PS-04.05.05 CONFORMATION ANALYSIS OF LIGNANS AND SYNTHETIC ANALOGUES IN SCHISANDRA CHINENSIS, B. Wu, National Laboratory of Biomacromolecules, Institute Biophys., Academia Sinica, Beijing, 100101, China. Y. Lu, Q.T. Zheng, Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, 100050, China.

Schisandra chinensis is a traditional medicinal plant. The compounds isolated from the ethanol extract of Schisandra chinensis are derivatives of dibenzocyclooctadiene lignan. These compounds together with diphenyl dimethyl bicarboxylates, synthetic analogues of schizandrin C, are found to be effective for improvement of liver function and clinical symptoms of chronic hepatitis, particularly for lowering the elevated SGPT. In order to understand structure characteristics and the relationship with their biological activity better, the crystal structures of several dibenzocycloctadiene compounds isolated from different schisandraceae family and diphemyl dimethyl bicarboxylates were determined by X-ray diffraction technique. The structural and conformational properties have been analysed systematically. The analysis indicates that these two types of compounds have similar conformation. Conjugative properties and orientation of side chain groups play a role in Hepatoprotective activity.

PS-04.05.06 CRYSTAL STRUCTURE AND MOLECULAR CONFORMATION OF THE ANTIMALARIAL DRUG: PRIMAQUINE DIPHOSPHATE. Michael Wisz* and T. Srikrishnan, Center for Crystallographic Research, Roswell Park Cancer Institute, Buffalo, NY 14263, USA.

The drug Primaquine [8-(4-amino-1-methylbutylamino)-6-methoxyquinoline], a derivative of 8-aminoquinone, is a potent antimalarial agent which was first isolated by Elderfield et al as early as 1946 (J. Amer. Chem. Soc., 68, 1524, 1946). In addition to its use as an antimalarial agent, it has been used to fight Pneumocystosis carinii, an opportunistic disease common to AIDS patients. An accurate crystal structural investigation of this compound was undertaken as a first step in a possible structure function elucidation of its action. The structural analysis can also be useful to determine as to why primaquine's two optical isomers have different effects in rhesus monkeys. These studies will also shed more light on whether it is primaquine alone or its metabolites that provide the radical treatment of malarial infections.

Samples of the title compound were purchased from Sigma chemicals and crystals were obtained by a slow evaporation of an aqueous solution at room temperature. The crystals belong to the triclinic system, space group $P\bar{1}$, with cell dimensions: a = 7.395 (1), b = 8.865 (1), c = 16.061 (2) Å, α = 82.40 (1), β = 79.81 (1), γ = 77.02 (1)°, V = 1005.3 (2) Å^3, D_{calc} = 1.505 g/c.c., Z = 2. Data was collected on a CAD4 diffractometer (4260 reflections 2492 $\geq 3\sigma$), structure was obtained by direct methods and refined by full matrix least squares to a final R value of 0.045. The crystal structure consists of two phosphate anions and a charged quinone ring. The 6-methoxy group is coplanar with the quinone ring and the lipophilic 4-amino-1-methyl-butylamino group is oriented trans to the quinone ring and has a zig-zag conformation. The molecules are held together by a network of hydrogen bonds between the phosphate anions and the protonated N1 of the quinone ring and N15 of the terminal lipophilic chain. The exact mechanism of action of primaquine is still unclear. Although it is conceived to be similar to chloroquine and melfoquine, their metabolic influences are very different. These have been reported to inhibit a haem polymerase enzyme and inhibit synthesis by nuclei.

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Primaquine diphosphate

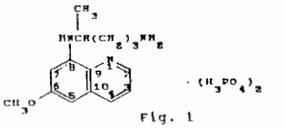


Fig. 1

8-(4-amino-1-methylbutylamino)-6-methoxyquinoline

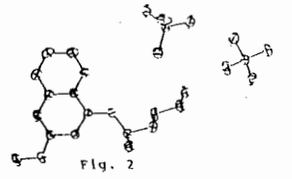


Fig. 2

PS-04.05.07 STUDIES ON THE STRUCTURE AND CONFORMATION OF TRIMETHOPRIM: X-RAY INVESTIGATION OF THE DRUG WITH THREE DIFFERENT CONFORMERS IN THE CRYSTALLINE STATE. Kanthi B. Dasari* and T. Srikrishnan, Center for Crystallographic Research, Roswell Park Cancer Institute, Buffalo, NY 14263, USA.

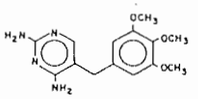
The drug trimethoprim [2,4-diamino-5-(3,4,5-trimethoxybenzyl)]pyrimidine is an antifolate drug, an inhibitor of Dihydrofolate reductase (DHFR) and an antibacterial agent. Trimethoprim (TMP) is most widely used as a broad spectrum antibiotic because of its high selectivity for bacteria rather than human. It is an antibacterial agent administered along with cyclosporine to transplant patients. It binds more tenaciously to DHFR than the folic acid substrate does. DHFR isolated from different sources have different sensitivity to these inhibitors and the enzyme inhibition can be modulated by small variations in the antifolate structure.

Recently we obtained beautiful crystals of TMP from an aqueous methanol solution. These crystals are triclinic space group $P\bar{1}$ with cell dimensions: a = 8.062 (3), b = 10.545 (1), c = 26.842 (5) Å, α = 93.88 (1), β = 94.94 (2), γ = 79.59 (2)°, V = 2233.2 (3) Å^3, μ(cuk α) = 7.36 cm^{-1}, D_{obs} = 1.29 g/cm^3, D_{calc} = 1.297 g/c.c., and Z = 6. Since this is a different crystal form of TMP, than the one solved by Koetzle and Williams (J. Amer. Chem. Soc., 98, 2074, 1976 and Acta cryst B34, 323, 1978), we decided to undertake the structural investigation of this triclinic form using CAD-data. 9365 reflections were collected, out of which 2580 had I $\geq 3\sigma$. The structure was solved by a combination of MULTAN and trial and error methods and refined by full matrix least squares to a final R value of 0.056. There are three independent molecules in the crystallographic asymmetric unit with widely different conformations. The conformation of TMP is described by the torsion angles τ_1 and τ_2 involving the bonds to the linking methylene carbon from the phenyl and pyrimidine ring. The values of τ_1 and τ_2 in the three molecules are 102.4, 47.6; 101.9, 22.1 and 76.6, 23.9° respectively.

The different conformations of TMP observed in this structure demonstrate a conformational flexibility of the molecule. This implies that the enzyme/drug interaction may occur with a variety of conformations of TMP and explains the different sensitivity of DHFR from different sources to TMP. Several analogs of TMP have been studied crystallographically. These studies provide very valuable data on the conformational preferences of TMP in the free state which could be used to carry out modeling studies of DHFR/TMP complexes so as to obtain details of the preferred conformations of TMP in the enzyme-bound state.

Work supported by the New York State Department of Health and the National Science Foundation.

TMP



ORTEP OF TMP