PS05.01.08 CRYSTAL STRUCTURE OF TOLTERODINE By B. Sellberg, Pharmacia & Upjohn , Uppsala, Sweden and I. Engstrm 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-phenylprolylamine hydrogen L(+)-tartrate ($C_{26}H_{37}NO_7$).The drug is used for the treatment of urinary frequency, urgency and/or urge incontinence. The synthesis of tolterodin 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 $P2_1$. The unit cell dimensions at 30 K are a = 9.1759, b = 16.3965 c =12.9196Å , = 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. Tramposch,+ 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 retinoidal 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, $C_{26}H_{31}Cl_2F_3NO^+ \cdot Cl^-$, crystallized in space group $P2_12_12_1$ with a=6.290(1), b=13.533(3), and c=30.936(6) Å, V=2633.2(7) Å^3, Z=4, R=4.68% for reflections with $|F_o| > 3\sigma(F)$. For the enantiomorph, R=5.99%.

PS05.01.11 STRUCTURAL AND CONFORMATIONAL STUDIES ON TAXOIDS M. Milanesio+ 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

show that: *i)* the gas-phase minimum energy conformation corresponds to that found in Taxotere while all other conformers have energy at least 2.0 kcal/mole higher; *ii)* when simulating a polar solvent by the continuum Onsager method, there are five different conformations differing by less than 1.0 kcal/mole, suggesting their possible coexistence in solution in keeping with the NMR results; *iii)* among these five conformations one is similar to that found in the crystal structure of Paclitaxel.

PS05.01.12 THE EFFECT OF SOLVENT AND CONFORMATIONAL CHANGES ON THE ELECTRON DENSITY AND ELECTROSTATIC POTENTIAL OF TAMOXIFEN [p-(DIMETHYLAMINO-2 ETHOXY)PHENYL]-1 *TRANS*-DIPHENYL-1,2 BUTENE-1. Dan A. Buzatu, and Edwin D. Stevens, Dept. of Chemistry, University of New Orleans.

The goal of the study was to investigate the effect of conformational changes and solvent on the electron density and electrostatic properties of the antitumor drug Tamoxifen. The different geometries were obtained by doing a molecular dynamics simulation using water as the solvent in C.H.A.R.M.M. The density and electrostatic potential surface for each conformation was calculated from experimental multipole model densities by assuming that the multipoles coordinate systems follow the changes in the atomic positions, and their populations remain unchanged. The X-ray data was collected using Mo Kα radiation at 100 K. These results were then compared with densities and electrostatic potential surfaces obtained from ab initio calculations at the 6-31G* level for the same conformations. The ultimate aim of this work is to simulate the behavior of a drug in blood.

PS05.01.13 FREE RADICAL CATION TETRACUPRO SALTS OF ANTIHISTAMINES. Masood_Parvez and Aaliya P. Sabir, Department of Chemistry,University of Calgary, Calgary, Alberta, Canada T2N 1N4

The free radical cations of a number of anti-histamines effective on H_1- receptor sites, e.g., clemizole (1), chlorpyramine (2) and triprolidine (3) have been synthesized and the crystal structures of the dications of these drugs in association with $CuCl_4^{2-}$ determined by the single crystal XRD method.

Crystal data:

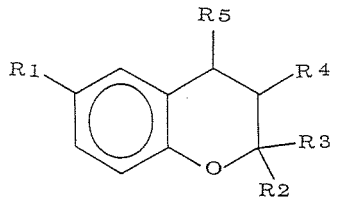
(1) $C_{19}H_{21}N_3 \cdot CuCl_4$, $M_r = 496.75$, triclinic, P 1, a= 9.595(5), b= 14.008(4), c= 9.413(5) Å, a= 93.53(3), ,ß= 117.14(4), γ = 85.03(3)°, V= 1121.3(10) Å^3, Z= 2, D_c = 1.47 Mg m^{-3}, λ(Mo Kα) = 0.71069 Å, ∝= 1.459 mm^{-1}, R = 0.039, wR = 0.036 for 2388 observed data with $I > 3\sigma(I)$.

