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Authors
James, Michael NG
Fraser, Marie E
Khan, Amir R
et al.

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Structural studies of conformationally-restricted ligands binding to aspartic peptidases.

Michael NG James[1], Marie E Fraser[2], Amir R Khan[3], Jonathan C Parrish[1], Whitney W Smith[4], Paul A Bartlett[5].

[1]Department of Biochemistry, University of Alberta, Edmonton, AB T6G 2H7, Canada
[2]Department of Biological Sciences, University of Calgary, Calgary, AB T2N 1N4, Canada
[3]School of Biochemistry & Immunology, Trinity College Dublin, Dublin 2, Ireland
[4]Collaborative Drug Discovery Inc., Burlingame, CA, 94010, USA
[5]Department of Chemistry, University of California, Berkeley, CA, 94720, USA

In a review paper in "Biochemistry", Blundell *et al*[1] pointed out that inhibitors binding to aspartic peptidases adopt an extended conformation such that alternate residues are in close proximity (i.e. P2 and P1'; P1 and P3). Covalent linking of the side chains of these alternate residues could have an increase in the potency of the inhibitor by locking it in the **bound** conformation thereby reducing the loss of conformational entropy on binding. Penicillopepsin is an aspartic peptidase isolated from the fungus *Penicillium janthinellum*[2]. This paper will discuss the structures of several phosphonate containing inhibitors bound to penicillopepsin. The tetrahedral geometry of the phosphonate moiety of the inhibitors resembles that of the cleavage transition state of the scissile carbonyl-carbon atom that forms during peptide bond hydrolysis. The proximity of the P2 Val and the P1' Phe of the pentapeptide inhibitor phosphonate analog, Isovaleryl-Val-Val-Leu^{P}-O-Phe-CO_2CH_3, suggested that a covalent bond between them could be engineered and synthesized if the P2 Val was substituted by an asparagine residue. The structures of the phosphonate-based macrocycle (Ki = 0.10 nM) having an amide link between the P2 Asn and the P1' Phe, and the acyclic analog (Ki = 42 nM) of that inhibitor were determined to 0.95 Å and 1.41 Å resolutions respectively. These structures and the enhanced potency of the macrocyclic-inhibitor will be discussed.

1. Blundell, T.L. *et al*, Biochemistry **26**, 5585-5590 (1987)
2. James, M.N.G. and Sielecki, A.R., J. Mol. Biol. , **163**, 299-361 (1983)