was used for column chromatography. Solutions in organic solvents were dried over anhydrous potassium carbonate.

O-Arylsulphonyloximes (3a—e): *General Procedure*.—Sodium hydrogen carbonate (1.65 g, 1.9 mmol) was added to a stirred solution of the oxime (2) (3.0 g, 4 mmol) in dry acetone (90 ml) after which the corresponding *para*-substituted benzenesulphonyl chloride (9.5 mmol) dissolved in dry acetone (60 ml) was added dropwise, during 1 h at 0—5 °C. The mixture was stirred for further 3 h after which the precipitate was filtered off and the filtrate evaporated under reduced pressure. The residue was suspended in dry ether and filtered to give *O*-arylsulphonyloximes (3a—e) (Table 1).

Erythromycin A Imino Ether (5).—*By the Beckmann rearrangement of erythromycin A 9-O-p-tolylsulphonyloxime* (3a). Water (50 ml) was added to a solution of the oxime tosylate (3a) (3.4 g, 3.8 mmol) in dichloromethane (50 ml) and the reaction mixture acidified with 2M-hydrochloric acid to pH 6. After the mixture had been stirred at room temperature for 15 min, the layers were separated and the aqueous layer extracted with dichloromethane (2 × 50 ml). The extraction was repeated at pH 6.5 (2 × 50 ml) and 8 (4 × 50 ml) and the extracts dried. Evaporation under reduced pressure of the extract collected at pH 8 gave the imino ether (5) (2.15 g, 78.3%), m.p. 128—131 °C; $[\alpha]_D^{20}$ −54.63 (*c* 1 in CH_2Cl_2); *m/z* 730 (M^+); $\nu_{max.}$ ($CHCl_3$) 1 725 (lactone CO) and 1 705 cm^{-1} (OC=N); δ_C($CDCl_3$) 178.1 (s, lactone CO), 163.9 (s, OC=N), and 52.6 p.p.m. (d, C-3).

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Table 8. Analytical data for the new ring-expanded erythromycins

Compound (Formula)	Yield (%)	M.p. (°C)	M^+ (m/z)	R_f	Found (%) (Required) C	H	N
(5) ($C_{37}H_{66}N_2O_{12}$)	78.3	128—131	730	0.782 (D) 0.285 (B)	68.5 (68.8)	9.2 (9.1)	3.5 (3.8)
(6) ($C_{29}H_{52}N_2O_9$)	89.9	109—113	572	0.164 (B)	60.4 (60.8)	9.5 (9.2)	4.7 (4.9)
(7) ($C_{21}H_{31}NO_7$)	55.6	164—168	415	0.412 (B)	60.3 (60.7)	9.2 (9.0)	3.4 (3.4)
(9) ($C_{37}H_{66}N_2O_{13}$)	63.0	83—86	748	0.121 (D)	59.8 (59.3)	9.3 (9.2)	3.6 (3.7)
(11) ($C_{37}H_{70}N_2O_{12}$)	79.6	113—116	734	0.219 (B)	60.1 (60.5)	9.9 (9.6)	3.7 (3.8)
(13) ($C_{21}H_{41}NO_7$)	51.8	193—196	419	0.466 (B)	59.9 (60.1)	9.6 (9.9)	3.6 (3.3)

By the Beckmann rearrangement of erythromycin A oxime (2). Toluene-*p*-sulphonyl chloride (4.9 g, 26 mmol) in acetone (42 ml) and sodium hydrogen carbonate (4.4 g, 52 mmol) in water (147 ml) were added dropwise over 2 h to a stirred solution of erythromycin A oxime (2) (9.6 g, 13 mmol) in acetone (120 ml) at 0—5 °C.

After the reaction mixture had been stirred for a further 2 h at this temperature, the acetone was evaporated under reduced pressure. Gradient extraction at pH 5.5, 6, and 8 with dichloromethane gave at pH 8 the imino ether (5) (7.6 g), identical with the product (5) obtained by the Beckmann rearrangement of (3a). The residue at pH 6 after evaporation of solvent was re-extracted (at pH 5.5, 6, and 8) to give additional (0.6 g) (5) (overall yield 86.5%).

12-O-*Desosaminylerythromycin A Imino Ether* (6).—(*a*) The imino ether (5) (10 g, 13.6 mmol) in methanol (500 ml) containing 1% hydrogen chloride was left for 2 days at ambient temperature. After neutralization with sodium hydrogen carbonate the solvent was evaporated. Chloroform (250 ml) was added to the residue, washed with 3M-hydrochloric acid and then with water.

The combined HCl extract was made basic (pH 10) with 3M-sodium hydroxide and then extracted with chloroform (3 × 70 ml); the combined chloroform extracts were washed with saturated aqueous sodium hydrogen carbonate and dried. Evaporation of chloroform to dryness afforded 12-*O*-desosaminylerythromycin A imino ether (6) (7.1 g, 89.9%), m.p. 109—113 °C; $[\alpha]_D^{20}$ 58.71 (*c* 1 in CH_2Cl_2); *m/z* 572 (M^+); $\nu_{max.}$ 1 735 (lactone CO) and 1 705 cm^{-1} (OC=N); $\delta_H(CDCl_3)$ 2.21 (s, 6 H, NMe_2).

