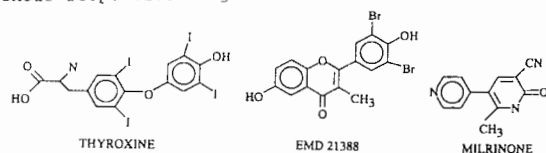


## 04-Crystallography of Biological Small Molecules

125

one, its desmethyl 5-amino parent compound, are members of a new class of oral nonglycosidic cardiac positive inotropic agents developed for the treatment of congestive heart failure. Structure activity correlations reveal that milrinone, but not amrinone, stimulates rabbit myocardial  $\text{Ca}^{2+}$ -ATPase activity as does thyroxine. To further develop this correlation, competitive binding studies were carried out which showed that in a similar manner, milrinone, but not amrinone, was a strong competitor for  $\text{T}_4$  binding to TTR. Comparison of a series of bipyridine structures revealed homology between the phenolic ring of  $\text{T}_4$  and the substituted ring of the bipyridine and a model which defined the conformational features required for activity was developed. The crystal structure of the milrinone-TTR complex was carried out and these data confirmed the model. Structure activity data for a membrane bound  $\text{T}_3$  transporter showed that benzodiazepine derivatives were potent inhibitors of  $\text{T}_3$  transport. Conformational comparison of their structures revealed homology with  $\text{T}_3$  and resulted in a model which incorporates key features of the benzodiazepine subclasses. Thus, these analyses revealed that TTR can be used as a prototypic model to explain the relative potency of these enzyme inhibitors. Based on these results, inhibitors can be designed with selective actions at their respective target sites.



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**MS-04.01.05** Structural Determination of Natural Products. By Angela Y. Lee and Jon Clardy, Department of Chemistry, Cornell University, Ithaca, N.Y. 14853-1301, USA.

Natural products have been a wonderful source of chemically novel and biologically active molecules, but they have also been a severe technical challenge to crystallographers. Most of our research has involved characterizing a variety of biologically active compounds, and more recently, their complexes with cellular receptors. The ultimate goal is to understand not only the structure but also the biochemical function of these compounds. We have worked with marine peptides for many years, and recently have become interested in a novel cyclic peptide from a marine sponge called cyclotheonamide. We never worked on this structure directly because of the inability to grow crystals. Cyclotheonamide is a serine protease inhibitor with  $K_i \sim 0.2$  nM with trypsin and  $\sim 1.0$  nM with thrombin. The three-dimensional structure of cyclotheonamide A complexed with bovine  $\beta$ -trypsin has been successfully determined at 2.3 Å resolution. This reveals not only the structure of cyclotheonamide but also its mode of action. The strong electron density and low thermal parameters allowed the conformation of bound cyclotheonamide A to be determined unambiguously—a result that has also clarified the stereochemistry.

**Key words:** natural product, novel protease inhibitor, mechanistic studies.

**MS-04.01.06** POLYMORPHISM AND BIOINEQUIVALENCE OF 6-METHYLURACIL. By N.B.Leonidov<sup>1</sup>, S.I.Uspenskaya, Institute "Bioeffect" of Ministry of Science, High School and Technical Policy of Russian Federation. Moscow, Russia; P.M.Zorky & A.E.Masunov, Chemical Department, Moscow State University, Russia.

New perspective trend in drug design is obtaining polymorphic modifications with different molecular conformations. Under consideration has been influence of polymorphism of drugs on their biological activity. Examples of influence of conformational polymorphism of drugs on changes in its biological characteristics in solutions are given. One of the explanations of this phenomenon is the difference between molecular agglomerates which are present in the crystals. The cooperative effect of molecular packing can fasten the details of molecular conformation. After dissolution of a substance such agglomerates or some fragments of them can occur in the solution for relatively long period of time. Specifically two crystal forms of 6-methyluracil differ in the antioxydative and wound-healing effect of their solutions.

X-ray data show that the cyclic dimers formed by a pair of  $\text{NH}\dots\text{O}=\text{C}$  bonds occur in both of them. However, in the form I the dimers are united by single H-bonds and wavy layers arise as a result. In the form II the dimers are joined into ribbons using pairs of H-bonds. It is very likely that hydrated dimers predominate in the solution of the crystals I, but rather long fragments of ribbons occur in the solution of the crystal II. Slightly different molecular conformations are to exist in the agglomerates of these two types. Thus, we obtain a probable explanation of the biological inequivalence of two polymorphs.

**MS-04.01.07** A STUDY ON STRUCTURE-ACTIVITY RELATIONSHIPS IN 16- AND 17-SUBSTITUTED ESTRANES AND ANDROSTANES. By S. Stankovic<sup>1</sup>, D. Miljkovic<sup>1</sup>, R. Kovacevic<sup>1</sup>, D. Lazar<sup>1</sup>, Lj. Medic-Mijacevic<sup>2</sup>, V. Pejanovic<sup>2</sup> and Ch. Courseille<sup>3</sup>, <sup>1</sup>Faculty of Sciences, University of Novi Sad, Trg D. Obradovica 4, 21000 Novi Sad, Yugoslavia, <sup>2</sup>ICN Galenika Institute, 29. novembra 111, 11000 Beograd, Yugoslavia, <sup>3</sup>Laboratoire de Cristallographie et de Physique Cristalline, Faculté de Sciences, Université de Bordeaux I, Talence, France.

A series of synthetic estranes (1-5) and androstanes (6-9) have been prepared and tested for anti-estrogenic and anti-androgenic properties. These steroids have been subjected to X-ray structural analysis to permit structure-activity relationship studies.

In the first series (1-5) a novel chemical rearrangement during acid-catalyzed hydrolysis of 16-oximino to 16-carbonyl group has been noticed. Namely, the benzyl moiety at C-17 changes its orientation from  $\alpha$ - to  $\beta$ -position. The new  $\beta$ -orientation of the benzyl moiety affects the chemical and biological properties of the C-17 centre.

Among the compounds from the first type (1-3) an expected phenomenon was noticed:  $\beta$ -orientation of the C-17 hydroxyl group produced higher biological activity. The compounds from the second type (7-9) showed differences in biological activity. Namely, the benzyl-derivative 7 possesses an anti-estrogenic activity, while the corresponding phenyl analogue 9 showed no activity at all. The phenyl analogue 8, with 17-OH group, showed *in vitro* an inhibitory effect on steroidogenesis.