

PS05.01.08 CRYSTAL STRUCTURE OF TOLTERODINE

By B. Sellberg, Pharmacia & Upjohn, Uppsala, Sweden and I. Engström and L.-E. Tergenius, Institute of Chemistry, University of Uppsala, Uppsala, Sweden.

Tolterodine is a drug substance containing (+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen L(+)-tartrate (C₂₆H₃₇NO₇). The drug is used for the treatment of urinary frequency, urgency and/or urge incontinence. The synthesis of tolterodine L(+)-tartrate is a well established procedure.

The crystal structure of tolterodine L(+)-tartrate was determined from single crystal x-ray data at room temperature and 30 K. The structure is monoclinic with two formula units in the unit cell and all the atoms in the general position of the space-group P2₁. The unit cell dimensions at 30 K are a = 9.1759, b = 16.3965, c = 12.9196 Å, β = 93.427°. In the final stage of the refinement the 3568 reflections recorded at 30 K were refined to an R-value of 4.0 %.

PS05.01.09 HYDROGEN BOND INTERACTIONS AND THEIR INFLUENCE ON CONFORMATION OF RETINOIDAL-ACTIVE AND INACTIVE AROMATIC ANILIDES.

Qi Gao, Kuo-Long Yu, Simon Chen, Jacek Ostrowski, John E. Starret Jr., Kenneth M. Trampusch, Peter R. Reczek, Muzammil M. Mansuri, Kevin J. Volk and Mike S. Lee, Bristol-Myers Squibb Company, Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA. Westwood-Squibb Pharmaceuticals, 100 Forest Avenue, Buffalo, NY 14213, USA

Am 580 is a potent synthetic retinoic acid derivative showing selectivity towards one of the retinoic acid receptors, RAR α. Previous studies on the structure-activity relationship and single-crystal analyses of Am580 and its analogs have concluded that their bioactivity is conformation dependent. An extended *trans* conformation is required for specific binding to the retinoid receptors and the loss of activity seems to be ascribed to a remarkable folded *cis* conformation. For a better understanding of the relationship between activity and conformation, we have synthesized a series of fluorinated and alkoxy substituted Am580 retinoids and examined their 3-dimensional structures by X-ray crystallography. All these molecules assume extended conformations in solid state while showing quite different *in vitro* and *in vivo* activity from the parent molecule Am580. This observation confirms that this amide moiety linkage indeed regulates the positional relation between the two groups at opposite ends of the molecules to give a *trans* conformation. However, there are pronounced differences in conformation which are apparently due to different intra- and intermolecular hydrogen bonding interactions involving the functional groups between the neighboring molecules in small molecule crystals. The geometric data of these interactions are consistent with relative intramolecular hydrogen bond strengths ranked in parallel infrared and NMR studies, suggesting a similarity of conformation in solid state and in solution. A detailed analysis of these hydrogen bonds is thus expected to provide some insight into the interactions between the retinoids and the receptors when forming complexes.

PS05.01.10 ABSOLUTE CONFIGURATION OF THE POTENT ANTIMALARIAL AGENT HALOFANTRINE. Jean M. Karle, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, D.C., USA

The absolute configuration of the single chiral center of halofantrine has been determined by x-ray diffraction to be S for (-)-halofantrine and R for (+)-halofantrine. This assignment allows comparison of (+)- and (-)-halofantrine's biological activity with either quinine or quinidine. Halofantrine, quinine, and quinidine are all clinically used amino alcohol antimalarial agents. Even though quinine and quinidine are diastereomers, the quinoline, amine, and alcohol portions of the molecule mirror each other. Although quinidine is more potent than quinine *in vitro*, halofantrine's enantiomers have not shown a difference in *in vitro* antimalarial activity. This may be due to the flexibility of halofantrine's acyclic amine portion of the molecule. The flexibility is exemplified by the O-C-N-H torsion angle being 32.9° for (-)-halofantrine HCl and 165.4° and 172.6° for the two (-)-halofantrine conformers in crystalline racemic halofantrine HCl (Karle & Karle, *Acta Cryst.* C45, 1248-1250, 1989). However, like quinidine, at higher doses of halofantrine, prolongation of the cardiac QT interval was observed clinically. Quinidine is more cardiotoxic than quinine and shares the same configuration with (+)-halofantrine of the carbon atom adjacent to the aromatic ring bearing the hydroxyl group and the same conformation of the hydroxyl group with respect to the aromatic ring. Quinine, the less toxic compound, shares the same absolute configuration with (-)-halofantrine as well as close to the same conformation of the hydroxyl oxygen atom with respect to the aromatic ring. Following oral administration of racemic halofantrine, the (+)-isomer has higher plasma concentrations than the (-)-isomer. Intermolecular hydrogen bonding with the alcohol and amine groups of halofantrine may be important for biological activity. Both groups form hydrogen bonds to different chloride anions.

(-)-Halofantrine hydrochloride, C₂₆H₃₁Cl₂F₃NO•Cl-, crystallized in space group P2₁2₁2₁ with a=6.290(1), b=13.533(3), and c=30.936(6) Å, V=2633.2(7) Å³, Z=4, R=4.68% for reflections with |F_o| > 3σ(F). For the enantiomorph, R=5.99%.

PS05.01.11 STRUCTURAL AND CONFORMATIONAL STUDIES ON TAXOIDS M. Milanese⁺ G. Appendino^{*P}, Ugliengo⁺ and D. Viterbo^{+Dip.} di Chimica IFM and ^{*Dip.} di Scienza e Tecnologia del Farmaco, Torino, Italy.

Paclitaxel (Taxol®) and some related molecules are important antitumor drugs, currently used for the treatment of ovarian and breast cancer. Structure-activity studies have shown that the terpenoid core behaves as a scaffold, keeping the aminoacidic side chain in the right place for the binding to the receptor surface. Because of the chain flexibility, it is not clear which conformation is recognized by the tubuline receptor and the present study is addressed to clarify this problem.

We have carried out the crystal structure analysis of baccatin III, corresponding to the terpenoid core of Paclitaxel, and of three other naturally occurring Taxoids. The conformation of the terpenoid core is very similar in all these compounds.

At the same time we have undertaken a theoretical conformational study on the aminoacidic side chain in order to assess the importance of intra- and intermolecular hydrogen bonds in dictating the most stable conformers in polar and apolar media. The possible conformations of the main skeleton of the side chain were taken from the crystal structures of Taxotere and Paclitaxel and from NMR results and molecular mechanics calculations. On these conformations we have carried out Hartree-Fock *ab-initio* calculations [6-31G(d,p) basis set and full geometry optimization] using a simplified model of the chain. The results of this analysis