Published by :
http://www.ijert.org

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 6 Issue 06, June - 2017

Applications of QSAR Study in Drug Design

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***Abstract*— Quantitative structure-activity relationship (QSAR) and quantitative structure-property relationship (QSPR) studies are important in silico methods in rational drug design. The aim of this methods are to optimize the existing leads in order to improve their biological activities and physico-chemical properties. Also, to predict the biological activities of untested and sometimes yet unavailable compounds.**

This article is a general review of different QSAR/QSPR studies in different previous researches. R2 and Q2 parameters are used in some studies to predict the predictability and robustness of the constructed models. In all mentioned articles QSAR study were good prediction tool for investigation drug activity or binding mode on specific receptors.

***Keywords*— Drug design, QSAR, QSPR, Molecular Descriptor, Coefficient of Determination R2, Squared Correlation Coefficient Q2.**

I. INTRODUCTION

Drug discovery and development is a process aims to design safe and effective medications to improve life's quality and to reduce suffering to minimum. However, the process is very complex, time consuming, and resource intensive, requiring multi-disciplinary expertise and innovative approaches. Recent estimates suggest that it takes up to 13.5 years and 1.8 billion U.S. dollars to bring a new drug to the market [1].

Technology in medicine and health care have rapidly changed over the past decades. Biomedical Engineering development has an essential rule in solving medical problems [2-7].

Over the past ten to twenty years, There is an increased effort to apply computational abilities to the combined chemical and biological space to simplify drug discovery, and designing processes [8].

Rational drug design methods minimize the time and cost needed in drug designing process in comparison to traditional drug discovery methods. QSAR/QSPR studies can be used to design and identify new inhibitors de novo or to optimize absorption, distribution, metabolism, excretion and toxicity profile of identified molecules from various sources. Advances in computational techniques and hardware have eased the application of in silico methods in the designing process. Drug design can be divided in two groups: Structure based drug design (SBDD) and Ligand based drug design (LBDD) [9]. SBDD is the approach applying the structural information of the drug target to develop its inhibitor. While LBDD is used in the absence of the receptor 3D information and it relies on molecules bind to the biological target of interest. Figure I explains all different groups and types of drug designing techniques.

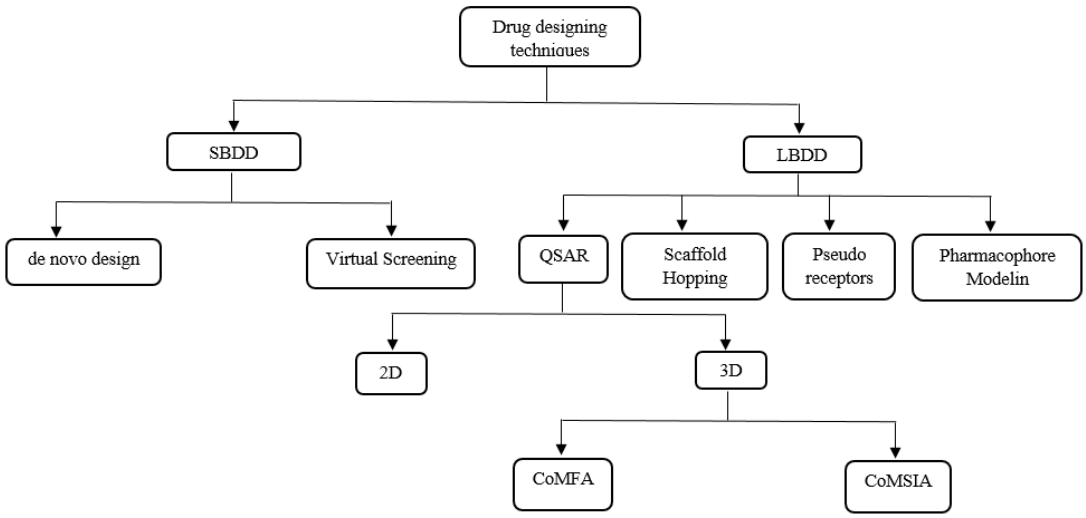

Fig I. Different groups and types of drug designing technique.

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 6 Issue 06, June - 2017

Quantitative structure-activity relationships (QSAR) have an essential role in drug design process these days, because they are cheaper alternative than the medium throughput in vitro and low throughput in vivo assays which [10].

