

CHAPTER 10

Conclusion on allopathic drug molecules

The geometrical and topological parameters of two allopathic drug molecules, donepezil and tacrine are studied and compared with each other. Charge density analysis, docking analysis, intermolecular interaction and the electrostatic properties reveals the difference between both forms of the molecules, in different phases. The gas phase and the active site study, insights the molecular flexibility in the active site and the modification of topological and the electrostatic properties of both molecules.

In both forms of donepezil, the ring 1 and 2 lies in same plane, whereas the rings 3 and 4 are not planar. But the deviation in (II) is different from (I). The difference in the geometrical parameters and the topological parameters between (I) and (II) of donepezil molecule is attributed to the different environments. The methoxy moieties and the C−O group in the outer core are mainly affected. The lowest docked energy of the donepezil molecule in the active site of AChE is -10.93 kcal/mol. It seems that, the molecule binds only with acyl-binding pocket-Phe330 and not with the choline binding site-Trp84. The dipole moment of the donepezil molecule lifted from the active site (II) is slightly higher (4.07 D) on comparing with the gas phase structure (I) (3.76 D). The ESP depicts the negatively charged regions of both forms, which differs significantly for different atoms. In donepezil, the oxygen and nitrogen atoms of the molecule (II) are highly influenced by the negative electrostatic potential. The rest of the molecule exhibit the positive electrostatic potential. Major difference could not be observed in the structural aspects between (I) and (II) forms of tacrine. The charges are also not much redistributed. In both the forms, the molecule is planar, there is not much deviation. The lowest docked energy of tacrine in the
active site of AChE and the value is -8.43 kcal/mol. On comparing with donepezil, the binding affinity of tacrine is relatively less; this may be due to the lack of interaction with Phe330 residue of the acyl-binding pocket, as it is found in donepezil. The active site of tacrine is slightly higher (3.98 D) than the corresponding gas phase (3.53 D). The ESP distribution of both the molecules are different as they are structurally different. However, tacrine is a highly rigid molecule on comparing with donepezil. Hence the ESP is not redistributed to other areas of molecule, but displaced, only it has been enhanced in the active site. This comparative study allows to understand the exact difference between these two molecules in the active site.