3. AIMS AND OBJECTIVES

Cancer is the most dreaded group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not proscribed, it can result in death. It is well known that the drug discovery and development process may take from 10 to 15 years of time and cost around 2 to 4 billion on an average for a new drug to be introduced into the market. Even after tremendous developments in diagnosis and treatment of cancer in the past few years, the problem remains more or less unsolved. Synthesis of huge number of molecules and their evaluation on equally large number of animals make it a difficult and tedious job.

Computational chemistry is a branch of chemistry that uses computer simulations in solving chemical problems and to design newer chemical molecules for desired biological targets. CADD involves diverse disciplinary aspects of physics and chemistry. The computational methods are helpful to reduce the cost, time, uncertainty, huge random use of chemicals and animals for synthesis and testing of the chemical molecules. Recent technological advances like structure based drug design, ligand based drug design and availability of large number of chemical and biological databases have made CADD more useful and interesting.

Aurora kinases are the mitotic serine/threonine kinases which are key regulators of mitosis that control cell cycle progression and signal transduction. These are of three types, aurora A, aurora B and aurora C kinases. In cell cycle, aurora kinases participate in the formation of the mitotic spindle assembly, attachment of the mitotic spindle to the kinetochore of the centrosome and other related processes. In short, these enzymes play vital role in control and progress of cell cycle. These enzymes are overexpressed in many of the human cancers, and therefore they have been widely considered as prospective targets for a new class of anticancer drugs.

Presently, more than a dozen of aurora kinase inhibitors are in different phases of clinical trials. The bulk of the aurora kinase inhibitors (VX-680, CYC116, PHA-739358, AMG 900, AT-9283, SNS-314, PF-03814735, R-763 and TAK-901) are pan-selective (isoform non-selective) while some are aurora A (MLN8237, ENMD 2076 and MK5108) and aurora B

(AZD1152 and GSK1070916) sub-type selective. In spite of various efforts towards development of aurora kinase inhibitors in the past decade, no aurora kinase inhibitor has reached the market. Fresh evidence in the field for development of novel aurora kinase inhibitors indicate that selective aurora A kinase sub-type inhibitors will possibly have advantage over pan-selective aurora inhibitors, by shunning aurora B mediated neutropenia.

With a better understanding of the structural requirements for the inhibition of aurora A kinase, it is possible to develop novel aurora kinase inhibitors. Therefore to understand these requirements with the help of computational chemistry, it was planned to develop multidimensional QSAR models. In the development of a QSAR model, the requirement of suitable conformations of molecules and systematic validation of the developed model to check the robustness and accuracy of the model are essential criteria. If wrong conformations of the molecules are used, the model may go wrong or misguide the user in the interpretation of the model. Considering these points the following studies were planned to be carried out:

- Identification of structural requirements for imidazo[1,2-*a*]pyrazine derivatives as aurora A kinase inhibitors by using docking based conformations and systematic validation of the developed model.

- Development of 4D-QSAR model which is having advantage of conformational flexibility over the 3D-QSAR model for the investigation of essential structural requirements for benzo[*e*]pyrimido[5,4-*b*][1,4]diazepin-6(11*H*)-one derivatives as aurora A kinase inhibitors. Further, a methodical validation of the developed model to check the robustness of the model was also planned.