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Anticancer Drug Design Utilizing Pharmacoinformatics

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Editorial

For the last couple of years pharmacoinformatic tools have been intrinsically playing a crucial role in the design of anticancer compounds which exhibit pharmacological actions against different types of cancer such as murine tumor, CNS tumor, breast cancer and other malignant solid tumors, etc. The malignancies cause brutal death of millions of people throughout the world and thus demand an extensive research in cancer chemotherapy, both in revealing pathobiology of the diseases and discovery of new leads. For the design and screening of novel anticancer compounds having higher selectivity and efficacy, there has been using a number of pharmacoinformatic tools such as ligand based screening includes quantitative structure-activity relationship (QSAR) and pharmacophore generation whereas techniques of structure based virtual screening include molecular docking. In contemporary drug design, a huge real or virtual combinatorial library of derivatives can be generated which, in turn, can be evaluated using either physicochemical properties or by theoretical properties. Various chemometric softwares including DRAGON, CODESSA, Cerius2 program, PreADMET, MDS 3.5 for theoretical descriptor calculation, LIGANDSCOUT and Catalyst package version 4.10 for pharmacophore generation whereas AutoDock, DOCK, FlexX, GOLD and ICM are well familiar for molecular docking study.

In most of the cases due to unavailability of the physicochemical data, QSAR can be developed for the candidate structures utilizing various structural descriptors, which are computed solely from the molecular structures. Theoretical molecular descriptors include topological indices or numerical graph invariants that are widely used in the theoretical QSAR research for predicting biological activities of chemical compounds. Molecular descriptors considered in our study consist of topological, constitutional, electrostatic, geometrical and physicochemical parameters of the chemical compounds. As the number of molecular descriptors exceeds the number of observations to a large extent, conventional regression methods are of no use and hence, ridge regression, partial least square and artificial neural network methodologies have been applied for an effective prediction. Quantitative structure-activity relationship models have been developed for 2,5-Bis (1-Aziridinyl) 1,4-Benzoquinone (BABQ) compounds utilizing calculated molecular descriptors. Through descriptor based QSAR modeling on BABQ compounds, prediction of a new molecule, expected to be highly active, has been predicted. It was seen that our model is in good agreement with the hypothesis made earlier in terms of in vitro and *in vivo* activities. Such studies have been continued for various phenolic compounds having activities against different cancerous cell lines such as murine leukemia cell line (L1210), human promylolytic cell line (HL-60), human breast cancer cell line (MCF-7) for a comparative study of the relative effectiveness of linear statistical methods versus nonlinear techniques, such as CPANN in modeling structure-activity studies. It has been established that the biological activities calculated by structural descriptors based QSAR models can give a better significant correlation compared to the activities predicted by physicochemical descriptor based models.

Studies of potent anticancer chemotherapeutics showed toxicity to the normal cell which may decrease the life span of the patients. Therefore, researchers have been devoted to discover less toxic new chemotherapeutics which can prevent damage to the normal tissues. This can be achieved by the inhibition of cancer progression due to abnormal signal transduction and stimulation of apoptosis via modulating compounds. Abnormal signal transduction is transmitted through the mutation of cell membrane receptors such as EGFr/FGFr/PDGFr belongs to sub classes of tyrosine protein kinases. Apoptosis can be done by the stimulation of caspase mediated programmed cell death. Abnormal signal transduction can be corrected by tyrosine protein kinase inhibitors including 4-anilinoquinazolines, 4-[ar(alk)ylamino] pyridopyrimidines, 4-phenylaminopyrrolo-pyrimidines as selective EGFr inhibitors, FGFr 1 kinase inhibitors such Pyrido [2,3-d]pyrimidine, Pyrrolo [2,1-f][1,2,4] triazine, and Pyrido[2,3-d] pyrimidin-7(8H)-one, 1-Oxo-3-aryl-1H-indene-2-carboxylic Acid etc. whereas 1-Phenylbenzimidazoles as PDGFr inhibitors which were shown well accepted anticancer activities. The introduction of targeted therapies using small molecule kinase inhibitors like sorafenib, everolimus, imatinib or growth factor-related antibodies like cetuximab or bevacizumab has shown that a direct interference with survival and cell death-related signaling pathways can significantly improve patient survival for various cancers.

An attempt has been made to design congeneric chemotherapeutics utilizing pharmacoinformatics. A number of 2D and 3D QSAR models based on computed molecular descriptors has been formulated for the aminopyrido [2,3-d]pyrimidin-7-yl derivatives and 4-anilinoquinazolines. 2D QSAR models have been developed by using some sophisticated statistical tool such as ridge regression that can predict the influence of different class of calculated molecular descriptors on biological activities of the molecules whereas molecular field analysis has been applied to generate 3D QSAR models for predicting the influences of steric, electrostatic and hydrophobic fields around the aligned molecules. Finally, molecular docking analysis has been carried out for better understanding of the interactions between EGFR target and 4-anilinoquinazoline inhibitors in this series. Hydrophobic and hydrogen bond interactions lead to identify active binding sites of EGFR protein in the docked complex. There is a huge scope to design more active potent anticancer leads considering other existing templates utilizing such pharmacoinformatic tools. One of the major applications of these tools is combinatorial library generation. Rational design of small focused virtual or real libraries is currently at the forefront of combinatorial library design. The advent of combinatorial chemistry for the generation of large number of hypothetical molecules which are filtered in property based virtual screening techniques has

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dramatically increased the rate of generating new lead compounds with desired potency and affinity towards target. Thus, computer-aided combinatorial chemistry reduces the cost, time, and labor required to synthesize and screen large libraries and increases the rate of success for designing new leads. For the designing of new molecules, a number of hypothetical compounds belonging to existing templates can be generated by the introduction of several substituents at different point of diversity of the basic scaffolds. Virtual screening are performed using Lipinski's rule of five, activity prediction by validated training QSAR model and structure based molecular docking to investigate the mode of binding of the highly predicted active ligand towards receptor. The predicted active combinatorial compounds having similar docking score and binding patterns with that of the existing lead molecule in this class of congeners could be proposed and boosted for the design of less toxic anticancer leads.