(*b*) Phosphorus pentachloride (1.1 g, 5.3 mmol) was added in portions to a stirred solution of the oxime (2) (1.3 g, 1.7 mmol) in chloroform (30 ml) after which the mixture was heated under reflux for 2 h and then poured into ice-water. The resulting solution was made alkaline by addition of 2M-aqueous sodium hydroxide to pH 10 and stirred for a further 3 h at ambient temperature. The layers were separated, and the aqueous layer was extracted with chloroform (3 × 30 ml) and dried.

The solvent was removed under reduced pressure to afford the crude product (1.02 g), which was recrystallized from chloroform–light petroleum (b.p. 40—60 °C) to yield the pure ether (6), m.p. 113—116 °C, identical with the sample prepared according to the method (*a*).

Erythronolide A Imino Ether (7).—(*a*) A mixture of 12-*O*-desosaminylerythronolide A imino ether (6) (1.0 g, 1.7 mmol), 2M-hydrochloric acid (20 ml) and chloroform (10 ml) was heated under reflux for 72 h. The mixture was cooled at room temperature, the layers were separated, and the aqueous layer was extracted with chloroform (2 × 5 ml). The pH of the aqueous solution was adjusted with 2M-aqueous sodium hydroxide to 9.0 and again extracted with chloroform (3 × 10 ml). The combined chloroform extract at pH 9.0 was dried and evaporated. T.l.c. revealed in a $CHCl_3$–MeOH (7:3) system a major spot moving much faster than (6) and several impurities. The analytical sample, m.p. 164—168 °C, was prepared by two recrystallizations from hot acetone solution; $[\alpha]_D^{20}$ 64.8 (*c* 1 in Me_2CO); *m/z* 415 (M^+); $\nu_{max.}$(Nujol) 1 712 (lactone CO) and 1 697 cm^{-1} (OC=N); $\delta_H[(CD_3)_2SO]$ 175.1 (s, lactone CO), 161.5 (s, OC=N), and 52.6 p.p.m. (d, C-3).

(*b*) Erythronolide A oxime (8) (5 g, 11.6 mmol), prepared by the procedure of Lablaikiew *et al.*,[4] underwent the Beckmann rearrangement according to the procedure described for (5) to yield erythronolide A imino ether (7) (2.63 g, 55.6%), identical with that obtained according to method (*a*).

Erythromycin A Lactone (9).—Toluene-*p*-sulphonyl chloride (0.384 g, 2 mmol) in ether (10 ml) was added dropwise at 0—5 °C during 30 min to a stirred solution of the erythromycin A oxime (2) (0.748 g, 1 mmol) in dry pyridine and the mixture stirred at this temperature for a further 2 h. The solvent was removed under reduced pressure and water (50 ml) and chloroform (30 ml) were added to the oil residue; the pH was adjusted to 5.5 with 20% aqueous sodium hydroxide and the mixture extracted with chloroform (2 × 20 ml). The extraction was repeated at pH 6 and 8.3 and the extracts were dried. Evaporation of the solvent at pH 8.3 gave the erythromycin A lactone (9) (0.471 g, 63%), m.p. 83—86 °C; $[\alpha]_D^{20}$ −44.0 (*c* 1 in CH_2Cl_2); *m/z* 748 (M^+); $\nu_{max.}(CHCl_3)$ 1 725 (lactone CO), 1 760 (amide CO), and 1 580 cm^{-1} (amide NC=O); $\delta_C(CDCl_3)$ 179.6 (s, lactone CO), 174.6 (s, lactone CO), and 48.8 p.p.m. (d, C-12).

2′,4″,13-N-Tetra-acetylerythromycin A Lactone (10).—The erythromycin A lactone (9) (3.0 g, 4 mmol) and acetic anhydride (10 ml) in pyridine (40 ml) was left at 25 °C for 3 days. The reaction mixture was then poured into ice-water (200 ml), the pH adjusted to 8.5 with 2M-aqueous sodium hydroxide and

extracted with chloroform. The organic layer was washed with water, dried, and evaporated to dryness to give the crude product (3.08 g). Column chromatography on silica gel with chloroform–methanol (9 1) as eluant, afforded the title compound (10) (1.45 g, 39.5%), m.p. 101—105 °C; $[\alpha]_D^{20}$ −39.0 (*c* 1 in CH_2Cl_2); *m/z* 916 (M^+); $\nu_{max.}$(CHCl$_3$) 1 730 (ester and lactone CO), 1 655 (amide CO), and 1 515 cm^{-1} (amide NC=O); δ_H($CDCl_3$) 3.27 (s, 3 H, OMe), 2.25 (s, 6 H, NMe_2), 2.10 (s, 3 H, 4''-Ac), 2.06 (s, 3 H, 2'-Ac), 2.03 (s, 3 H, 13-Ac), and 1.97 (s, 3 H, *N*-Ac); δ_C($CDCl_3$) 179.3 (s, lactone), 174.7 (s, lactam), 170.5, 169.9, and 169.2 (3 s, *O*-Ac), 171.9 (s, *N*-Ac), and 45.1 p.p.m. (d, C-12).

10-Dihydro-10-deoxo-11-azaerythromycin A (11).—(*a*) Imino ether (5) (6.0 g, 8 mmol) was catalytically hydrogenated in acetic acid (60 ml) over PtO_2 (0.125 g) under hydrogen (70 atm) at room temperature for 2 h. The catalyst and solvent were removed and the residual oil was dissolved in water (160 ml) and extracted with dichloromethane at pH 6.0, 6.5, and 8.3. The extract at pH 8.3 was dried and evaporated to dryness under reduced pressure to give the title compound (11) (4.8 g, 79.8%), m.p. 113—116 °C; $[\alpha]_D^{20}$ −33.91 (*c* 1 in CH_2Cl_2); *m/z* 734 (M^+); $\nu_{max.}$ 1 725 (lactone CO) and 1 640 cm^{-1} (NH); δ_C($CDCl_3$) 178.5 (s, lactone), 57.3 (t, C-10), and 56.7 p.p.m. (d, C-12).

