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Small-sized HIV Protease Inhibitors Containing Allophenylnorstatine Exhibit Antiviral Activities

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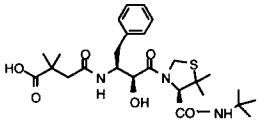
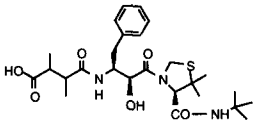
Based on the substrate transition state, we designed and synthesized a novel class of HIV protease inhibitors containing allophenylnorstatine [Apns; (2S,3S)-3-amino-2-hydroxy-4-phenylbutyric acid] with a hydroxymethylcarbonyl (HMC) isostere. Among them, the tripeptide KNI-272 was a highly selective and superpotent HIV protease inhibitor (Ki=5.5pM). KNI-272 exhibited potent antiviral activities against both AZT-sensitive and -insensitive clinical HIV-1 isolates as well as HIV-2 with low cytotoxicity. After i.d. administration, bioavailability of KNI-272 was 42.3% in rats. Also, KNI-272 exhibited in vivo anti-HIV activities in human PBMC-SCID mice. X-ray crystallography and molecular modeling studies showed that the HMC group in KNI-272 interacted excellently with the aspartic acid carboxyl groups of HIV protease active site. This result implies that the HMC isostere is an ideal transition state mimic and thus leads to small-sized dipeptide inhibitors (KNI-413 & -549; Fig.). These exhibited antiviral activity and improved pharmacokinetic properties.



KNI-413



KNI-549

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Synthetic Peptides from Conserved Regions of HIV-1, HIV-2, and SIV Fusion Proteins are Potent Antivirals (Inhibitors of Viral Fusion). **S. Barney, K. Guthrie, D. E. Davis-Rhodes, Robyn Medinas, T. Bucy, T. Hauser, J. Erickson, Betty DiMassimo, Tom Venetta, M. K. Lawless, G. Merutka, D. M. Lambert. Trimeris, Inc., Durham, NC**

The fusion proteins of enveloped viruses are required for virus-mediated membrane fusion and infection. Inhibitors targeted to these proteins would represent a novel class of antiviral agents that act at the cell surface. T20 (Pentafuside, DP-178) is a 36-mer synthetic peptide derived from the HIV-1 transmembrane protein, with *in vitro* fusion and infection inhibition in the low ng/ml levels (1 ng/ml and 80 ng/ml respectively). T20 has also been shown to inhibit *in vivo* replication of a clinical isolate of HIV-1 in the HuPBMC-SCID mouse mode of infection. Since HIV-1, HIV-2, and SIV sequence homologies are relatively high within the region of T20, we examined the antiviral activities, as well as cross-inhibitory activities, of synthetic peptides derived from each of these viruses. In addition, antibody recognition, structural similarities, and binding profiles were compared. Peptides from all of the three viruses are potent fusion and infection inhibitors against their respective viruses (HIV-1 = 1 ng/ml, SIV = 1 ng/ml, and HIV-2 = 1 ug/ml). Interestingly, peptides from all three viruses inhibit both HIV-1 and SIV with greater potency than HIV-2, despite greater sequence homology between SIV and HIV-2, suggesting a possible structural/functional difference in the HIV-2 fusion glycoprotein. In addition to antiviral properties, direct and competitive binding, antibody competition and recognition, and structural analysis data all support HIV-1 and SIV structure/function similarities and significant differences from HIV-2. These studies may provide insight into more rational antiviral drug design for peptides as well as small molecules.