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Isotope Effects on Inhibitors Binding to HIV Reverse Transcriptase

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Abstract : In order to understand in details the interactions between ligands and the enzyme isotope effects were studied between clinically used drugs that bind in the active site of Human Immunodeficiency Virus Reverse Transcriptase, HIV-1 RT, as well as triazole-based inhibitor that binds in the allosteric pocket of this enzyme. The magnitudes and origins of the resulting binding isotope effects were analyzed. Subsequently, binding isotope effect of the same triazole-based inhibitor bound in the active site were analyzed and compared. Together, these results show differences in binding origins in two sites of the enzyme and allow to analyze binding mode and place of newly synthesized inhibitors. Typical protocol is described below on the example of triazole ligand in the allosteric pocket. Triazole was docked into allosteric cavity of HIV-1 RT with Glide using extra-precision mode as implemented in Schroedinger software. The structure of HIV-1 RT was obtained from Protein Data Bank as structure of PDB ID 2RKI. The pKa for titratable amino acids was calculated using PROPKA software, and in order to neutralize the system 15 Cl- were added using tLEaP package implemented in AMBERTools ver.1.5. Also N-terminals and C-terminals were build using tLEaP. The system was placed in 144x160x144Å3 orthorhombic box of water molecules using NAMD program. Missing parameters for triazole were obtained at the AM1 level using Antechamber software implemented in AMBERTools. The energy minimizations were carried out by means of a conjugate gradient algorithm using NAMD. Then system was heated from 0 to 300 K with temperature increment 0.001 K. Subsequently 2 ns Langevin−Verlet (NVT) MM MD simulation with AMBER force field implemented in NAMD was carried out. Periodic Boundary Conditions and cut-offs for the nonbonding interactions, range radius from 14.5 to 16 Å, are used. After 2 ns relaxation 200 ps of QM/MM MD at 300 K were simulated. The triazole was treated quantum mechanically at the AM1 level, protein was described using AMBER and water molecules were described using TIP3P, as implemented in fDynamo library. Molecules 20 Å apart from the triazole were kept frozen, with cut-offs established on range radius from 14.5 to 16 Å. In order to describe interactions between triazole and RT free energy of binding using Free Energy Perturbation method was done. The change in frequencies from ligand in solution to ligand bounded in enzyme was used to calculate binding isotope effects.

Keywords : binding isotope effects, molecular dynamics, HIV, reverse transcriptase
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