(2) $C_{16}H_{22}ClN_3 \cdot CuCl_4$, M_r= 497.18, monoclinic, P21/a, a = 14.355(2), b= 7.836(2), c= 20.353(2) Å, ß= 106.74(1)°, V = 2192.3(6) Å^3, Z=4,D_c= 1.51 Mgm^{-3},l (MoKα)=0.71069Å, μ= 1.610mm^{-1}, R=0.036, wR =0.035 for 1212 observed data with $I > 3\sigma(I)$.

(3) $C_{19}H_{24}N_2 \cdot CuCl_4$, M_r = 485.77, monoclinic, P21/n, a= 10.100(2), b= 11.777(3), c= 18.291(2) Å, ß= 94.32(1)°, V= 2169.6(7) Å^3, Z=4,D_c= 1.49Mgm^{-3}, λ (MoKα)=0.71069Å, μ= 1.512mm^{-1}, R=0.092, wR= 0.086 for 1176 observed data with $I > 3\sigma(I)$.

PS05.01.14 CONFORMATIONAL ANALYSES OF FIVE NOVEL SMOOTH MUSCLE RELAXANT AGENTS. Qing-chuan YANG, Hong-ming LI, You-qi TANG (Department of Chemistry, Peking University, Beijing 100871, PRC) Wenlong Huang (Institute of Pharmacochemistry, China Pharmaceutical University, Nanjing 210009, PRC)

The benzopyran compounds have been extensively studied as potassium channel activator which relax smooth-muscle and lower blood pressure. Praeruptorin C isolated from chinese "Qian-Hu" herbal drug, also belonging to benzopyran compound, was demostrated to cause inhibition of the calcium-induced tension development in vascular smooth muscle and myocardial muscle, similar the effects of a calcium antagonist. According to the molecular feature of praeruptorin C, 50 analogue compounds were synthesized. the conformational analyses of the five compounds showing higher inhibition of the calcium entry into smooth muscle cells induced by high-K^+ were carried out with single-crystal X-ray analyses.



Compound	R1	R2,R3	R4	R5
1	NO_2	CH3	H	:NOCOC$_6$H$_5$
2	NO_2	CH3	4-ClC$_6$H$_4$COO	4-ClC$_6$H$_4$COO
3	CN	CH_3	OH	OH
4	CN	CH_3	H	4-(CH$_3$O)C$_6$H$_4$COO
5	CN	cyclo(CH$_2$)$_5$	H	:NOCOCH$_3$

PS05.01.15 STRUCTURE - ANTIVIRAL ACTIVITY CORRELATION OF CONFORMATIONALLY RESTRICTED NUCLEOSIDE ANALOGS. Gurskaya G.V.,* Zavodnik V.E., Krayevsky A.A., Engelhardt Institute of Molecular Biology, Russian, Academy of Sciences, 32 Vavilov Str., 117984 Moscow, Russia, *Karpov Institute of Physical Chemistry, 10 Obukha Str. 103064 Moscow, Russia

Recent search for new drugs revealed some modified nucleosides with antiretroviral activity, including the anti-HIV. The molecular mechanism of such activity is based on incorporation of their 5'-triphosphates into the new DNA strand during catalysis by DNA-polymerases and viral reverse transcriptases and ensuing interruption (termination) of elongation. In the case of viruses this results in inhibition of their reproduction. The modified nucleoside triphosphate affinity to each type of DNA-polymerase is determined both by the chemical nature of substituent groups in the nucleoside moiety and molecular conformation of nuc-leoside analogs.To investigate the structure - activity correlations, we studied X-ray structures of some conformationally restricted modified nucleoside series : 3'- methyl nucleoside analogs; 2',3'-dideoxy-2',3'-didehydronucleosides; nucleosides containing in their furanose cycles an additional three-membered fused ring in endo- or exorientation, as well as conformationally restricted compounds with an additional oxymethyl group at 4'-position. It can be suggested that the conformation of such conformationally restricted nucleosides is preserved in the DNA-synthesizing complexes, and mimicks the active conformation of a native substrate if conformationally restricted nucleotides reveal substrate properties.