Study of the Flexibility of FDA Approved HIV-1 Protease Inhibitors

Amy Coan and Carol Parish
Department of Chemistry, University of Richmond
Richmond, VA 23173

This study used molecular modeling methods to understand the flexibility of the eight FDA approved HIV-1 Protease Inhibitors: BMS-232632, Ritonavir, Indinavir, Amprenavir, Lopinavir, Nelfinavir, TMC-114 and Saquinavir. The OPLS2005 force field was used to perform conformational searching of each inhibitor in order to describe the potential energy surface, and to find the global minima and low energy structures. Ensembles generated for each of the FDA approved inhibitors were then grouped into geometrically similar families using the XCluster program. XCluster defines conformational families based on RMS differences between specified atoms in pairs, in either torsional or Cartesian space, and classifies the conformations into geometrically similar bundles in a stepwise, hierarchical fashion. This clustering was used to evaluate the conformational flexibility of each inhibitor in the aqueous phase, as well as to draw conclusions about the similarities and differences among the inhibitors. To study the flexibility of the molecules in relation to interactions with the protease, the longest intramolecular distances were compared to get a feel for the general bending and stretching of the inhibitors. The shape and flexibility of the structures of the inhibitors are very important when docking into the binding pockets of the protease's active site.