(*b*) To a stirred solution of the imino ether (5) (12 g, 16 mmol) in absolute methanol (300 ml) sodium borohydride (12 g, 0.316 mol) was added in portions at 4 °C over 4 h, and then left at ambient temperature for 24 h. Carbon dioxide was bubbled through the mixture until precipitation was completed, after which the precipitate was filtered off, the filtrate evaporated to dryness, and the residue redissolved in chloroform (100 ml). Water was added and the mixture then acidified to pH 2.5 with 2*M*-hydrochloric acid, it was then stirred for 15 min, after which the pH was adjusted to 6 by addition of 20% aqueous sodium hydroxide and extracted with chloroform. The extraction was repeated at pH 6.5 and 8.3. Evaporation of the dried chloroform extract at pH 8.3 left a solid which as a suspension in dry ether was stirred for 2 h whilst cooled with ice; the mixture was then filtered and the filtrate evaporated to afford the title compound (11) pure (7.3 g, 60.5%); it was identical with that obtained according to the method (*a*).

10-Dihydro-10-deoxo-11-azaerythronolide A (13).—(*a*) A mixture of *6-O-desosaminyl-10-dihydro-10-deoxo-11-azaerythronolide A* (12) (9.3 g, 16.1 mmol) [prepared from (11) by a standard procedure],[28] 6*M*-hydrochloric acid (150 ml) and chloroform (75 ml) was heated under reflux for 70 h. The pH of the reaction mixture was adjusted with 20% aqueous sodium hydroxide to 5.0, after which the aqueous layer was separated and extracted with chloroform (2 × 30 ml). The extractions with chloroform were repeated at pH 7.5 (3 × 30 ml), and pH 9.0 (3 × 30 ml). The combined extracts at pH 9.0 were dried and evaporated to yield a colourless residue (5.96 g) which on crystallization from ether gave (13) (3.5 g, 51.8%), m.p. 193—196 °C; *m/z* 419 (M^+); $\nu_{max.}$ 1 710 (lactone CO) and 1 630 cm^{-1} (NH); δ_C($CDCl_3$) 176.9 (s, lactone), 56.8 (t, C-10), and 58.3 p.p.m. (d, C-12).

(*b*) The erythronolide imino ether (7) (0.350 g, 0.84 mmol) was catalytically hydrogenated in acetic acid (10 ml) over PtO_2 (0.0135 g) under hydrogen (40 atm) at room temperature for 10 h. The catalyst and the solvent were removed and the residual oil was dissolved in water (10 ml) and extracted with chloroform at pH 5.0 (3 × 2.5 ml), pH 7.5 (3 × 2.5 ml), and pH 9.0 (3 × 3.0 ml). The combined extracts at pH 9.0 were dried and evaporated to dryness under reduced pressure to give the title compound (13), identical with that obtained according to the method (*a*).

Hydrolysis of 10-Dihydro-10-deoxo-11-azaerythronolide A.—Hydrolodic acid (0.316 ml) was added dropwise to a stirred solution of 10-dihydro-10-deoxo-11-azaerythronolide A (13) (1 g, 2.4 mmol) in dry acetone (60 ml). After the mixture had been stirred at 25 °C for 15 min the solvent was removed under reduced pressure and the residue was dissolved in acetone (reflux); the solution was then filtered and left overnight at ambient temperature to give crystals suitable for *X*-ray analysis, m.p. 225—228 °C.

Crystal Structure of (7).—*Crystal data*. $C_{21}H_{37}NO_7 \cdot 1.5H_2O$ M_r = 885.11 Triclinic, *a* = 12.928(6), *b* = 10.601(5), *c* = 9.645(5) Å, α = 101.49(5), β = 109.57(4), γ = 83.85(6)°, *V* = 1 221 Å, space group *P*1, *Z* = 2, D_c = 1.204 g cm^{-3}, *F*(000) = 482, μ (Mo-K_α) = 0.99 cm^{-1}

Data were collected on a Philips PW1100 automatic diffractometer using graphite monochromated Mo-K_α radiation (λ = 0.7107), ω—2θ scan in the range 2° > θ > 30° with scan width 1.60°, scan speed 0.04° s^{-1}. Three standard reflections were monitored every 2 h and showed no significant deviation. 5 095 Unique reflections were recorded but owing to the very poor quality of crystals only 2 948 [$I > 10\sigma(I)$] were used in the refinement. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by MULTAN[27] and refined initially with isotropic and at the later stage with anisotropic temperature factors for the atoms belonging to the basic ring and with isotropic temperature factors for terminal atoms. The refinement converged at *R* = 0.122 (R_w = 0.171). The function minimized was $\Sigma_w([F_o] - [F_c])^2$ with $w = 1/\sigma^2(F_o)$. The refinement of the positional and temperature parameters of the methyl atom C(31) in both (A) and (B) molecules was unsatisfactory so that they were located in a difference Fourier map and included in the calculations at the fixed positions. The isotropic temperature factors for O(101) and C(111) in the molecule (B) were also not refined in the final cycles. Hydrogen atoms were located either in a difference Fourier synthesis or generated from assumed geometries. The hydrogen atom positions were not refined. Atomic scattering factors were taken from ref. 28. Calculations were made on the UNIVAC 1110 computer of the University Computing Centre in Zagreb with the system of programs XRAY 76[29] and locally written programs for data reduction and CSK program for chemical connectivity relationship.

