CONCLUSIONS AND FUTURE DIRECTIONS

Computational drug design approach has a great potential in accelerating the drug discovery process. Structure-based drug design and ligand-based drug design are the two broad classes of computational drug design. PDK-1 is a well validated anti-cancer target and developing inhibitors for PDK-1 has the potential to be developed as the anti-cancer therapeutics. In the work combined herewith, I have show the potential of computational approaches for screening of wide class of inhibitors using PDK-1 as our target.

An attempt has been towards both structure-based and ligand-based drug design strategies for screening and validation of wide class of inhibitors against PDK-1.

In ligand based study ligand-based lead optimization by using wide class of known PDK-1 inhibitors as the staring lead molecule.

Since naphthyridine, benzo naphthyridine and celocoxibe derivatives are one of the frequently encountered sub-structure as kinase inhibitors, so based on these lead molecule, the developed 3D-QSAR model exhibit the potential to predict and guide the rational design of new class of lead molecule as PDK-1inhibitors.

A data set of 83 compounds of selective PDK-1 inhibitors with their respective activities ranging over a wide range of magnitude has been

used to generate pharmacophore hypothesis to predict the activity successfully and accurately. A highly predictive pharmacophore model was generated based on 21 training set molecules, which had two hydrogen-bond acceptor, one hydrogen bond donor and one hydrophobic aliphatic groups as chemical features which described their activities towards PDK -1 kinase. The validation of the model was based on 62 test set molecules, which finally showed that the model was able to accurately differentiate various classes of PDK-1 inhibitors with a high correlation coefficient of 0.87 between experimental and predicted activity. Further validation of Hypo1 was done by decoy set method. The Decoy set method exhibited the GH score of 0.73 which reflect that designed model have very high efficiency in screening the molecules from database. Hierarchical virtual screening protocol have been used here to identify new hits against PDK-1. Currently I have used the ligand-based screening, rigid docking, flexible docking lipinski as well ADMET as screening filters during virtual screening protocol. Hypo1 was used as a 3D query to screen the potential molecules from the NCI database as well Maybridge database. The hit compounds were filtered subsequently by Lipinski's rule of five and ADMET filtration. Further molecules were refined by docking study. After docking studies finally we screened the 3 molecules (NSC_218342, NSC_24871, NSC_211930) which having different scaffold shows better docking energy as well as shows better interaction. By using this strategy three promising new hits were identified for the development of a novel anticancer therapeutic as PDK-1 kinase inhibitor. The inhibitor identified in this study serves as a good starting point for future rational drug design of PDK-1 inhibitors. Our

virtual screening approach may also be applied to discovery of new lead molecules for other drug targets.

It may be further emphasised that molecular-docking based virtual screening is an important tool in drug discovery that is used to significantly reduce the number of possible chemical compounds to be investigated.

The side effects of the currently used drug for cancer treatment has given a lead to explore an alternative and traditional approach to finding out new drug compound from the natural origin , compounds which are having anti cancerous activity and also not having any side effects to human normal cell These plant compounds which are also having high binding affinity for many receptors which are over expressed in many cancers could lead to be an alternative treatment for cancer(Kawaii et al., 1999; Pouget et al., 2001).. Natural compounds are far beneficial than synthetic compounds due to less toxicity, more accessibility and being less expensive

In this structure-based lead drug designing approach which involve a comparative evaluation of various natural compounds as   potential anticancer compounds wherein the effectiveness has been studied with reference to PDK-1 Kinase inhibition. The molecular docking results exhibited the effectiveness of three natural flavonoids among all the compounds were taken for the study. Finally best hit i.e Myricetin was subjected to molecular dynamic simulation study, evaluating the binding stability of complex under body environmental conditions. The simulation results have been with reference to Protein Ligand interaction and molecular dynamic simulation in water. These studies depict that the

role of some crucial amino acids involved in proper binding of inhibitors with the active site of PDK-1 can be useful for designing better drugs to combat cancer. Further these studies supported the potential role of Myricetin in cancer which should be further studied for modulation of other signalling pathways as PDK-1 kinase being master regulators of other downstream regulators protein PIP3 kinase, AKT kinase.

Molecular docking studies of natural compounds with reference to PDK-1kinase revealed that Myricetin is a effective natural compound against PDK-1. But due to low oral bioavailability, clinical use of Myricetin is limited. Therefore molecular modifications of Myricetin can improve its pharmacological properties.

The final objective of my study has been towards screening of 95% similar analogues from PubChem data base. Insilico screening of analogues study concluded that all the screened analogues were have better ADMET profiles as compared to the Myricetin. Apart of better ADMET profile these compounds belonged to different scaffold. Best docking energy (-42.0 kcal/mol) was shown by di fluoro substituent of Myricetin. Fluorine has become an essential tool in drug discovery. Including fluorine atoms in potential medicines can have a variety of dramatic effects on the molecules' properties, perhaps making them more selective, increasing their efficacy, or making them easier to administer.

One of the most important factors in drug design is that fluorine is much more lipophilic than hydrogen, so incorporating fluorine atoms in a molecule will make it more fat soluble, hence the fluorinated molecule has a higher bioavailability. This provide a better insight for further development of new series of inhibitors by using these scaffold as starting

molecule. These may hold better potential as drug candidates that inhibit the PDK-1 kinase.

Based on the study conducted following conclusions can be made:

1. Successfully development of ligand based 3D QSAR Model.

2. Successfully prediction of biological activity of entirely new compounds stored in various database (NCI & Maybridge) by pharmacophore base virtual screening.

3. Screened top hits will used as starting molecules for development of new series of inhibitors against PDK-1in future.

4. Docking and dynamic simulation based screening of effectiveness of selected natural compounds against PDK-1.

5. Molecular docking and dynamic simulation studies revealed the effectiveness of Myricetin against PDK-1

6. Chemical structure based screening of 95% similar analogues of myricetin stored in PubChem database was performed to screen new class of molecules as PDK-1 inhibitors.

7. Insilico docking and ADME studies of these analogues revealed the effectiveness of some analogues (CID_5281701, CID_ 13964550, CID_24721178, CID_5315126, CID_6477685 and CID_66574000) as compared to Myricetin,

8. Better pahrmacokinetics profile of these analogues revealed that we can used as these compounds as future inhibitor of PDK-1 kinase in future.

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