Conformational Analysis of Selected Substrate Envelope HIV-1 Protease Inhibitors

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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. There is a great amount of interest in drug therapies targeting the inhibition of the active site of HIV-1 protease. However, the evolution of drug-resistant forms of the protease remains a difficult limiting factor. Altman et al. in their *HIV-1 Protease inhibitors from Inverse Design in the Substrate Envelope Exhibit Subnanomolar Binding to Drug-Resistant Variants* designed inhibitors with shapes that stay within the substrate pocket boundary and have minimum contact with possible mutation spots of the protease active site. This study analyzes the conformational behavior of 14 of those inhibitors using molecular modeling. Conformational searching was utilized to locate all low energy conformations of each inhibitor. Generated structures were grouped into families based on geometrical similarities using the XCluster program. Longest intramolecular distances between two most widely varied atoms were measured for each inhibitor ensemble. Experimental cystal structures were available for 5 of the 14 inhibitors; these were superimposed with low-energy conformations of corresponding theoretical inhibitors. Quantum mechanical minimization was used for further validation. Conclusions were drawn about the conformational flexibility of the inhibitors and similarities and differences in conformational behavior were examined.