6. CONCLUSION

Cancer is a communal term used for a group of diseases that are distinguished by the loss of control of the division, growth and spread of a group of cells, which leads to a primary tumor that assaults and demolishes neighboring tissues. Through metastasis these cells or tissues may also spread to other parts of the body. This is the main reason for 90% of cancer deaths. According to WHO report, there were 14.1 million new cases of cancer and 8.2 million cancer deaths reported worldwide in 2012. More than 60% of the world's total new annual cases occur in Africa, Asia and Central and South America. These regions account for 70% of the deaths because of cancer in the world.

Round the year many antineoplastic agents have been reported and many remain under development. These agents act at different levels in the cell cycle to control the cancer condition. Various drugs have been discovered which act at different stages of cell cycle. Despite having such a vast number of sites or targets for action there is no permanent cure for cancer. This noncompliance is mainly because of short therapeutic index of anticancer drugs or development of toxicity. In such conditions, functional genomic data is helpful for the identification of therapeutic target proteins which regulate the cell cycle and get differentially expressed in tumors compared to the normal cells of the adult tissues.

Protein kinases are enzymes that modify other proteins by phosphorylation. Among the various mitotic regulatory kinases, the aurora kinases belong to serine/threonine kinases, which play vital role in the cell cycle regulation. It is observed that this family is expressed at high levels in several human cancers. Along with its vitally important role in cell division, members of this family also functionally interact with different critical oncoproteins and tumor suppressor proteins. These kinases are essential for genetic material alignment, dispersion and cytokinasis during mitosis. Aurora kinase family is divided into three subclasses, aurora kinase A, aurora kinase B and aurora kinase C.

Presently, more than a dozen of aurora kinase inhibitors are in different phases of clinical trials. Some of them are isoform non-selective (VX-680, CYC116 etc) and a few are subtype selective (MLN8237, ENMD 2076 etc). In spite of various efforts towards development of aurora kinase inhibitors in the past decade, no aurora kinase inhibitor has reached the market.

The knowledge of structural requirements for the development of selective inhibitors may help in the discovery of novel aurora kinase inhibitors. Therefore to understand these requirements with the help of computational chemistry, it was planned to develop multidimensional QSAR models. Two different QSAR (one 3d-QSAR and one 4D-QSAR) models were developed using two different series of aurora A kinase inhibitors and the developed models were systematically evaluated by using different validation parameters.

The 3D-QSAR model was developed by using Tripos-SYBYL and AutoDock4 softwares. This 3D-QSAR model (CoMSIA-SEHD) was developed for the study of structural requirements of imidazo[1,2-*a*]pyrazine derivatives as aurora A kinase inhibitors from a series of 51 compounds reported previously by Merck Research Laboratories. In this model, docking based conformation of the most active compound was used as the template for alignment. The developed (CoMSIA-SEHD) model showed good predictive ability with predictive coefficient of determination (r^2) value of 0.752. The best model was validated systematically by using different validation parameters. This model highlighted the role of steric, electrostatic, hydrophobic and hydrogen bonding features present in the molecules, in the development of active inhibitors.

In the second model the conformation flexibility was used as the fourth dimension in the development of 4D-QSAR model. In this work, a 4-D-QSAR model using an LQTA-QSAR approach with previously reported 31 derivatives of benzo[*e*]pyrimido[5,4-*b*][1,4]diazepin-6(11*H*)-one as potent aurora kinase A inhibitors was developed. The conformational ensemble profile was generated for each ligand with the help of trajectories and topology information retrieved from molecular dynamics simulations performed in GROMACS and were aligned and used for the calculation of intermolecular interaction energies at each grid point. The descriptors generated on the basis of these Coulomb and Lennard-Jones potentials as independent variables were used to perform a PLS analysis using biological activity as dependent variable. From this study a good predictive model was generated with 9 field descriptors and 5 latent variables (LV). The model showed Q_{LOO}^2 = 0.718; R^2 = 0.915 and R_{pred}^2 = 0.839. This model was further validated systematically by using different validation parameters.

Both these models gave valuable structural information to recognize features essential to adapt and develop novel potential Aurora kinase inhibitors.