Crystal Structure of (13).—*Crystal data*. $C_{21}H_{41}NO_7$, M_r = 547.57, Orthorhombic, *a* = 25.304(10), *b* = 9.494(4), *c* = 11.924(5) Å, *V* = 2 864.6 Å^3, space group $P2_12_12_1$, *Z* = 4, D_c = 1.268 g cm^{-3}, *F*(000) = 1 136, μ (Mo-K_α) = 10.55 cm^{-1}

Three-dimensional data were collected on the same diffractometer as for the aglycone (7), using Mo-K_α radiation (λ = 0.7107 Å), ω — 2θ scan technique in the range 3 > θ > 30°, scan width 1.20 °C and scan speed 0.04° s^{-1}. 3 595 Reflections were considered observed [$I > 3\sigma(I)$] and included in the structure determination and refinement. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by means of the three-dimensional Fourier synthesis based upon the iodine atom co-ordinates obtained from Patterson synthesis. The co-ordinates of all non-hydrogen atoms were refined by the least-squares method using anisotropic temperature factors up to an *R* index of 0.14 (R_w = 0.20). Unit weights were allotted to all observations. Hydrogen atoms were located either in a difference Fourier map or at calculated positions since they were all bonded to carbon or oxygen of well defined geometry. They were not refined. Calculations were performed in the same manner and on the same computer as for the structure of aglycone (7) using the set of programs SYST75.[29]

Hydrogen atom co-ordinates and anisotropic temperature

factors for both compounds (7) and (13) are available as a Supplementary Publication [SUP No. 56631 (12 pp.)]* Structure factor tables are available on request from the Editorial office.

* For details of the Supplementary Publication scheme see Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1

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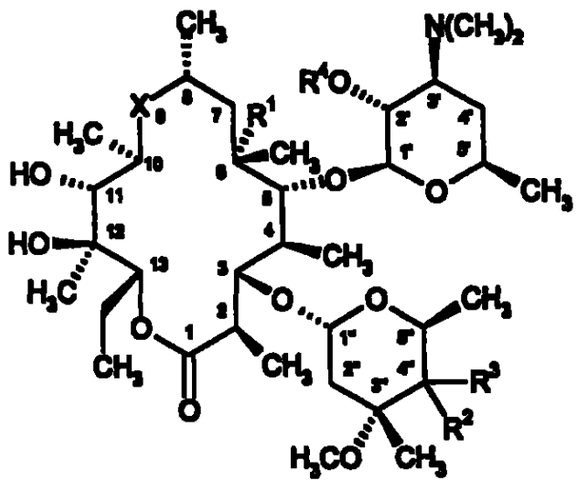
Published
With international search report.

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

(57) Abstract

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



(1)

will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 4 mg/kg/day to about 60 mg/kg/day is most desirably employed. Variations may nevertheless occur depending upon the species of mammal, fish or bird being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time-period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day

The active compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the active compounds may be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active compound may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof

For parenteral administration, solutions of an active compound in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are

suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques will known to those skilled in the art.

Additionally, it is also possible to administer the active compounds of the present invention topically and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard pharmaceutical practice.

For administration to animals other than humans, such as cattle or domestic animals, the active compounds may be administered in the feed of the animals or orally as a drench composition.

The active compounds may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The active compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide phenyl, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoylresidues. Furthermore, the active compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The following Examples further illustrate the method and intermediates of the present invention. It is to be understood that the present invention is not limited to the specific details of the Examples provided below.

Table 1

The compounds of Examples 1-18 have the general formula 6 below with the R substituents indicated in the table below. The compounds were prepared as described in Preparations 1-6 below. In the table, the yield and mass spectra ("Mass Spec") data apply to the final product.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Carlos R. Olarte **Oficio Nº 4577**
Apoderado
PFIZER PRODUCTS INC.

REFERENCIA	**Radicación**	**01 287**
	Trámite	**002**
	Evento	**001**
	Actuación	**430**
	Folios	**009**

Como resultado del examen de patentabilidad de la solicitud de patente de invención Nº 01 287, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

- El resumen y el capítulo descriptivo de la invención en los folios 194 y 130 a 187 respectivamente.
- Las cláusulas 1 a 22 relacionadas en el capítulo reivindicatorio de la solicitud y que se encuentran en los folios 188 a 193.
- El primer examen de forma de la solicitud realizado a la solicitud de oficio No. 936 que se encuentra en el folio 201.
- La copia de la solicitud original mediante la cual se reivindica prioridad de Estados Unidos US60/178.481 de 27/01/2000 en los folios 84 a 129, junto con su traducción correspondiente en los folios 14 a 83.
- La respuesta al primer examen de forma, allegada mediante memorial de fecha 23/07/2001, que se encuentra en los folios 204 a 212.
- La solicitud de examen de patentabilidad junto con el pago de la tasa correspondiente que se encuentra en los folios 214 y 215.
- El primer examen de fondo efectuado a la solicitud No. 813 y que se encuentra en los folios 217 a 235.
- La respuesta al primer examen de fondo allegada a esta dependencia mediante memorial de fecha 03/10/2005 y que se encuentra en los folios 238 a 250.
- El nuevo capítulo reivindicatorio allegado en atención a las recomendaciones formuladas en el primer examen de fondo y que se encuentra en los folios 245 a 250 con veinte cláusulas reivindicatorias.
- El requerimiento de información técnica efectuado en virtud del artículo 46 de la norma Andina de oficio No. 14620 y concepto técnico No. 1941 que se encuentra en los folios 251 y 252.
- La respuesta al requerimiento de información técnica allegada mediante memorial de fecha 02/02/2007 que se encuentra en los folios 253 a 262.

