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Large-Scale Fragment Molecular Orbital Calculations toward Evaluating the Drug Effects of AIDS Agents

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In our continuous efforts to evaluate and predict the drug effects of currently approved HIV-1 protease inhibitors, we have carried out a large-scale fragment molecular orbital (FMO) calculation at FMO-MP2/6-31G level on the complexes of HIV-1 protease with five different peptidomimetic HIV-1 protease inhibitors such as Ritonavir (RTV), Indinavir (IDV), Nelfinavir (NFV), Darunavir (DRV), and Saquinavir (SQV) using ABINIT-MP/BioStation system [1-3]. In addition, we performed the analogous FMO calculations toward four different complexes of renin and pepsin with RTV and SQV to explore a relationship between the computed energies and the unwanted side effects of HIV-1 protease inhibitors. Renin and pepsin are aspartic proteases and exist in human kidney and stomach, respectively. It has been reported that RTV gives acute renal failure and severe gastrointestinal injury, while no renal toxicity is attributed to SQV.

FMO computations of five different inhibitor-bound HIV-1 protease complexes indicated that the calculated binding energy for the HIV-1 protease complexes can be correlated to the clinically measured pharmacokinetic parameters such as maximum drug concentration (Cmax) and area under the drug concentration-time curve (AUC) of the AIDS agents. We found that HIV-1 protease inhibitors having large values of Cmax and AUC such as RTV can strongly interact with HIV-1 protease, and that HIV-1 protease inhibitors with relatively large binding and interaction energies can be highly effective as an AIDS agent [1-3]. When a drug was administered, it reaches its peak level in the blood. A drug travels through the blood to tissues in the body, is then metabolized and removed from the blood. Cmax exhibits the highest drug level in the blood. AUC is universally regarded as a measure of the extent of drug absorption. Although the reasons for the correlation of the computed energy with Cmax and AUC are not clear, these two pharmacokinetic parameters may be useful as indications for drug effects of AIDS agents [3]. For the human protease complexes with RTV and SQV, the binding energy of RTV is larger than that of SQV. Furthermore, it was found that the interaction energy of RTV with the active site aspartic acid in both human proteases is large, while that of SQV with the active site is very small. We can safely say that the large interactions between the human proteases and RTV are implicated as a possible cause of renal dysfunction and severe gastrointestinal injury due to RTV inhibitor. Similar FMO4-MP2 calculations are under way to discuss the protease-inhibitor interactions in more detail.

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