03. CRYSTALLOGRAPHY IN BIOCHEMISTRY AND PHARMACOLOGY

03.2-5 BACE INHIBITORS: STRUCTURAL STUDY REGARDING STATINS IN LINEAR OGLIOPEPTIDES. By S. Frébigoux, G. Geoffire, M. Benfallouch, M. Cotrait, G. Frébigoux, Lab. Crystallography, University of Bordeaux I, France.

The proteolytic enzyme cleaves the substrate angiotensinogen 1. The decapeptide substrate transformed by converting enzyme into the oxytocine 3-carboxy substance angiotensinogen II. Interruption of this proteolytic cascade by inhibition of renin could be a way to treat hypertension.

The general aspartyl protease inhibitor pepstatin is a naturally occurring pentapeptide containing two units of statine, an unusual amino acid.

To try to understand the conformational role of the statine residue, we have solved the crystal structures of two pepstatin analogues, I and II.

pepstatin
Isovaleryl-Val-Val-Sta-Ala-Sta
analogues
I Boc-Leu-Leu-Ala-Ala-OMe
II Boc-Leu-Leu-Ala-Ala-OMe

For analogues I and II the notation "m" is an abbreviation for y(C=C), trans.

In spite of very different environments and interactions in the crystal, the observed conformations for molecules I and II are almost identical at the level of the central statine. The peptide main chain is folded back at the Sta and Ala residues to form a twelve membered ring with an intramolecular hydrogen bond between the carbonyl oxygen of Leu and the nitrogen atom of the last statine residue.

03.2-6 CONFORMATIONAL ANALYSIS OF ANGIOTENSINOGEN FRAGMENTS. By M.B. Hossain and G. Van der Helm. Department of Chemistry, Oklahoma University, Norman, OK, USA.

The (8-13) equtat angiotensino gen octapeptide (his-pro- phe-his-Leu-Val-tvr) is described as the minimum endogenous substrate sequence needed for efficient renin activity. We have studied the conformations of several fragments or analogs, in order to determine the most probable conformation in the neighbourhood of the "Leu-Val" scissile bond.

\[ HIS-PRO-PHE-HIS-LEU-LEU-VAL-TVR \]

I Ac-PRO-PHE-LEU II Ac-PRO-PHE-LEU-VAL-TVR (OMe)
III Ac-PRO-PHE-HIS IV BOC-HIS-LEU-VAL-PHE (OMe)
V HIS-PRO-PRO-PHE-VI (HIS-PRO-PHE-VAL-PHE (OMe)

The I, II, III, IV, VI oligopeptides have been crystallized in a form suitable for X-Ray analysis. We have observed:
- the (C=O) \( \beta \)-terminal part presents a type I \( \beta \)-turn at pro-phe with intramolecular hydrogen bond between O(3)C=O and N(H)(Ile).
- A theoretical conformational analysis of T, confirms this type of \( \beta \)-turn.
- The C-terminal part observed in the crystals of I, II, IV, VI, is in \( \beta \)-pleated sheet conformation with the side chains alternatively situated on the left and right of the main chain.

03.2-6 THE MOLECULAR STRUCTURE OF DIDE MIN B, AN ANTIVIRAL AND CYTOTOXIC DEPSIPEPTIDE. By H.B. Hossain and S.K. Sanduja and A.J. Weinheimer, Department of Medicinal Chemistry, University of Houston, Houston, Texas, USA.

Dide mim B, a highly active depsipeptide was originally isolated from a Caribbean tunicate of the family Didemminidae and a chemical structure for the compound was proposed from spectroscopic and chemical studies (K.L. Rinehart, J.B. Groer, J.C. Cook, S.A. Missak and T.A. Schali, J. Am. Chem. Soc., 1981, 103, 1857-59):

\[ R=\text{MeLeu} \rightarrow \text{Leu} \rightarrow \text{Hisp} \rightarrow \text{Leu} \rightarrow \text{Pro} \rightarrow \text{MeTyr} \rightarrow O \]

where \( R = \text{CH}_{3}\text{CHCONH}=\text{CH} \rightarrow \text{OC} \rightarrow \text{CO} \rightarrow \text{CH} \rightarrow \text{CH} \rightarrow \text{CH}_2 \)

and Hips is hydroxyisovalerylpropionyl.

The X-ray structure determination of depsipeptide revealed a slightly modified structure, showing the presence of iso-statine instead of statine. The depsipeptide ring is substantially folded and the overall molecular conformation is stabilized by three intramolecular N-H..O hydrogen bonds (shown by dashed lines in the Figure). Details of structural results will be presented.

Crystal Data: \( C_5 H_{15} O_{10} N_2 S = 1.5 C_2 H_2 \cdot H_2 O \), orthorhombic, \( C_{22} 2 \), \( a = 14.959(3), b = 22.574(4), c = 41.112(9) \) \( A, v = 13312 \), \( z = 8, o = 1.190 \text{ gm cm}^{-3}, CuK \alpha \) radiation.