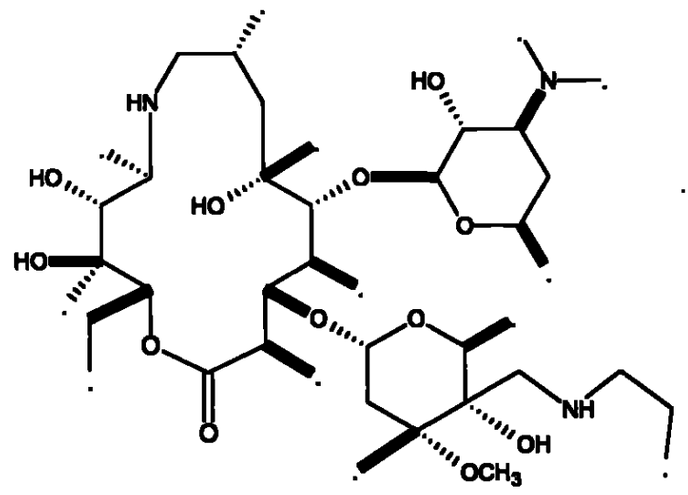
2. OBJETO DE LA INVENCIÓN:

La solicitud hace referencia a ***"Compuestos antibióticos de azalida"***

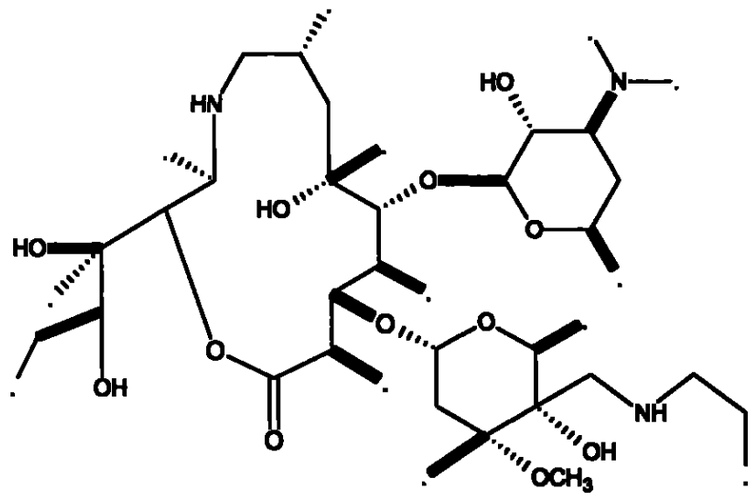
- **Reivindicación 1:**

Se reivindica una composición que comprende:

a) el compuesto de fórmula (I):



Y el compuesto de fórmula (II):



En una proporción desde aproximadamente 90% ± 4% a aproximadamente 10% ± 4% respectivamente.

b) agua; y
c) uno o más ácidos presentes a una concentración total desde aproximadamente 0,2 mmol a aproximadamente 1,0 mmol/ml de la composición.

- **Reivindicación 2:**

Se reivindica un método para obtener la composición de la reivindicación 1, que comprende la etapa de calentar hasta una temperatura desde aproximadamente

50°C a aproximadamente 90°C una mezcla que comprende:

a) el compuesto de fórmula (I),
b) agua; y
c) uno o más ácidos presentes en una cantidad que varía desde aproximadamente 0,2mmol a aproximadamente 1,0mmol/ml de la mezcla;

y el pH de la mezcla varía desde aproximadamente 5,0 a aproximadamente 8,0.

- **Reivindicaciones 3 a 11 y 16 a 18:**

Se reivindica una composición que comprende:

a) Una primera mezcla de:

i) el compuesto de fórmula (I) y el compuesto de fórmula (II), en una proporción desde aproximadamente 90% ± 4% a aproximadamente 10% ± 4%, respectivamente;
ii) agua; y
iii) uno o más ácidos presentes a una concentración total desde aproximadamente 0,2 mmol a aproximadamente 1,0mmol/ml de la primera mezcla, dentro de los que se encuentran el ácido acético, ácido bencensulfónico, ácido cítrico (0,02mmol a aproximadamente 0,3mmol/ml de la composición), ácido bromhídrico, ácido clorhídrico (presente en cantidad suficiente para lograr un pH entre 5 y 6), ácido D- y L-láctico, ácido metanosulfónico, ácido fosfórico, ácido succínico, ácido sulfúrico, ácido D- y L-tartárico, ácido p-toluensulfónico, ácido atípico, ácido aspártico, ácido canforsulfónico, ácido 1,2-etanodisulfónico, entre otros...

b) uno o más codisolventes miscibles en agua, presentes en una cantidad desde aproximadamente 250 a aproximadamente 750mg/ml de la composición, que se selecciona del grupo formado por: etanol, isopropanol, dietilenglicol monometil éter, dietilenglicol butil éter, dietilenglicol monoetil éter, dietilenglicol dibutil éter, polietilenglicol-300, polietilenglicol-400, propilenglicol (en una cantidad desde aproximadamente 450 a 550 mg/ml de la composición), glicerina, 2-pirrolidona, N-metil-2-pirrolidona, glicerol formal, entre otros...

