QM/MM-based charge density analysis of protein-ligand complexes: Towards medicinal chemistry and drug design perspective

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Intermolecular interactions are very crucial point to understand exhaustively in the part of rational drug design. Interestingly, the electronic level information of these intermolecular interactions is not possible to determine without high resolution x-ray diffraction measurements. However, this measurement is more familiar for small molecules and still demand to challenge the protein-ligand complexes. The design of drug with improved physical and chemical properties are major driving forces in the medicinal chemistry. To achieve this, quantum crystallographic approach helps to estimate the stability of interactions obtained from the ligand molecule with their target amino acid residues. Indeed, recent methodology development reports [1-3] helped us to study as well as compute intermolecular interaction energies of protein-ligand complexes. Therefore, the present study is mainly focused to determine the different type of interactions between protein and ligand at electronic level. To accomplish this, the desirable protein-ligand complexes like enzyme-drug, enzyme-inhibitor and metal proteins-inhibitor complexes were subjected to QM/MM calculation followed by quantum theory of atoms in molecules (QTAIM) analysis which helps to understand the strength of intermolecular interaction and charge density distribution of protein-ligand complexes and these results compared with already reported experimental results. Electron density, Laplacian of electron density and hydrogen bond dissociation energy of metal interactions are very higher than the other interactions which confirms that the metal coordination is partially covalent bond. Hirshfeld surface analysis along with subsequent fingerprint maps were plotted to quantify the intermolecular contacts between ligand and amino acid residues. Non-Covalent Interaction (NCI) analysis has proved method for the qualitative analysis of hydrogen bonds which plays a crucial role and the accurate NCI energies of these bonds are essential to understand the binding mechanism in the formation drug-receptor complexes. NCI isosurface map of intermolecular interactions of protein-ligand complex clearly visualized the strong and weak interactions. Therefore, the quantum crystallographic based interaction energy calculation is a better alternative to docking score-based modelling. The results will be discussed at the time presentation.

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