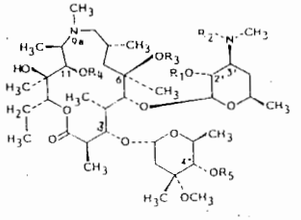
04-Crystallography of Biological Small Molecules

PS-04.01.12 STRUCTURAL STUDY OF TRIAZOLE ANTIFUNGALS. By T. Hata*, Y. Furukawa, T. Konosu+ and S. Oida+, Analytical and Metabolic Research Laboratories, +Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., Tokyo, Japan

New triazolylmethyl-oxazolidine and -amidoalcohol derivatives were designed and synthesized as potential inhibitors against fungal cytochrome P-450 14α-demethylase. Among them, (4*R**,5*R**)-5-(2,4-difluorophenyl)-4-methyl-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-3-[4-(trifluoromethyl)benzoyl]oxazolidine shows excellent antifungal activity, in contrast to poor activity for the (4*S**,5*R**)-diastereoisomer. And (2*R**,3*R**)-2-(4-chlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-[[4-(trifluoromethyl)benzoyl]a mino]-2-butanol also has potent activity. The crystallographic studies of these three compounds have revealed the relationship between three-dimensional structures and activities. In the two diastereoisomers, the different configuration at the 4-position of the oxazolidine ring causes the differences in the ring conformation and in the three-dimensional structure. The molecular structure of the amidoalcohol derivative is similar to that of the (4*R**,5*R**)-diastereoisomer of the oxazolidine derivative. These two active compounds are superimposable on lanosterol, which is a substrate of cytochrome P450 14α-demethylase. The methyl groups at the 4-position of the oxazolidine derivative and at the 3-position of the amidoalcohol derivative are situated in same orientation as the 13β-methyl group of lanosterol. These methyl groups are expected to play an important role in antifungal potency, since the corresponding demethyl analogs of the oxazolidine and amidoalcohole derivatives are significantly less active.

PS-04.01.13 STRUCTURAL INVESTIGATIONS OF AZITHROMYCIN, ITS DERIVATIVES AND COPPER COMPLEX. By B. Kamenar*, N. Košutić-Hulita, D. Mrvoš-Sermek, A. Nagl, I. Vicković, Laboratory of General and Inorganic Chemistry, Faculty of Science, The University, Zagreb, Croatia, S. Đokić, G. Kobrehel, G. Lazarevski, N. Lopotar, M. Vinković, PLIVA, Pharmaceutical Industry, Research Institute, Zagreb, Croatia, B. Metelko, D. Vikić-Topić, Ruđer Bošković Institute, Zagreb, Croatia.

Azithromycin (1) was the first representative of a new class of 15-membered macrolide antibiotics with improved pharmacokinetics and greater activity as compared to erythromycin A (Đokić, S. *et al.*, 1988, J. Chem. Res. (S) pp. 152-153). Here we report the structures of one of its derivatives (2), 2:1 solvate of azithromycin with dimethyl sulfoxide (3), and 1:2 complex of copper(II) with azithromycin (4). Both (1) and (2) are dihydrates.



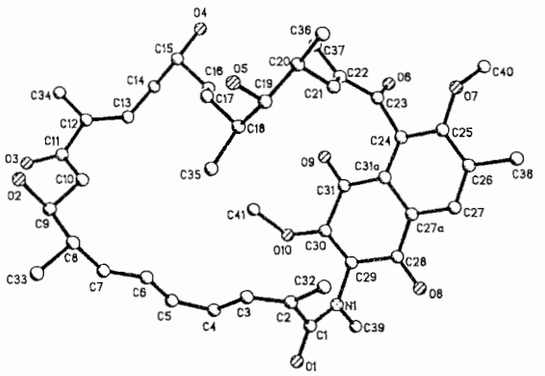
(1) $R_1=R_3=R_4=R_5=H$ $R_2=CH_3$
(2) $R_1=R_2=R_3=R_4=R_5=H$
(3) as (1) but a solvate with DMSO