En particular se reivindica la composición en la cual la concentración de la primera mezcla varía desde 50mg/ml a aproximadamente 200mg/ml y más específicamente entre 90mg/ml y 110mg/ml. Y en la que el ácido cítrico está presente en una cantidad desde aproximadamente 0,02 mmol a aproximadamente 0,3mmol/ml de la composición y el ácido clorhídrico está presente en una cantidad suficiente para lograr un pH de la composición entre 5 y 6; el propilenglicol está presente en una cantidad desde aproximadamente 450 a aproximadamente 550mg/ml de la composición y el monotioglicerol en una cantidad desde 4mg/ml a 6 mg/ml de la composición.

- **Reivindicaciones 12 a 15:**

Se reclama la composición definida en la cláusula 3 que además comprende un agente antioxidante en una cantidad desde 0,01 a 10 mg/ml de la composición, que se selecciona del grupo: bisulfito de sodio, sulfito de sodio, metabisulfito de sodio, tiosulfato de sodio, formaldehído sulfoxilato de sodio, ácido L-ascórbico, ácido eritórbico, acetilcisteína, cisteína, monotioglicerol (4mg/ml a 6mg/ml de la composición), ácido tioglicólico, ácido tioláctico, tioúrea, ditiotreitol, ditioeritreitol,

glutation, palmitato de ascorbilo, hidroxianisol butilado, entre otros...

- **Reivindicación 19:**

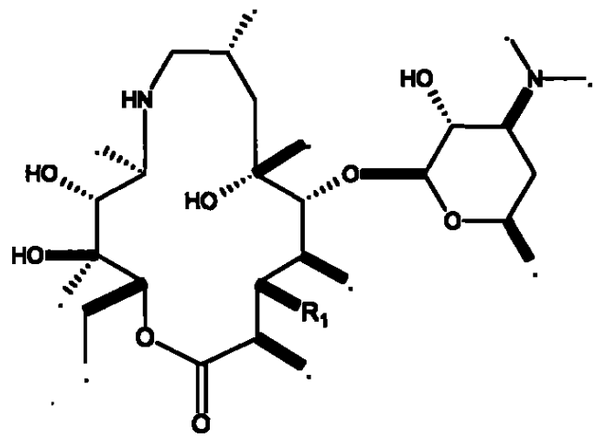
Se reivindica un método para obtener la composición descrita en la cláusula 3 que comprende la etapa de calentar hasta una temperatura desde aproximadamente 50°C a aproximadamente 90°C una mezcla que comprende:

a) el compuesto de fórmula (I)
b) agua; y
c) uno o más ácidos en una cantidad que varía desde aproximadamente 0,2mmol a aproximadamente 1,0mmol/ml de la mezcla;

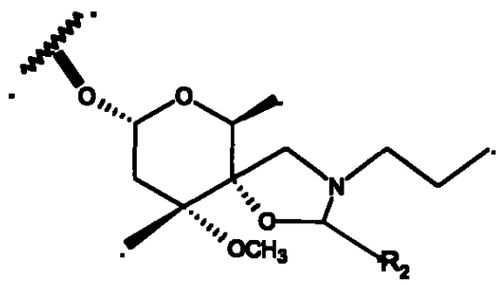
y uno o más codisolventes miscibles en agua se añaden antes, durante o después de la etapa de calentamiento, en una cantidad desde aproximadamente 250 a aproximadamente 750mg/ml de la composición.

- **Reivindicación 20:**

Se reclama un compuesto de fórmula:



O su sal farmacéuticamente aceptable, en la cual R_1 es OH ó



Y en la cual R_2 es H o CH_3.

Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K $^{31}/_{7048}$ de la Clasificación Internacional de Patentes.**

3. CLARIDAD DE LA SOLICITUD:

- El **artículo 28** de la Decisión 486 contempla que: *"La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla.*

La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información:

b) la tecnología anterior conocida por el solicitante que fuese útil para la comprensión y el examen de la invención, y las referencias a los documentos y publicaciones anteriores relativas a dicha tecnología;

c) una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior;

e) una descripción de la mejor manera conocida por el solicitante para ejecutar o llevar a la práctica la invención, utilizando ejemplos y referencias a los dibujos, de ser éstos pertinentes".

- El **artículo 30** de la Decisión 486 contempla que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

De acuerdo con el aparte descriptivo de la solicitud las mejoras a las formulaciones farmacéuticas convencionales en lo que a estabilidad se refiere se hacen palpables en la actividad farmacológica superior de las composiciones reivindicadas porque contienen un isómero en particular de un compuesto antibiótico de azalida cuyo anillo de lactona y los azúcares de las azalidas no se hidrolizan con facilidad (ver folios 16 y 17).

En consecuencia, esta Dependencia no ha solicitado de manera caprichosa los estudios comparativos que hagan referencia a una medida de la actividad de los compuestos formulados de manera novedosa con respecto a las formulaciones convencionales que sufren descomposición y por consiguiente pérdida de la actividad farmacológica. El interesado, en el aparte descriptivo de su solicitud, ha esgrimido que parte del problema técnico constituía la disminución de la actividad farmacológica de las composiciones convencionales porque no contenían los isómeros de fórmulas (I) y (II) que han sido formulados de manera inventiva y constituyen el objeto reclamado.

