CONCLUSION

Conclusion

This thesis is focused on evaluation of QSAR analysis some drug molecules and also molecular docking, MD simulation was carried out for some inhibitor and its receptors. The major findings obtained from the studies are given below

Renin is a key enzyme, initiates the enzymatic cascade producing the angiotensin peptides that control blood pressure, cell growth, apoptosis and electrolyte balanced. Binding energy data shows that inhibitors are good binding pose. Hydrogen bonding interactions are important for stability of the complex. All docking results show that common hydrogen bonds formed between P1 moiety and Asp226. Also Gly228 makes a hydrogen bond with the P3' moiety of the 72X. It observed that Asp226 and Gly228 residues are important for binding. Hydrophobic interactions are also crucial for the stability of the complex. LogP value suggests that the inhibitor has hydrophobic environment. P1, P2, P1', P2'and P3' residues of the inhibitor surrounded by hydrophobic residues of the protein such as Thr15, Thr18, Tyr20, Tyr83, Thr85 , Pro118, Phe119, Leu121, Ala122, Phe124, Val127, Thr224, Thr227, Ala229, Tyr231, Met303, Leu252 (B) and Phe253(B).

Type IIa receptor protein tyrosine phosphatases (RPTPs), such as RPTPσ, LAR and RPTPδ, are cell surface receptors which play an important role in neuronal development, function and repair. From the analysis it is clear the motion of the protein is distributed among the PCAs. Hydrogen bonds formed between the hydroxyl groups of SER50 and TYR216 (HB6). Another hydrogen bond formed between the backbones carbonyls of ILE42 and backbone amide of VAL214 (HB7) in Ig1-Ig2pro-rich loop. It was found that hydrogen bond between the backbones carbonyls of ILE42 and backbone amide of VAL214 (HB6) remain intact during the whole simulation time.

QSAR analysis was performed on a series of 34 inhibitors of anthrax lethal toxin and validated through six QSAR model. Descriptors are used for multiple regression analysis. A QSAR model (model 6) was obtained with LOO cross-validation values of 0.56. The model 6 predictive ability as differentiate by the testing on the external test set and also useful to explain the relationship between compound structure and biological activities and make easy to design of more potent hydroxamate inhibitors.

Aminoacyl -tRNA synthetases catalyze the attachment of amino acids to their specific tRNAs in protein synthesis. In higher eukaryotes several of these enzymes are found in a multienzyme complex. Jeong et al. solved the NMR structure of multifunctional peptide motifs in human bifunctional glutamyl- prolyl tRNA synthetase. To understand the motional properties and mode of action of the human bifunctional glutamyl- prolyl -tRNA synthetase, molecular dynamics simulation of human bifunctional glutamyl-prolyl-tRNA synthetase, in aqueous environment was carried out using the software, GROMACS. From the time evolution, Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF) and Radius of gyration (Rg), it was found that the toxin was relatively flexible. Principal Component Analysis (PCA) was also performed for better understanding of motional properties in reduced dimension. All these observations help us to understand the structure and function of human bifunctional glutamyl-prolyl-tRNA synthetase

In this communication, we came out with a mathematical model that involved accepted quantum mechanical parameters and topological indices. This model was applied for screening derivatives of triazine (MAP-kinase inhibitors). We have been able to predict activities that might be taken to inhibitors prior to synthesis. Thus a screening regime might emerge from this study that would lead to efficacies at a relatively reduced cost and telescoping the time-frame as well.

The mitogen-activated protein (MAP) kinases a group of serine/threonine kinases function as critical mediators of signal transduction. MAP kinase causes several diseases, such as asthma osteoarthritis, rheumatoid arthritis, and chronic inflammatory autoimmune disease. Triazine analogues are inhibitor of p38 MAP kinase. Docking of MAP inhibitors are performed using AutoDock and binding energy for the inhibitors are calculated and regression equation is formed using HT29. Effect of substitution is analyzed. It is found presence of morpholinoor anilino ring is essential. Some compounds are designed and their binding energy is calculated. It is seen that designed compound also inside the binding pocket.

In future research rigid docking can be used and further AutoDock Vina can be used for docking of the compounds whose crystal structure is not known. DFT based QSAR modeling; 4D QAR and Molecular Modeling can be performed.