The oxazolidinones are a class of orally active, synthetic antibacterial agents being studied by investigators at Pharmacia and Upjohn. Their activity is potent against Gram-positive pathogens, such as staphylococcus and streptococcus, and Mycobacterium tuberculosis. At Pharmacia and Upjohn, we have two drug candidates, a piperazinyl fluorophenyl oxazolidinone and a morpholinyl fluorophenyl oxazolidinone and they are currently in Phase I human clinical trials.

We have determined some crystal structures of a few oxazolidinones in an attempt to understand their activity. The morpholinyl fluorophenyl oxazolidinone, U-100766, has been used as a model for structure activity relationships in order to develop other potential candidates. Through changing substituents on the aromatic ring and the effect of fluorine substitution, the biological activity differences have been pronounced. In addition, we have seen some interesting changes in conformation from these compounds.

Steroids

**PS05.05.01 STRUCTURE OF 17-β-ESTRADIOL BENZOATE AND ITS INTERACTION WITH TAF-2 DOMAIN OF ESTROGEN RECEPTOR (ER) BY MODELING.** Víctor Bolaños-García1,2, Gabriela Jurdé-Martínez1, Enrique Rudino-Piñera1, Kaliyamoorthy Panneerselvam1 and Manuel Soriano-García1. 1Instituto de Química, UNAM, Instituto de Fisiología Celular, UNAM, Círculo Exterior, Ciudad Universitaria, Deleg. Coyoacan, Mexico, D.F.

This work presents the molecular structure of 17 β-estradiol benzoate, which was solved by X-ray diffraction and proposed a model for 17 β-estradiol benzoate-TAF-2 domain interaction. It is an estrogen regulated target cell proliferation, growth, and differentiation through a defined sequence of molecular events triggered by their binding to the intracellular estrogen receptor (ER). The transcriptional activation is mediated by TAF-1 in the N-terminal domain which corresponds to DNA binding domain and TAF-2, which is localized in the C-terminal end and corresponds to the hormone binding domain. Although, essential aspects about TAF-2 structure remains largely unknown. We demonstrated that this domain belongs to a class A amphipathic helix based in Eisenberg hydrophobic moment (μH = 0.42 Kcal/mol per residue) and polar residues distribution. Additionally, based in surface pressure calculation, the active surface is higher (43.87 mN/m) in comparison with other transcriptional activator protein domains and resemble some features presented in lipid transfer proteins. By molecular modeling it is estimated the importance of polar residues in TAF-2 domain and proposed a mechanism in order to explain the 17 β-estradiol benzoate-TAF-2 interaction at molecular level.

Interestingly, these findings would be valid for other hormone receptors as glucocorticoids and progestins.

**PS05.05.02 AN INTERESTING STEROID DIMER WITH AN EXTREMELY LONG CELL AXIS: TETRAGONAL P4212, a=b=9.17Å, c=85.90Å, V=7225.06Å³.** Fusen Han and Roger G. Williams, Pharmacia and Upjohn Inc., Kalamazoo, MI 49001, USA

An impurity in the methylprednisolone precursor was found in August of 1987 from five SOLU-MEDROL lots in the former Upjohn Company. It was the cause of insoluble residues present in the reconstituted solutions. In support of the structure determination, the analogous compound in the hydrocortisone series was synthesized. In experiments on decomposition routes of hydrocortisone, a sample dissolved in deoxygenated methanol was treated with 45% potassium hydroxide. The crude product mixture was purified by chromatography on silica gel with a chloroform eluant. One of the primary fractions proved to be a dimeric condensation product whose structure was unknown.

The X-ray diffraction data of this compound were collected with Siemens P4 diffractometer. The control software XSCANS, could not determine the cell from its default parameters. After modification, it derived a unusual tetragonal cell: P4(2)12, a=b=9.17Å, c=85.90Å, V=7225.06Å³. To verify it's extremely long c axis, three axial photos were taken. The cell parameters were confirmed from these photos. 6839 reflections were collected with Σ scan at -40°C.

The trial solution of this structure could not be easily obtained from the direct methods either. The short a, b and extremely long c axis could be the reason for the difficulties. The structure was finally solved with 10,000 direct methods attempts using SHELXS program package. The structure refinement is underway.

**PS05.05.03 MONOCLINIC FORM OF VITAMIN D3.** Ivan Lebun, Faculty for Chemistry and Chemical Technology, University of Ljubljana, 61001 Ljubljana, Slovenia; Rudolf A.G. de Graaff, Leiden Institute of Chemistry, Gorlaeus Laboratories, University of Leyden, 2300 RA Leyden, The Netherlands; René de Gelder, Nijmegen SON Research Center, University of Nijmegen, 6525 ED Nijmegen, The Netherlands; Johan Turkenburg, Department of Chemistry, University of York, York Y01 5DD, UK and Leiden Institute of Chemistry, Gorlaeus Laboratories, University of Leiden, 2300 RA Leiden, The Netherlands; Keith S. Wilson and Zhiginev Dauter, European Molecular Biology Laboratory (EMBL) c/o DESY, D-22603 Hamburg, Germany.

The development of the experimental diffraction techniques (synchrotron radiation) and the direct methods together with the graphical modelling and molecular fitting facilities normally used in protein crystallography enable to solve and refine the crystal structure of the monoclinic form of ergocalciferol (vitamin D₂). There are four independent molecules of the steroid skeleton with the ruptured B ring C₂₉H₄₄O in the asymmetric unit of the monoclinic unit cell [a=20.985(8)Å, b=7.277(4)Å, c=36.123(9)Å, β=103.07(5)°] in space group P 2₁. Molecules exist in the elongated form, the hydroxy OH groups attached to C3 forming an infinite hydrophobic helical spirals along short b-axis with the A rings in turns in two different conformations [a chair (equatorial OH) and b chair (axial OH)]. The outer parts of the hydrophobic side chains at C17 for b conformers are disordered. The packing of the molecules in the monoclinic form is completely different to that in the orthorhombic structure.