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QSAR and 3D-QSAR in Drug Design Anti-Tubercular Drug Discovery Studies

Joshi SD and Aminabhavi TM*

Department of Pharmaceutical Chemistry, SET's College of Pharmacy, Dharwad-580002, India

***Corresponding author:** Tejraj M Aminabhavi, Department of Pharmaceutical Chemistry, Soniya College of Pharmacy, Dharwad-580002, India, Tel: 09449821279; E-mail: aminabhavit@gmail.com

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Editorial

The relationships between lipophilicity and unspecific biological properties, such as narcotic, fungicidal, bactericidal, hemolytic and toxiccity properties have been known ever since the turn of the century. Research publications of Free Wilson method [1] and that of Hansch analysis [2] during 1964 served as the milestones in development of quantitative structure-activity relationships (QSAR). Later, introduction of Hansch and Free Wilson models enabled the pharmaceutical chemists to formulate hypotheses of structure-activity relationships quantitatively for checking these hypotheses by means of statistical models.

QSAR is essentially a computerised statistical method, which tries to explain the observed variance to understand the biological activity of certain classes of compounds in terms of molecular changes caused by substituents. It assumes the potency of a certain biological activity exerted by a series of congeneric compounds is a function of various physico-chemical parameters. Once the statistical analysis shows that certain physico-chemical properties are favorable to the activity, and the latter can be optimized by choosing such substituents, which would enhance their physico-chemical properties.

QSAR involves mathematical as well as statistical analyses of SAR-data, which helps to reduce the number of educated guesses for molecular modifications. Description of molecular structure, electronic orbital reactivity and the role of structural as well as steric components has been the subject of mathematical and statistical analyses. The ultimate objective of such studies has been to understand the forces governing the activity of a particular compound or a class of compounds.

QSAR studies also play very important roles in drug discovery and designing as the ligand-based approach. Such approaches are explicitly judgmental to provide not only reliable prediction of specific properties of new compounds, but also help to elucidate possible molecular mechanisms of receptor-ligand interactions, if experimental NMR or crystal structure data of the target protein is unavailable.

Since 1964, the QSAR equations have been used to describe thousands of biological activities within different series of drugs and drug candidates. Especially, enzyme inhibition data have been successfully correlated with physico-chemical properties of ligands. In certain cases, where X-ray structures of proteins were available, the results of QSAR regression models have been interpreted with additional information from 3D- structures.

The 3D-QSAR model is a mathematical expression that relates the variation of biological response in a series of related compounds to the variation in their 3D chemical structures. In 1988, the method of Comparative Molecular Field Analysis (CoMFA) was proposed and developed. In drug design and discovery area, CoMFA, a 3D-QSAR technique has been one of the widely used computational tools especially in cases where classical QSAR method fails. This molecular field-based method constitutes the first real 3D-QSAR method. However, in contrast to Hansch or Free Wilson analysis, CoMFA is better suited to describe ligand-receptor interactions, because it considers the properties of ligands in their (supposed) bioactive conformations. From the results of CoMFA analysis, the regions in space are identified that are favorable or unfavorable for ligand-receptor interactions.

CoMSIA is another 3D-QSAR model developed by Klebe in 1994 in which molecular imilarity indices are calculated at the interactions of a surrounding lattice. It is expressed in terms of different physico-chemical properties originating from electrostatic, steric, hydrophobic and H-bond donor and acceptors.

So far, in our laboratory, we have reported several hundred pyrrole [3,4] analogs as antimycobacterial, antifungal, antibacterial agents and docking, 3D- and 2D-QSAR studies of all these compounds have been carried out [5]. We have also described docking study of pyrrolyl-1,3,4-oxadiazoles, phthalazine/pyridazines against ENR [6] as well as QSAR (CoMFA and CoMSIA) studies on pyrrolyl-imides, thiazoles as schiff bases and 1,3,4-oxadiazole derivatives [7-9] as antitubercular agents. The 3D plots obtained from these CoMFA, CoMSIA investigations, matched perfectly with in vitro antitubercular and antibacterial results of the compounds investigated.

QSAR is therefore a major scientific achievement with an economic necessity to reduce empiricism in drug design research to ensure that every drug synthesized and pharmacologically tested should be as meaningful as possible. These efforts are under active investigations in our laboratories for over more than a decade.

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