Also, in drug discovery and environmental toxicology, QSAR models are now regarded as a scientifically credible tool for predicting and classifying the biological activities of untested compounds, drug resistance, toxicity prediction and physicochemical properties prediction.

The QSAR methodology is based on the concept that the differences observed in the biological activity of a series of compounds can be quantitatively correlated with differences in their molecular structure. As a result, al biological activities and functions of molecules relate to specific molecular descriptors and specific regression techniques can be used to estimate the relative roles of those descriptors contributing to the biological effect [11].

II. METHODS

A. QSAR Definition and Development

Quantitative structure activity relationship (QSAR) is one of the widely used approaches in ligand based drug designing processes.

In QSAR/QSPR studies quantitatively correlate and recapitulate the relationships between trends in chemical structure alterations and respective changes in biological endpoint for comprehending which chemical properties are most likely determinants for their biological activities or physicochemical properties [12].

Quantitative Structure Activity Relationships (QSARs) mean computerized statistical method which helps to explain the observed variance in the structure changes caused by the substitution. In this concept it is assumed that the biological activity exhibited by a series of congeneric compounds is a function of various physio-chemical analysis is performed it shows that certain physio-chemical properties are favorable to the concern activity, the latter can be optimized by choosing such substituent's which would enhance such physiochemical properties. A major goal of Quantitative Structure Activity Relationship (QSAR)/ Quantitative Structure Property Relationship (QSPR) studies is to find a mathematical relationship between the activity or property under investigation, and one or more descriptive parameters or descriptors related to the structure of the molecule [13].

In QSAR, the structure of a molecule must contain the features and properties responsible for its physical, chemical, and biological activities [14]. Figure II describes different stages the development QSAR model process.

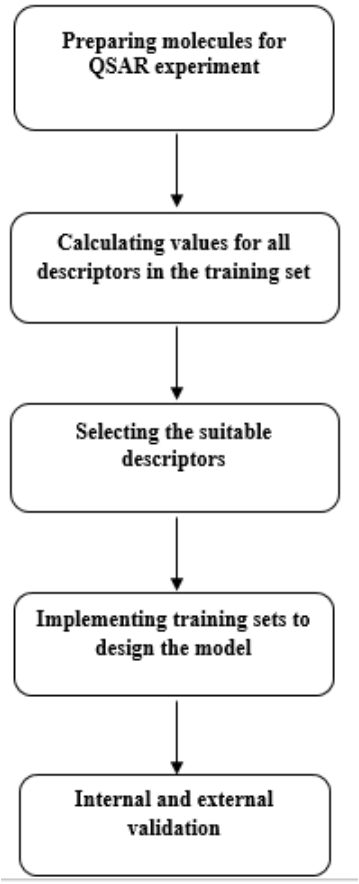

Fig II. QSAR Development process.

There are a lot of softwares available for QSAR development and they are either commercial or free. These include specialized software for drawing chemical structures, interconverting chemical file formats, generating 3D structures, calculating chemical descriptors, developing QSAR models, and general-purpose software that have all the necessary components for QSAR development. For Structure Drawing or File Conversion the most common programs are ChemDraw, ACD/ChemSketch and Open Babel software. Soft wares for 3D Structure Generation are CORINA, Concord, Frog, smi23d. Descriptor Calculation can be made by using Dragon, Molconn-Z, PaDEL-Descriptor software.

The first major step in a QSPR/QSAR study is the entry of the molecular structures and generation of the 3-D models. The 3-D molecular models are needed for geometric descriptor calculations. The second major step in a QSPR/QSAR study is the generation of the molecular structure descriptors. Selection of the most important descriptors is the third step and it can be achieved by using feature selection methods. The fourth major step in a QSPR/QSAR study is the generation of the QSPR/QSAR models using the descriptor sets. The fifth and last step is to validate the model by predicting the activity of compounds in the external prediction set. The results obtained by the predictions should be compared to those achieved for the training set and cross validation set to easily understand model's fitness level [15].

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ISSN: 2278-0181
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- Molecular Descriptors

Molecular descriptors are final products of mathematical procedures transforming chemical information encoded within a molecular structure to a numerical representative. Dimensionality of molecular descriptors can identify QSAR model type as described below:

0D QSAR- These are descriptors derived from molecular formula e.g. molecular weight, number and type of atoms etc.

