Series of HIV-1 Protease Nanomolar Inhibitors; Binding to WT and Mutant Protease

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HIV protease cleaves polyprotein of immature human immunodeficiency virus and contributes thus to formation of active mature virus. Inhibition of HIV protease is one of the ways which are used to break life cycle of HIV and several inhibitors of HIV protease are already used as drugs against AIDS in clinical practice.

A series of chemically similar pseudo-tetrapeptide inhibitors of HIV-1 protease (K_i in the range from 0.1 to 1000 nM, [1]) was selected for structural analysis. The inhibitors have different peptide bond isosteres and they differ in amino acid residue in P2' binding position. Binding to wild type protease and to mutants A71V, V82T, I84V or L63P, A71V, V82T, I84V was compared.

It was found that, in binding pockets S1' – S3', binding stays similar in the series of nine structures and low B factors were refined. On the contrary, flexibility and variability exists in the P1 binding position and in the peptide bond isostere region.

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[1] Konvalinka J., Litera J., Weber J., Vondrášek J., Hradílek M., Souček M., Pichová I., Majer P., Štrop P., Sedláček J., Heuser A.M., Kottler H., Kräusslich H.G., *Eur. J. Biochem.*, 1997, **250**, 559-566.

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