(2): space group $P2_12_12_1$, $Z=4$ $C_{37}H_{70}N_2O_{12}\cdot 2H_2O$, $a=19.627$, $b=16.651$, $c=14.534$ Å. (3): space group $P2_1$, $Z=2$ $(C_{38}H_{72}N_2O_{12})_2\cdot(CH_3)_2SO$, $a=18.422$, $b=16.301$, $c=16.385$ Å, $\beta=109.10^0$. (4): space group $P2_1$, $Z=2$ $Cu(C_{38}H_{71}N_2O_{12})_2$, $a=19.143$, $b=23.491$, $c=12.486$ Å, $\beta=95.71^0$. All structures were determined by direct methods. At the present stage of refinement the *R* indices are 0.087, 0.114 and 0.154 for 2396 (structure 2), 4643 (structure 3) and 2333 (structure 4) observed reflections, respectively. The crystals of (4) were of poor quality, and decomposed significantly during the data collection. The characteristic feature of the structures is a strong intramolecular hydrogen bond (2.60 to 2.73 Å) between OH(R_3) group and N9a atom. Also, in all structures the azithromycin molecules as well as the solvent molecules participate in the extended hydrogen-bonding networks built up in the crystal structures. In the metal complex the copper atom, chelated by two azithromycin molecules, is bonded to two tertiary nitrogen (2.01 and 2.05 Å) and two hydroxyl oxygen atoms (1.87 and 1.92 Å) from two desosamine-sugar components.

The molecular conformations of the azithromycin molecules in (1) and (3) were determined also in solutions by NMR spectroscopy and molecular mechanics calculations in order to compare them with those found in the crystal structures. In the crystal structure of (1) the azithromycin molecule in the region between C3 and C5 exists in a "folded-out", while in solution it predominantly adopts a "folded-in" conformation. This is opposite than observed in the structures of azithromycin-DMSO solvate and in the 14-membered erythromycin derivatives in which the macrolide rings retain the same conformations in solutions as in the solid state. Also, in the crystal structure of (4) both azithromycin ligands adopt a "folded-in" conformation. It seems that the contributions of the "folded-out" conformers increase with the polarity of solvents.

PS-04.01.14 CRYSTAL STRUCTURE OF 30-DECHLORO-30-METHOXY-25-O-METHYL-N-METHYLNAPHTHOMYCIN A By C. Burla[1], M. Brufani[2], L. Cellai[3]*, S. Cerrini[3], W. Fedeli[4], W. Keller-Schierlein[5], D. Lamba[3], [1]Università di Perugia, [2]Università di Roma, [3]Istituto di Strutturistica Chimica, CNR, Roma, [4]Università dell'Aquila, [5]E.T.H. Zurich.

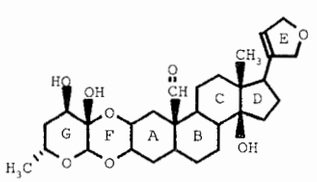
Naphthomycin A is an antibiotic antagonist of vitamin K, active on Gram-positive bacteria and fungi (M. Balerna, W. Keller-Schierlein, C. Martins, H. Wolf, H. Zahner, Arch. Mikrobiol. 1969, 65, 303-317). It also displayed a significant activity against Ehrlich ascitic carcinoma in mice, the tumoricidal action being due to the inhibition of enzymes partecipating in nucleic acid biosynthesis (T. Okabe, B.D. Yuan, F. Isono, I. Sato, H. Fukazawa, T. Nishimura, N. Tanaka, J. Antibiot. 1985, 38, 230-235).
Several attempts to crystallize Naphthomycin A failed, while it was possible to obtain crystals of two derivatives prepared by methylation with CH_3J/Ag_2O. By X-ray analysis, one of the two derivatives proved to be 25-O-methylnaphthomycin A imminomethyl ether (W. Keller-Schierlein, M. Meyer, L. Cellai, S. Cerrini, D. Lamba, A. Segre, W. Fedeli, M. Brufani, J. Antibiot. 1984, 37, 1357-1361), while the other is the title compound.
In the crystal structures of both derivatives the molecules display a similar chair-like shape.



Crystal data: S.G. Orthorombic $P2_12_12_1$, a=12.925(3), b=14.160(4), c=23.970(6) Å, $C_{43}H_{53}NO_{10}.CH_3OH.H_2O$, Fw=793.9, D_c=1.202 Mg/m^3, Z=4, Mo-Kα radiation; R=0.093 and wR=0.083 for 3002 Fo>>2.0 (Fo).

