6. CONCLUSION

A larger number of world population is affected by cancer. Wide varieties of chemotherapeutic agents are used for its cure but unfortunately cancer still remains an enigma for the world’s science community. Newer targets are being identified to develop more efficacious and less toxic anticancer drugs. One such target is telomerase enzyme, responsible for making the cancerous cells almost immortal. The concentration of telomerase in the carcinogenic tissue is found very high in comparison to the normal tissues.

It was envisaged that arresting telomerase activity in cancer cells would force them to adopt apoptosis without affecting the normal tissues. So, telomerase inhibitors could offer a very big advantage over the existing anticancer agents which treat all the cells (normal or cancerous) alike. Telomerase inhibitors would arrest the growth of cancerous cells without affecting the normal cells.

A large numbers of chemical entities have been evaluated in the literature as telomerase inhibitors. These compounds bind physically with the guanine tetrad present in the G-quadruplex of telomerase thereby blocking biochemical role. These compounds belong to various categories like acridines, anthraquinones, acridones, triazines, perylenes, porphyrines etc.

In the current work, efforts have been made to develop reliable 3D-QSAR models for optimization of a few series of chemicals as telomerase inhibitors. Initially, 3D-QSAR CoMFA/CoMSIA models were developed for acridine and pentacyclic acridine derivatives. Molecular docking provided predicted bioactive conformations for alignment for derivation of 3D-QSAR models. Molecular docking studies also helped us to identify right protonating nitrogen atoms in situ. The QSAR models showed good correlative and predictive capabilities in terms of $q^2$ and $r^2$ values. High bootstrapped $r^2$ values and small standard deviations indicate that the derived models are statistically significant. 3D-QSAR models have been validated in various ways and were found to be reliable and robust models.

Another 3D-QSAR study was performed on anthraquinone and acridone derivatives to gain structural insights for selective G-quadruplex stabilization for telomerase inhibition. 3D-QSAR CoMSIA method has been applied successfully to
rationalize the anti-telomerase activity of these derivatives. The developed models showed good statistical significance in internal ($q^2$, cross-validation and bootstrapping) validation and performed very well in predicting the biological activity ($pEC_{50}$) of the compounds in the test set.

Next, 3D-QSAR studies were performed on triazine derivatives as G-quadruplex mediating telomerase inhibitors. In this work, CoMSIA studies were performed to gain insight into their telomerase enzyme inhibition. Highly predictive CoMSIA models using an alignment based on the bioactive conformation derived from molecular dynamics simulated annealing rather than from the minimum energy conformer of the most active member of the series. The models derived showed high quantitative predictive ability.

After developing independent 3D-QSAR models for G-quadruplex mediating telomerase inhibitors belonging to different chemical classes, a universal model for all these derivatives was derived using 169 telomerase inhibitors with different chemical classes. The data set comprises of large structural diversity and variable biological activities. This makes the data set ideal for the development of a universal model. The CoMSIA studies produced equally good models expressed in terms of the $q^2$ values. The predictive powers of the derived models were demonstrated to be reliable. It is hoped that this model could be useful for predicting the telomerase inhibitory activity of any compounds having aromatic central core with two side chains on either side before their actual synthesis.

All the models developed using CoMFA/CoMSIA 3D-QSAR techniques were validated using external data set, and by using well established statistical tools. The universal model developed using four different classes of chemical compounds could be used for prediction of activity of any unknown compound from these categories for its telomerase inhibiting activity.