Conformational Analysis of Selected FDA Approved HIV-1 Protease Inhibitors

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Molecular modeling was used to understand the conformational behavior of seven FDA approved HIV-1 protease inhibitors: Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, and Saquinavir. In an effort to understand the role of molecular flexibility in drug preorganization and protease binding, we utilized conformational searching to locate all low energy structures of each system. The conformational searches were performed using the combined 50:50 Low Mode: Monte Carlo method and using the GB/SA continuum solvent model to simulate an aqueous environment and the OPLSA2005 force field. The resulting structures were then grouped into families based on structural similarities using the XCluster program. The low-energy conformations were also compared and analyzed by superimposition of ensembles with experimental crystal structures along with quantum mechanical minimization validation. Conclusions were drawn about the conformational flexibility of the inhibitor drugs and similarities and differences in conformational behavior were examined.