C-1-10

Binding Mechanism of KNI-272 with HIV-1 Protease

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Keywords: FMO, HIV-1 protease, neutron crystallography, structural water, X-ray crystallography

The complex of structure of HIV-1 protease (HIV-1 PR) with a transition-state analog inhibitor KNI-272 has been determined recently by both neutron and high-resolution X-ray crystallographies. As shown in Figure 1, the complex structure contains several structural water molecules, which can mediate hydrogen-bonding interactions between HIV-1 PR and KNI-272. [1] In this study, MM/MD and ONIOM (QM/MM) (M06-2X/6-31G*: Amber) calculations were carried out to quantitatively examine possible roles of these structural water molecules. After the ONIOM optimization, we performed the FMO-Inter Fragment Interaction Energy (FMO-IFIE: HF/6-31G*) analysis of KNI-272 with amino acid residues and structural water molecules, and examined the energitic contribution of each structural water molecule in the binding. Catalytic Asp25/25' residues have the largest contribution to the binding. Figure 2 shows FMO-IFIE together with the classical dispersion ones (E_{disp}). As can be seen in Figure 2, W1 (water molecule 1 shown in Figure 1), intervening between KNI-272 and Ile50/50' in HIV-1 PR, makes the most potent hydrogen-bonding interaction. W2 and W3 (water molecules 2 and 3) are also important for the binding of KNI-272 with between HIV-1 PR through hydrogen-bonding/electrostatic interactions. These results confirm that these structural water molecules inside HIV-1 PR play a decisive role in the binding of KNI-272 with HIV-1 PR, and suggest that it is very necessary to consider the "hydrogen-bonding/electrostatic network" among an inhibitor, HIV-1-PR and structural water molecules, when designing a new potent inhibitor of HIV-1 PR.

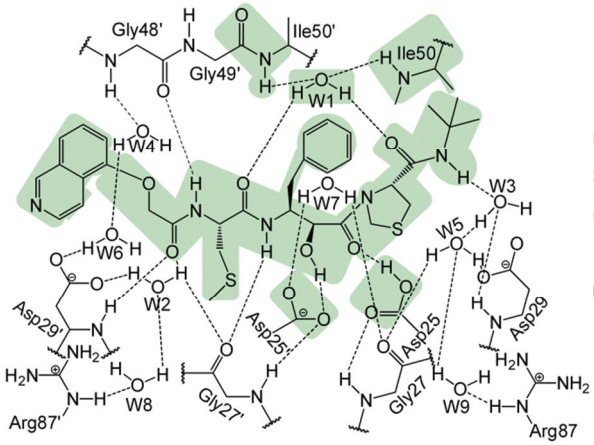

Figure 1. Complex of HIV-1 PR with KNI-272. Atoms in shadow areas are treated as the quantum region in the ONIOM optimization.

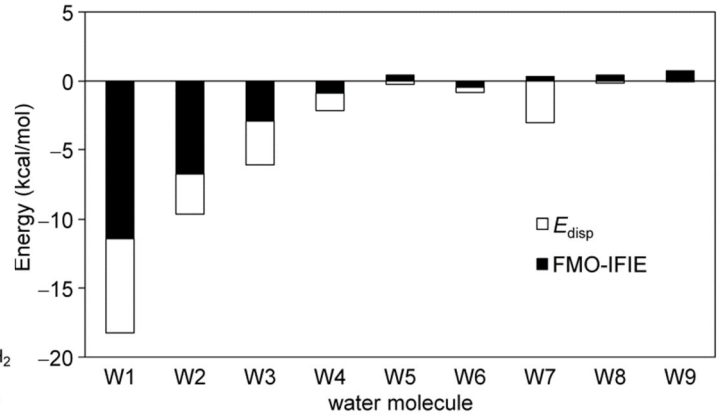

Figure 2. FMO-IFIE and E_{disp} of KNI-272 with structural waters in HIV-1 PR.

[1] M. Adachi *et al.*, *Proc. Natl. Acad. Sci.USA*, **2009**, *106*, 4641–4646.