FMO-guided Structure-based Design of Darunavir Analog against HIV-1 Protease

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By cleaving viral polyproteins that contribute to mature structural and functional proteins[1], human immunodeficiency virus type-1 protease (HIV-1 PR) is likely to be a key target in the suppression of acquired immunodeficiency syndrome (AIDS) progression. One of the effective HIV-1 PR inhibitors (PIs), darunavir (DRV), is approved by the Food and Drug Administration[2]; nonetheless, HIV-1 PR mutations alleviate DRV susceptibility. Modern structure-based drug design was enhanced by understanding the binding interaction between known drugs and target proteins obtained through quantum mechanical approaches[3]. Herein, the design of the DRV analog was guided by a decomposition analysis of pair interaction energy determined by the fragment molecular orbital approach. From 189 designed analogs, the top ten DRV analogs interacted considerably better with the HIV-1 PR's active site than DRV, according to molecular docking and molecular dynamics simulation. These analogs' potency and effectiveness make them potential candidates for PIs development. The most appropriate analogs will be synthesized and assessed for biological activity in further research.

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