Conformational Analysis of Selected Novel HIV-1 Protease Inhibitors Designed using Substrate Envelope Restrictions

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Abstract

The human immunodeficiency virus (HIV) is a retrovirus that can lead to acquired immunodeficiency syndrome (AIDS). One potential path to suppress HIV in the human body is to inhibit the activity of HIV-1 protease – an enzyme essential to the development of mature HIV virons. A great amount of drug therapy research has focused on the inhibition of the active site of HIV-1 protease. However, the development of drug-resistant strains of the HIV-1 protease mandate continued effort. Altman et al. designed inhibitors using a Substrate Envelope Hypothesis. This hypothesis states that inhibitors that adopt conformations that stay within the substrate pocket boundary and display minimum contact with possible protease mutation sites will remain active against both wild type and mutated HIV-1 proteases. This study analyzes the conformational behavior of 14 of those inhibitors using the classical OPLS2005 force field and the GBSA continuum solvent model for water. An HIV-1 protease substrate peptide MA-CA was characterized using OPLS2005 and AMBER94 forcefield for comparison with the inhibitors. The hybrid Low Mode:Monte Carlo (LM:MC) conformational search method was utilized to locate all low energy structures of each structure. The resulting ensembles were clustered into geometrically similar families using the XCluster program. The molecular mechanics structures and relative energies were compared to quantum mechanical geometry optimizations. Experimental cystal structures were available for 5 of the 14 inhibitors in the presense of the protease active site; these were superimposed with low-energy conformations to assess the ability of each inhibitor to preorganize in solvent for binding to the active site. Conclusions were drawn about the flexibility of the inhibitors and substrate and similarities and differences in conformational behavior were examined.