PREFACE

Now a day's *computational* drug designing approach has become most promising area in the drug disco very process. Both 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.

Both structure-based and ligand-based drug design strategies have been used for identification of new potential hits against PDK-1.

In ligand based drug designing approach a 3D QSAR pharmacophore was identified for screening of new potential hits deposited in NCI (National cancer institute) and Maybridge databases of small molecules. By using Hypo 1 as 3D query, three potential hits have been screened which mapped the all chemical features of generated pharmacophore very well.

Molecular docking method has been used for screening of natural inhibitors (deposited in PubChem Data base) as potential hits for PDK-1. *In silico* docking and molecular dynamic simulation based study was used for screening of potential natural flavonoids as PDK-1 kinase inhibitors. Molecular dynamic simulation study supported that Myricetin can acts as potential hit against PDK-1 kinase as myricetin and PDK-1 complex was stable during entire simulation (10ns).

But due to low oral bioavailability, clinical use of Myricetin is limited, an attempt was made towards structure based screening of new potential analogues deposited in PubChem database. Further *Insilico* ADME/

Toxicity and molecular docking studies was carried out to check the pharmacokinetics properties of as well as binding interactions of screened molecules. It was concluded that myricetin and their analogues have better binding interactions with PDK-1 kinase (PDB: 1UU7.) The binding energies of the protein- ligand interactions also confirmed that the ligands were fit into the active pockets of receptor tightly. Insilico ADMET study concluded that all the analogues were have better profiles when compared to myricetin. These may hold better potential as drug candidates that inhibit the PDK-1 kinase. Further development and modification of these analogs may lead to generation of novel high potent anticancer drug in future.

The data presented in the thesis are the results of my long efforts aimed to cover these aspects and relate these with the assumptions and presumptions of others in the field. A lot more could have been harvested and incorporated in the present volume, I take the responsibility of any sort of drawback in planning and implementation of research plan.

The thesis has been conveniently divided into six chapters comprising of:

Introduction **(Chapter 1)**, Literature review **(Chapter 2)**, 3D QSAR Based Designing Of Pharmacophore and Pharmacophore Based Virtual Screening **(Chapter 3**), Docking Based Screening and Validations of Some Selected Natural Inhibitors Against PDK-1 Kinase **(Chapter 4),** Molecular Docking And *Insilico* ADMET Study of Myricetin and their Analogues **(Chapter 5) and** Conclusions and future directions (**Chapter 6).**