1D QSAR- A substructure list representation of a molecule can be considered as a one-dimensional (1D) molecular representation and consists of a list of molecular fragments (e.g. functional groups, rings, bonds, substituents etc.).

2D QSAR- A molecular graph contains topological or two dimensional (2D) information. It describes how the atoms are bonded in a molecule, both the type of bonding and the interaction of particular atoms (e.g. total path count, molecular connectivity indices etc.).

3D QSAR- These are calculated starting from a geometrical or 3D representation of a molecule. These descriptors include molecular surface, molecular volume and other geometrical properties. There are different types of 3D descriptors e.g. electronic, steric, shape etc.

4D QSAR- Four dimensional information is described in this type of models, and the fourth dimension is an ensemble of conformation of each ligand [16].

5D-QSAR – Five dimensional information is described in this type of models, and the fifth dimension is the possibility to represent an ensemble of up to six different induced-fit models.

The descriptors are fall into 4 classes: Topological, Geometrical, Electronic and Hybrid.

Topological descriptors in chemistry are graph invariants generated by applying the theorems of graph theory. Examples of topological descriptors are: atom counts, ring counts, molecular weight, weighted paths, molecular connectivity indices, substructure counts, molecular distance edge descriptors, kappa indices, electro-topological state indices, and some other invariants [17].

Aspects of the structures related to the electrons are encoded by calculating electronic descriptors. Examples of electronic descriptors are: partial atomic charges, HOMO or LUMO energies, dipole moment.

Geometric descriptors are used to encode the 3-D aspects of the molecular structure such as moments of inertia, solvent accessible surface area, length-to-breadth ratios, shadow areas, gravitational index [18].

A class of hybrid descriptors called charged partial surface area descriptors encode the propensity of compounds to engage in polar interactions. The set of cpsa descriptors is based on the partial atomic charges and the partial surface area of each atom. The two attributes lists are mixed and a set of approximately 25 cpsa descriptors can be generated by matching the two mixed lists with different weighting schemes. Examples of cpsa descriptors can include: fractional positive surface area, charged weighted negative surface area [19].

- QSAR models validation

Validation process aims to provide a model which is statistically reliable with selected descriptors as a consequence of the cause-effect and not only of pure numerical relationship obtained by chance. However, non-statistical validations such as verification of the model in terms of the known mechanism of action or other chemical knowledge are necessary; it is not acceptable to rely on statistics only in validation process. Actually, this is somehow a hard procedure for cases where no mechanism of action is known or where data sets are small [20].

Validation methods are needed to establish the predictiveness of a model. There are two types of validation methods: Internal and external. Internal methods depend on training datasets like Q^2 (squared correlation coefficient), R^2 (coefficient of determination or the coefficient of multiple determination for multiple regression), chi-squared (X^2), and root-mean squared error (RMSE). The major disadvantage of this approach is the lack of predictability of the model when it is applied to a new data set [21]. However, external methods depend on the testing set and it is considered as best validation method [22].

It was reported that, in general, there is no relationship between internal and external predictivity [23-24]: high internal predictivity may result in low external predictivity and vice versa. In many cases, comparable models are obtained where some models show comparatively better internal validation parameters and some other models show comparatively superior external validation parameters. This may create a problem in selecting the final model. Therefore, it is must to develop some good validation techniques to overcome the entire above mentioned disputes.

B. QSAR in Drug design

QSAR is involved in drug discovery and designing to identify chemical structures with good inhibitory effects on specific targets and with low toxicity levels [25- 41].

The implementation of QSAR in designing different types of drugs as antimicrobial, and antitumor compounds by numerous works is a strong evidence of its efficiency in drug designing. Previous research in this field has been undertaken by different researchers.

Researchers investigated QSAR study on a series of 8-substituted xanthines as adenosine antagonists have been carried out. The chemical structure was described with parameters effect the receptors affinity [25].

IN [26], two multilayer feed forward neural networks and docking studies were developed to investigate the hypothetical binding mode of the target compounds.

Two 3D-QSAR models for a series of non-purine xanthine oxidase inhibitors were designed to study different factors affect the oxidase inhibitors [27].

QSAR model of xanthine oxidase inhibitory flavylium salts was implemented to predict the inhibitory potency of anthocyanidins as a function of their molecular properties [28].

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ISSN: 2278-0181
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A three-dimensional QSAR study has been implemented to study epothilones – tubulin depolymerization inhibitors [29].

