CONCLUSIONS AND FUTURE PROSPECTS

9.1 PART I

The receptor–ligand interactions are mediated by strong and weak hydrogen bonds in the active sites of receptors. Unlike in small molecule crystallography, resolution limits are important in the structural study of hydrogen bond geometries in macromolecules. Main chain hydrogen bond geometries are better represented than the side chain. Hydrogen bond donor/acceptor furcation is very often encountered in the active sites. The amalgamation of strong and weak hydrogen bonds typically forms characteristic hydrogen bond patterns (supramolecular synthons). The geometries for strong hydrogen bonds are consistent, while the weak ones have variable geometries. Apart from hydrogen bonds there exist other weak interactions in the receptor–ligand interface. Key residues in the active sites frequently participate in hydrogen bonding with the ligand. Ligands usually maintain an optimum level of acceptor and donor ratio while interacting with the receptor. Hydrogen bonds involving water molecules in the active sites are noteworthy. With suitable computational tools, very large numbers of strong and weak intermolecular interactions in the receptor–ligand interface may be analyzed reliably. These findings have possible implication in drug discovery research.

9.2 PART II

Some successful implementations of molecular modeling in computer aided drug design are presented. Pharmacophore modeling, docking and virtual screening have been performed on two therapeutically important targets. The virtual screening exercise was carried out through database screening. In chapter 7 the selectivity of model was tested in the database mining of EGFR and EGFR spiked non-EGFR kinase inhibitors. In chapter 8, a composite pharmacophore model was used to identify novel inhibitors of AChE in an external database. These exercises resulted in (a) design of a selective pharmacophore model for EGFR kinase inhibitors, (b) identification of possible inhibitors for AChE. The molecular docking study on EGFR kinase domain reveals selectivity for anilinoquinazoline and cyanoquinoline type of inhibitors based on the active and inactive state of the receptor. Similar docking study in AChE suggest that, each compound class has specific hydrogen bonding interactions in the active site, and these can be categorized into

five clusters. Further, the inhibitory activities were successfully predicted for both EGFR and AChE inhibitors.

In this thesis I have tried to present some aspects of molecular recognition between receptor and ligand through a comparative crystallographic and molecular modeling study.