Title

Estimation of the binding free energy of AC1NX476 to HIV-1 protease wild-type and mutations using free energy perturbation method

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Short Title: Binding free energy of AC1NX476 to HIV-1 protease

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Abstract

The binding mechanism of AC1NX476 to HIV-1 protease wild-type and mutations was studied by the docking and molecular dynamics simulations. The binding free energy was calculated using the double-annihilation binding-free energy method. It is shown that the binding affinity of AC1NX476 to wild-type is higher than not only ritonavir but also darunavir making AC1NX476 become attractive candidate for HIV treatment. Our theoretical results are in excellent agreement with the experiment data as the correlation coefficient between calculated and experimentally measured binding free energies $R = 0.993$. Residues Asp25-A, Asp29-A, Asp30-A, Ile47-A,

Gly48-A, and Val50-A from chain A, and Asp25-B from chain B play a crucial role in the ligand binding. The mutations were found to reduce the receptor-ligand interaction by widening the binding cavity and the binding propensity is mainly driven by the van der Waals interaction. Our finding may be useful for designing potential drugs to combat with HIV.