Ahora bien, si solo se efectuaron estudios relacionados con la estabilidad mejorada para esta Dependencia no es claro cuál es el marcador que se utiliza para cuantificar la estabilidad del producto - que en realidad debe ser relativo al principio activo o a un excipiente determinante -.

Si bien es cierto, el ejemplo 2 de los folios 59 a 67, contiene un estudio estadístico por bloques que compara ensayos en los que se varía la concentración de la mezcla, el pH, la adición de un codisolvente e incluso la adición de ácido en formulaciones selladas en viales de vidrio y sometidas a almacenamiento durante 12 semanas y a una temperatura de 50°C, nunca se hizo referencia a las composiciones convencionales que constituyen el marco de referencia para cuantificar la estabilidad

superior de las formulaciones inventadas. Por el contrario todos los datos sólo hacen referencia al porcentaje del isómero (I) y del isómero (II) que permanece intacto al interior de los viales.

4. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la solicitud en estudio - 27.01.2000-, relacionados con la materia técnica reivindicada:

Nº	Documento	Título	Fecha de Publicación
D1	WO9856802	"4´´-substituted-9-deoxo-9A-aza-9A-homoerythromycin a derivatives"	17/12/1998
D2	Artículo 1	"Erythromycin series. Part 11. Ring expansion of erythromycin a oxime by the beckmann rearrangement"	1986
D3	WO9856801	"C-4-substituted macrolides derivatives"	17/12/1998

Anterioridad D1 en los folios 217 a 227, anterioridad D2 en los folios 254 a 262 y anterioridad D3 en los folios 263 a 265.

5. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD:

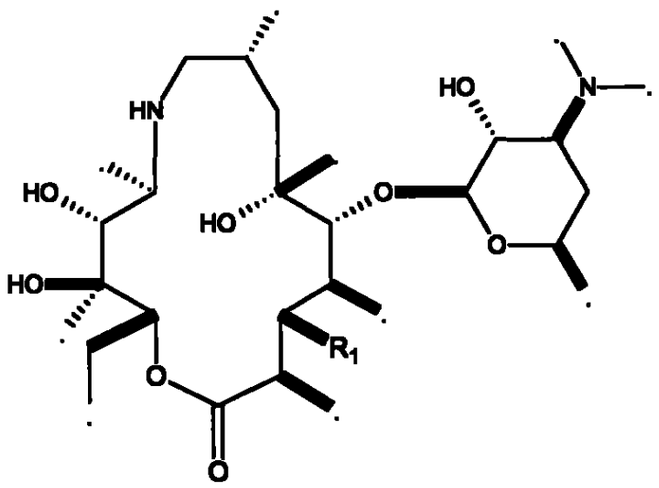
El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*"

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

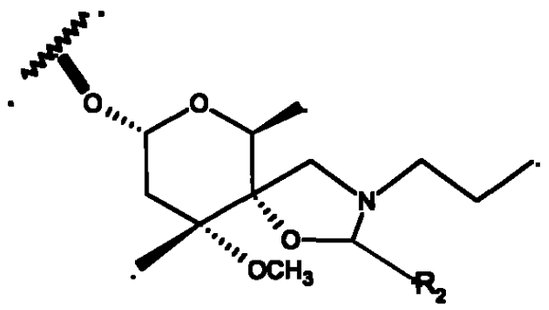
5.1 Evaluación de NIVEL INVENTIVO:

El artículo 18 de la decisión 486 dispone "*Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica*".

Teniendo en cuenta que la cláusula 20 continúa reclamando un compuesto de fórmula:

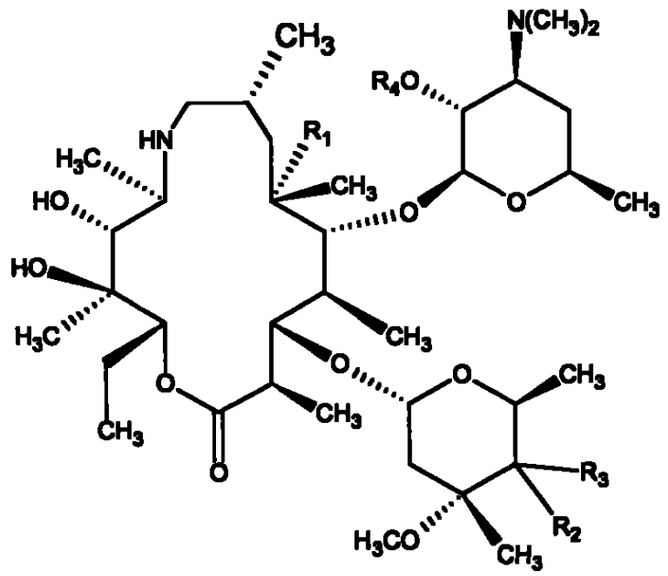


O su sal farmacéuticamente aceptable, en la cual R_1 es OH ó



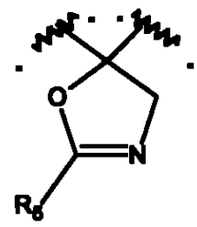
En la cual R_2 es H o CH_3.

