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their common K⁺ channel opening activity. Like flunarizine, the geometries of the latter molecules were also optimized by means of force field starting from their respective X-ray conformations. The experimental maps of the optimized structure of dazoxazine, flunarizine and the four low energy conformers of pinemidil were compared. The experimental map of dazoxazine allows a good analogy with that of two calculated conformations of pinemidil (both different from that in crystal).

Recent studies (Schwemmele, H., Brandl, L., Behrenz, S., Schwebel, U. and Funk, B., J. Pharma., 1992, 156, 291-101) have suggested that dazoxazine and pinemidil could exert their activity on the parietal K⁺ ATP channel after interaction with a common binding site. Neurontin's conclude that the moderate activity of pinemidil on the insulin release from parietal K⁺-cells could be explained by adaption for pinemidil of a low energy conformation which can be reasonably failed on dazoxazine both from the point of view of atom positions and of stereoelectronic properties.

PS-05.01.07 MODELLING OF SOME RETROVIRAL ASPARTYL PROTEINASES: STUDY OF THE SHORTER SEQUENCE REQUIRED FOR THE IN VITRO ENZYMATIC ACTIVITY.


The Bovine Leukemia Virus (BLV) and Human T-cell Leukemia Virus (HTLV) aspartyl proteinases are required as proteolytic proteins, made of 126 and 125 amino acids respectively ('long sequences').

Since all known aspartic proteinases contain a conserved active site core structure, it is reasonable to attempt to use them to model the unknown structure of another aspartic proteinase. The crystal structures of Rous Sarcoma Virus (RSV PR) and Human Immunodeficiency Virus (HTLV-1 PR) were used to align the sequences of BLV and HIV-1 PR and to construct models.

These models show that BLV and HTLV-1 PR sequences made of only 116 and 115 amino acids respectively ('short sequences') display three-dimensional structures similar to that observed for other retroviral proteinases. The two amino acids at the carboxy terminal of the BLV and HTLV-1 'long sequences' do not have any equivalent residue in the alignment of the active site 235 and HIV-1 PR and would not act in the catalytic process.

The real value of our models is underlined by the in vitro activity and inhibition of the synthetic BLV protease made of only 116 amino acids.

PS-05.01.08 DIRECTIONAL PREFERENCES OF BINDING OF FUNCTIONAL GROUPS.


The directional preferences for binding of functional groups to different molecules are studied by use of the Cambridge Structural Database (CSD). Data on intermolecular interactions to a selected functional group and large numbers of small-

molecule crystal structures are analysed. These are analyzed in a statistical manner by use of contourd scatterplots in order to determine the variability in such binding. The results can then be used for macromolecules, studied to lower resolution, in order to suggest modes of ligand binding. Two types of interactions will be described here.

Hydrogen bonding and metal binding to nitrogen-containing heterocycles has been studied in this way to give ranges within which such binding deviates from the plane of the ring system and from the line dissecting the C-N-C angle. The results are compared with X-ray structural data at lower resolution for some acridine-oligonucleotide complexes and the surroundings of histidine rings in some protein crystal structures.

Additionally, the stereochemistry of binding of functional groups to metal cations, such as divalent magnesium, manganese and cobalt, will be described, and the relevance of such binding to enzyme mechanisms will be discussed.

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