SUMMARY

In this thesis quantitative structure-activity relationship (QSAR), molecular docking and molecular dynamics simulation were performed.

This thesis contains total nine chapters. First and second and third chapter describe introduction, review of this work, Materials and Methods respectively.

Chapter four comprises MD simulation of rennin and molecular docking of its inhibitors. Molecular docking studies were carried out with AutoDock 4.2. and molecular dynamics simulation was performed using GROMACS. Inhibitor 72X was successfully docked into the active site of human renin. There are many hydrogen bonds formed between inhibitor and protein. It is observed that Asp226 and Gly228 residues are important for binding. All docking results show that hydrogen bond formed between P1 moiety and Asp226 of 72X. Also Gly228 makes a hydrogen bond with the P3' moiety of the 72X. A careful inspection of the binding pocket indicated that the inhibitor in hydrophobic cage surrounded by mainly hydrophobic residues of renin. It is examined that two aspartic acid residues Asp38 and Asp226 placed at the P1 moiety and maximum number residues in chain A involve in the binding process whereas only two residues Leu252 (B) and Phe253 (B) of chain B in the binding process. Region having amino acids Asp226, Gly228 and Ser230 are most important residues for initiating the interaction with ligand and good binding.

Chapter five describes molecular dynamics simulation of chick Type IIa receptor protein tyrosine phosphatases sigma to understand the folding and structural behavior of cheek RPTP σ. Molecular dynamics simulation is performed using software GROMACS to understand the motional properties of the protein. Root Mean Square Deviation (RMSD), Radius of gyration (Rg) and Principal Component Analysis(PCA) has been carefully

done. The residues of binding site are also studied extensively. From the analysis it is clear the motion of the protein is distrusted 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-Ig2 pro-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.

Chapter six describes the QSAR studies of Hydroxamate inhibitors of Anthrax Lethal toxin. Constructed QSAR models by stepwise regression analysis is developed using quantum chemical descriptors. After considering training set and test set we have also designed seventeen compounds and predicted their activity. This work may be helpful in screening and synthesis of Anthrax inhibitor.

Chapter seven comprises molecular dynamics simulation of 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

Chapter eight describes screening of Triazine derivatives (MAP-kinase inhibitors) through mathematical modeling and molecular Modeling. Triazine derivatives possess

various pharmacological actions against breast, lung, and ovarian cancers.These derivatives bind with MAP-kinase p-38. In this work four QSAR models were developed using 16 compounds and its predictive ability was assessed using a test set of 9. We computed several graph theoretical indices along with quantum chemical parameters and constructed regression equations. We have also designed a series of triazine derivatives and predicted their activity. We intend to suggest some compounds, which have high predicted activity.

In the last chapter describe molecular docking of Triazine analogues. Docking of MAP inhibitors were 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 morpholino or anilino ring is essential for inhibition. Some compounds are designed and their binding energy is calculated. It is seen that designed compound also good binding energy and inside the binding pocket of MAP-kinase p-38.