04--Crystallography of Biological Small Molecules

MS-04.01.02 STRUCTURAL STUDIES ON BIOACTIVE PEPTIDES. By G. Précigouët, S. Lido, S. Geoffrè and P. Picard, Laboratoire de Cristallographie, Université de Bordeaux I, 33405 Talence, France.

Among the bioactive peptides, one of the widely studied families is constituted of the aspartic protease inhibitors.

There are two strategies for the design of such inhibitors: the replacement of the scissile peptide bond of a substrate with other hydrolyzable moities, or the substitution of an usual endogenous aminoacid by an unusual one.

All the aspartic proteases are known to be inhibited by pepstatin A (isovaleryl-Val-Val-Val-Ala-Val), where (Val) is ([45,35]-4-amino-3-hydroxy-6-methylheptanoic acid). Statine has been found to be essential for inhibitory potency of pepstatin and is widely used in the design of inhibitors.

In spite of the great interest of statine, only a limited number of X-ray diffraction studies have been carried out on statine alone and on statine containing peptides. However, the number of conformations observed in the crystal state is large enough to allow a study aimed at determining the main conformational preferences of statine and the conformational role of its two additional main chain carbon atoms.

MS-04.01.03 DESIGN, STRUCTURE AND ACTIVITY OF CONFORMATIONALLY SPECIFIC PEPTIDES. By P.P. Singh, Department of Biophysics, All India Institute of Medical Sciences, New Delhi-110029, India.

\(\alpha,\beta\)-dehydro-amino acids have emerged as a very effective tool in the design of specific peptide structures. These residues occur naturally in a variety of peptide antibiotics and in some proteins. The peptides can be prepared in the laboratory with substitutions of \(\alpha,\beta\)-dehydro-residues at desired sites. Our investigations suggest that a dehydro-residue adopts three sets of site specific \(\Phi,\Psi\) values: \(\Phi,\Psi\) if dehydro-residue is at (1-2) position, -60, 120° while at (1-1) and (1-3)0° in a sequence of dehydro-residues separated by one or two saturated residues. Therefore, a \(\alpha\)-turn II, \(\beta\)-turn III and a \(3^1\) helical conformations can be produced very specifically. The dehydro-Ala with only methylene group at the \(\alpha\)-position adopts an extended chain conformation and in a peptide sequence gives rise to a mixed \(\beta\)-strand structure similar to those observed in large loops of proteins. These studies, thus, offer a highly promising and effective principle of peptide design.

MS-04.01.04 MOLECULAR STRUCTURE AND BIOLOGICAL ACTIVITY: TRANSMEMBRANE-INHIBITOR BINDING INTERACTIONS AS A TARGET SITE MODEL. Vivian Cody, Medical Foundation of Buffalo, 73 High St., Buffalo, NY 14223 USA.

Recent structural activity data show that many pharmacological agents are strong competitors for thyroxine (T4) binding to transthyrin (TTR), a serum thyroxine hormone transport protein. Furthermore, the marked similarity in the structural features required for relative binding affinity to TTR and activity of thyroid-responsive enzymes such as thyroxine dioxygenase (TDO), Ca2+-ATPase or membrane T4 transporters suggests homology between the TTR hormone binding site and those enzyme active sites. Understanding how diverse classes of molecules such as hydroxyurea analogues, plant flavonoids, inorganic dipyridine and benzodiazepines can act as inhibitors of TTR binding, computer graphic modeling studies of inhibitor structures were carried out. Crystallographic analysis of thyroxin hormones reveals that the tyrosyl 3,3-todiones cause the diphenyl ether core to adopt a skewed conformation, whereas removal of this bulk releases this constraint. Flavonoids, a broadly distributed class of hydroxy substituted phenyl benzopyrones or benzofurans plant pigments, are also potent inhibitors of TTR hormone binding and T4D activity. Although these structures have less conformational flexibility and are in general planar, computer graphic modeling data suggest homology between the hormone phenolic ring and that of the flavonoids and reveal that the flavonoids can bind in the TTR hormone site. From these studies the benzoflavanone, EME 2128, was designed as a potent TTR and T4D inhibitor. To test this model, the structure of TTR-flavonoid complexes were undertaken and reveal a complex binding pattern which indicates the flavonoids have multiple binding modes to TTR. Milrinone (2-methyl-5-cyano), 4'-bipyridinyl-6-(1H-one) and amrin-