Pensri Srivub 2007: Theoretical Investigation on Y181C and K103N/Y181C HIV-1 Reverse Transcriptase Complexed with Efavirenz, Based on ONIOM Method. Doctor of Philosophy (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor: Associate Professor Supa Hannongbua, Dr.rer.nat. 93 pages.

Two- and three-layered ONIOM methods was used to study the interactions between efavirenz and the different binding sites of HIV-1 reverse transcriptase: the wild-type, a single mutation (Y181C) and a double mutation (K103N/Y181C). Binding energies were determined and compared to describe the loss activity of efavirenz with the mutant HIV-1 RT binding pocket. The calculated binding energies for the efavirenz/Y181C HIV-1 RT complex is about -19.49 kcal/mol using the MP2/6-31G(d,p):B3LYP/6-31G(d,p): PM3 method. It is not significantly different when compared to the results obtained from the wild-type complex (-20.52 kcal/mol). In contrast, the calculated binding energy for the efavirenz complexed with the K103N/Y181C HIV-1 RT is less than that of the wild-type complex by approximately 7.91 kcal/mol. It was found that interaction energies calculated at MP2/6-31G(d,p) level of calculations between efavirenz and each individual residues surrounding the binding pocket for both wild-type and Y181C HIV-1 RT are not significantly different excepted for V179 residue while interaction energies between efavirenz and individual residues surrounding the binding pocket of the K103N/Y181C enzyme were demonstrated that the attractive interactions between efavirenz and K101/K103 were reduced compared to the wild-type by 5.52 and 3.62 kcal/mol, respectively. It is important to note that hydrogen bonding occurring between efavirenz and K101 was also disturbed. Moreover, N103 in the binding pocket of the K103N/Y181C enzyme creates a repulsive interaction with the inhibitor. Understanding these particular structural interactions can be useful for the design of inhibitors which are specific to the HIV-1 RT allosteric site and have greater potency against the mutant enzyme. Therefore, ONIOM methods, especially MP2/6-31G(d,p):B3LYP/6-31G(d,p):PM3 method, is accurate and efficient for modeling interactions between inhibitor molecules and HIV-1 RT.

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