

Title: Quantum mechanical analysis of newly synthesized HIV-1 protease inhibitors: evaluation of wild-type and resistant strain binding interactions

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Abstract: Inhibition of HIV-1 protease is a cornerstone of antiretroviral therapy. However, the notorious ability of HIV-1 to develop resistance to protease inhibitors (PIs), particularly darunavir (DRV), poses a major challenge. Using quantum chemistry and computer simulations, this study aims to investigate the interactions between two novel PIs, GRL-004 and GRL-063, as well as a wild-type (WT) HIV strain and a DRV-resistant mutant strain. To do this, we used molecular docking, molecular dynamics simulations, and quantum mechanical calculations to check how well GRL-004 and GRL-063 bound to both WT and DRV-resistant proteases. The results show that GRL-004 and GRL-063 bind very well to ASP29 in the WT strain. ASP29 is an important amino acid in the HIV protease dimer. Remarkably, amino acids such as ILE50 in the WT strains showed substantial binding energies to both drugs. Quantum energy calculations showed a slight reduction in the energy affinity of the interaction between the MUT strain and the ligand GRL-063, compared to the WT strain. GRL-004 showed similar interaction energy for both strains, suggesting that it has greater plasticity than GRL-063 despite its lower interaction affinity. Furthermore, GLY49B demonstrated strong binding energies regardless of mutations. Other relevant residues with strong binding energies include GLY49B, PHE82A, PRO81A, ASP29A, ASP25A and ALA28B. This study improves our understanding of receptor–ligand dynamics and the adaptability of new protease inhibitors (PIs), which has profound implications for the innovation of future antiretroviral drugs.

Key words: HIV-1 protease Protease inhibitors (PIs) Darunavir resistance GRL-004 GRL-063 Molecular docking

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