<u>Y que la anterioridad D1 comprende compuestos de fórmula:</u>



Para la cual:

R_1 es H
R_2 y R_3 forman juntos el radical del anillo de oxazol tal como se señala a continuación:



R_4 es H
R_5 es alquilo de 1 a 10 átomos de carbono

Se señala al interesado que por tratarse de compuestos ampliamente conocidos en el estado de la técnica y análogos estructurales de los compuestos revelados por la anterioridad en mención D1, se encuentra afecto el requisito de nivel inventivo.

La diferencia mencionada por el interesado en la que se recurre a la estructura resonante de oxazolidina, no resulta relevante porque cualquier persona versada en la materia técnica reconoce que la diferencia en comento que tiene su asiento en la estructura reducida correspondiente al anillo de 4,5-dihidrooxazol, no marca diferencia alguna respecto del comportamiento biológico del compuesto.

Tanto el compuesto reclamado como el que afecta su nivel inventivo conservan el mismo grupo farmacofórico, en consecuencia la estructura de fórmula (I) al derivarse evidentemente del estado de la técnica no precisa un salto cualitativo en la regla técnica.

La anterioridad **D2** también constituye un indicio amplio y suficiente respecto de la derivación evidente que constituye la inclusión de un grupo etilo y la reducción del anillo de oxazolidina para formar un grupo N-etil-4,5-dihidrooxazol sobre un macrólido de estructura más compleja que presenta en el carbono 3 una sustitución de tipo cladinosilo (ver folio 254).

En este orden de ideas si se combinan las enseñanzas de los documentos **D1** y **D2** resulta más clara la afectación del requisito de nivel inventivo respecto del alcance de la cláusula 20 que reivindica un compuesto estructuralmente análogo a los revelados por las publicaciones en comento.

La publicación **D3** enseña que para la formulación de macrólidos análogos a los reclamados por la solicitud se utiliza comúnmente soluciones buffer que presenten pH de 8 y un diluente líquido que garantice la isotonicidad. El documento en particular señala el uso de soluciones acuosas de propilenglicol disolvente.

En consecuencia, como la solicitud reclama protección para las formulaciones farmacéuticas que contengan compuestos de fórmulas (I) y (II) en agua y uno o más ácidos (ver folio 134 de la descripción) y como dicho concepto inventivo había sido previamente utilizado para formular compuestos análogos estructurales de los isómeros (I) y (II) que se emplean en la formulación reclamada, resulta claro que existe derivación evidente del estado del arte.

De otro lado si la solución al problema técnico consiste en el diseño de un sistema de formulación que no permita la isomerización y que admita conservar uno solo de los dos isómeros posibles o una proporción fija de ellas, cuya composición comprende solamente agua y ácido, resulta claro que la anterioridad **D3** ya señalaba el camino para formular sistemas líquidos, para análogos estructurales de los compuestos reclamados, que comprendiera agua y ácido.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO9856802	20	Nivel Inventivo
D2	Artículo 1	20	Nivel Inventivo
D3	WO9856801	1 a 19	Nivel Inventivo

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única Nº 10 de 2001.

Álix Carmenza Céspedes de Vergel
Jefe División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 19 ABR. 2007

CONCEPTO TÉCNICO Número 0559	**EXAMINADOR TÉCNICO** Código 202044

WO0155158.

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INTERNATIONAL SEARCH REPORT

Inter vel Application No
PCT/IB 00/01824

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H17/00 A61K31/70 A61P31/04 A61P33/02

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, PAJ, MEDLINE, BIOSIS, 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	WO 98 56802 A (BRONK BRIAN SCOTT ;LETAVIC MICHAEL ANTHONY (US); YANG BINGWEI VERA) 17 December 1998 (1998-12-17) cited in the application scheme 3	1-5,21, 22
A	WO 98 56801 A (BRONK BRIAN SCOTT ;LETAVIC MICHAEL ANTHONY (US); YANG BINGWEI VERA) 17 December 1998 (1998-12-17) the whole document	1-5,21, 22

-/-

[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
19 April 2001	02/05/2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-4040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Scott, J

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

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/IB 00/01824

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DJOKIC S ET AL: "ERYTHROMYCIN SERIES. PART 11. RING EXPANSION OF ERYTHROMYCIN A OXIME BY THE BECKMANN REARRANGEMENT" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1,CHEMICAL SOCIETY. LETCHWORTH,GB, no. 11, 1986, pages 1881-1890, XP002077691 ISSN: 1472-7781 page 1887, compound 12	22
P,A	WO 00 69874 A (RAFKA ROBERT JOHN ;PFIZER PROD INC (US); ALLEN DOUGLAS JOHN MELDRU) 23 November 2000 (2000-11-23) the whole document	1-5,21, 22

·2

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

EXAMEN TECNICO DE FONDO			
Nº Radicación	01-287	Fecha de presentación	03/01/2001
Nº Prioridad	US60/178,481	Fecha de Prioridad	27/01/2000

Palabras clave:	ANALOGOS DE AZITROMICINA	AZALIDA	MACROLIDOS

CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
A61K31/7048

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES	
Patente Original	
WO0155158	

BASES DE DATOS CONSULTADAS	
ESPACENET	EPOLINE

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Oficina	Fecha	Reivindicaciones
EPO		

ANTERIORIDADES ENCONTRADAS		
Documento	Relevancia	Reivindicaciones afectadas
WO9856802	Novedad	22

LITERATURA NO PATENTES		
Documento no Patentes	Relevancia	Reiv. Afectadas

Observaciones	(Requerir 46**)

Fecha del examen	19/05/2006