PS-04.01.15 CRYSTAL STRUCTURE OF CALACTIN, A CARDENOLIDE FROM ASCLEPIAS LINARIA By T. Hernández-Quiroz*, M. Soriano-García, A. Rodríguez-Romero, C. Valencia, L. Hernández and F. Aguirre. Instituto de Química Uninversidad Nacional Autónoma de México, Delegación Coyoacán, México D.F. 04510, México and Area de Productos Naturales, Departamento de Biotecnología, Universidad Autónoma Metropolitana-Unidad Iztapalapa, Delegacíon Iztapalapa, México D.F. 09340, México.

Cardenolides constitute one of the several groups of plant secondary compounds that are sequestered by phytophagous insects for defense against predation. Most members of the genus Asclepias (Asclepiadaceae) produce the cardiac steroids at varying concentrations. The molecular structure is determined from the X-ray data and confirms the structure previously assigned on the basis of chemical and spectroscopic evidence.The title compound, $C_{27}H_{39}O_9 \cdot 2H_2O$, is crystallized in orthorhombic space group, $P2_12_12$ with Z=8. The cell parameters are : a=29.868(7), b=12.567(4), c=14.705(5) Å, R=0.064 and Rw=0.066. In the two independent molecules rings A, B, C, F and G have chair conformations, ring D adopts an envelope conformation and ring E is almost flat. The A/B, B/C, A/F and C/D, F/G ring junctions are *trans* and *cis*, respectively. The crystal structure is stabilized by a three-dimensional network of hydrogen bonds and a number of C-H···O hydrogen bond interactions.



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PS-04.01.16

UNCOMPLEXED IONOPHORE ANALOGS-CRYSTAL STRUCTURE OF MODIFIED 25-CROWN-7 ETHER

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Crown ether macrocycles undergo conformational changes when complexed with various metal salts. The conformation of complexes are often quite different for different salts but in general they all feature the O atoms directed towards the cavity of the macrocycle and the C and H atoms on the periphery. But uncomplexed crown ethers often adopt a more elongated conformation with methylene groups pointing into and filling the cavity. This is usually accomplished by rotation about the bonds to give torsion angles which differ markedly from the expected ±60° for C-C bonds. But only a very small number of C-O torsion angles are usually affected to a major extent when the macrocycle geometry is deformed in order to optimize specific ligand - substrate or intraligand interactions. The 25-Crown-7 ether crystallizes in space group $P\bar{1}$ with a = 10.809(1), b = 10.945(1), c = 10.256(1)Å°, α = 107.85(1), β = 104.15(1), γ =87.27(1)° and Dc =1.318gcm^{-3} for Z=2. The structure was solved and refined to an R-index of 0.049. Three torsion angles in the macrocycle take up gauche conformation in contrast to the usual anti conformation. The crystal structure is stabilized by intramolecular van der Waals forces and C-H...O and C-H...N types of interaction. Stacking of the pyridine rings is a noticeable packing feature in the crystal lattice. Other structural details will also be presented.

PS-04.01.17 STRUCTURE AND FUNCTION STUDY ON DITERPENOID LACTONE IN TRIPTERYGIUM WILFORDII HOOK.F.BY Y.Lu*, Z.Y. Tian, Q.T. Zheng, Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, 100050, China

In china there are three kinds of celastraceue Tripterygium Wilfordii Hook.f., that is Tripterygium Wilfordii Hook.f, Tripterygium hypoglaucum Hutch and Tripterygium Sprague et Takeda, which are distributed in Southwest China, South China and Northeast China.

At the beginning of 30's Chinese scientist Zhao Chenggu first isolated Tripterine from the root to Triperygium wilfordii Hook.f and its structure was determined. Up to now, nearly 20 diterpenoid compounds have been found, which have anti-inflammatory, antitumor, antifertility and immunosuppressive properties. In 1972 Kupchan et al isolated three diterpenoid compounds and found that these compounds have protective action or antitumor activity. The research group in our country showed that these compounds exhibited various biological activities including anti-inflammatory, antitumor, antifertility and immunosuppression.

The crystal structures of Triptolide, Tripdiolide, Triptolidenol, Triptriolide, Tripchlorolide, Tripdioltonide, 16-Hydroxytriptolide and their derivatives have been determined by X-ray diffraction techniques. The structural and conformational properties with bond lengths, bond angles and torsion angles are analysed systematically. Molecular mechanical calculations have been carried out to optimize conformation and structure in solution. The stereostructure-activity relationship is discussed by molecular graphics method.