Glide/Ligand Docking of Inverse Designed HIV-1 Protease Inhibitors

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The Human Immunodeficiency Virus (HIV) has been the cause of millions of deaths worldwide; in particular, devastating third world countries in disproportionate amounts. There are two primary forms, HIV-1 and HIV-2. Both forms have the ability to mutate, conferring drug resistance. Thus, the need to develop drugs to inhibit specific HIV proteins is urgent. In this work, we focus on the HIV-1 protease. Recently, Altman, et al. published an article entitled *HIV-1 Protease Inhibitors from Inverse Design in the Substrate Envelope Exhibit Subnanomolar Binding to Drug-Resistant Variants* in which 18 HIV-1 protease inhibitors were designed to emulate the structural and chemical features of the substrate. They employ a "substrate envelope hypothesis" – if the inhibitor makes the same and/or fewer interactions with the protein than the substrate, then inhibitor effectiveness will be less susceptible to mutations. Low energy structures for each inhibitor were identified by exhaustive conformational scans of the OPLS2005/GBSA(water) surface. The lowest energy structures of each inhibitor were docked into the HIV-1 Protease using SP (Standard Percision) and XP (Extra Percision) Ligand Docking portion of the *GLIDE* program. Poses for each inhibitor were generated and the lowest energy pose was ranked according to the *GLIDE* scoring function. Based upon the XP G-Scores, the ranked inhibitors were compared to the experimental K_i values.