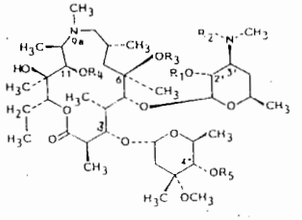
04-Crystallography of Biological Small Molecules

PS-04.01.12 STRUCTURAL STUDY OF TRIAZOLE ANTI-FUNGALS. 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 anti-fungal 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.