QSAR models is established for the toxicity of polycylic aromatic hydrocarbons (PAHs) [30].

Four dimensional QSAR models is used to study a set of 18 structurally diverse antifolates including pyrimethamine, cycloguanil, methotrexate, aminopterin and trimethoprim, and 13 pyrrolo [2,3-d] pyrimidines [31].

The utility of Topological polar surface area (TPSA) was demonstrated in 2D QSAR for 14 sets of diverse pharmacological activity data [32].

QSAR of Hydrazones of N-Amino-N‘-hydroxyguanidine as Electron Acceptors for Xanthine Oxidase was built [33].

Antiviral QSAR models are implemented to predict by the first time an mt-QSAR model for 500 drugs tested in the literature against 40 viral species. The Markov Chain theory is used to calculate new multi-target entropy that fits a QSAR model [34].

III. RESULTS & DISCUSSION

A. QSAR Implementing in Drug Designing Results

It is very important to validate the model's performance to conclude whether the results satisfy researcher's expectations or not. R^2 and Q^2 are two statistical measures used for this purpose [35-41]. Values of R^2 and Q^2 obtained from different previous researches are listed in Table I.

R^2 (called as coefficient of determination or the coefficient of multiple determination for multiple regression.) is a statistical measure of how close the data are to the fitted regression line; High R-squared indicates that the model has a good fit. According to previous research [22], R^2 should be $\geq$ 0.6 to consider the model fits well. As it is shown in Table I, all QSAR models developed have a higher R^2 value than 0.6.

Q^2 is squared correlation coefficient and it is used as a criterion of both robustness and predictive ability of the model. It can be considered as an indicator of the high predictive power of the QSAR model. However, high Q^2 value is not enough to conclude that the model has acceptable predictive ability; models should be tested for their ability to predict the activity of compounds of an external test set also [22].

It was proven that for good predictability $R^2 - Q^2$ value should not be larger than 0.3 [42]. $R^2 - Q^2$ values are calculated for researches [35-41] and added in Table I.

As it can be noticed from Table 1, only in [36] the $R^2 - Q^2$ value exceeds 0.3, while in all other works the values are very small (lower than 0.3), which indicates a good predictability of the constructed models in these works.

However, QSAR predictability and robustness levels cannot be proved by R^2 and Q^2 values only; more parameters should be involved to obtain a strong conclusion, as: chi-squared (χ^2), root-mean squared error (RMSE), correlation coefficient R between the predicted and observed activities, slopes k and k' of the regression lines through the origin [43]. Also, the chemical space of training and test sets has to be discussed and studied; real outliers, with respect to character and structure similarities, have to be found and removed [22]. Only a small number of reported QSAR studies were implementing numerous different validation characteristics in their QSAR validation processes [44-45].

TABLE 1. R^2 AND Q^2 VALUES OBTAINED BY APPLYING QSAR MODELS IN DIFFERENT WORKS. $R^2 - Q^2$ VALUES ARE CALCULATED FOR EACH WORK.

Reference	Paper Title	Descriptors	R^2 value	Q^2 value	$R^2 - Q^2$
[35]	More Effective DPP4 Inhibitors as Antidiabetics Based on Sitagliptin Applied QSAR and Clinical Methods	Hydrophobicity, counts of rotatable bonds, hydrogen bond donor and acceptor atoms, and topological polar surface area.	0.85	0.77	0.08
[36]	Molecular modelling studies of 3,5-dipyridyl-1,2,4-triazole derivatives as xanthine oxidoreductase inhibitors using 3D-QSAR, Topomer CoMFA, molecular docking and molecular dynamic simulations	Steric, electrostatic, and hydrophobic fields.	0.988	0.578	0.41
[37]	Prediction of caspase-3 inhibitory activity of 1,3-dioxo-4-methyl-2,3-dihydro-1h-pyrrolo[3,4-c] quinolines: QSAR study	HOMO, LUMO energies	0.955	0.885	0.07
[38]	Predictive QSAR modeling on tetrahydropyrimidine-2-one derivatives as HIV-1 protease enzyme inhibitors	Radial Distribution Function (RDF)	0.824	0.773	0.05
[39]	Development of an in Silico Model of DPPH• Free Radical Scavenging Capacity: Prediction of Antioxidant Activity of Coumarin Type Compounds	van der Waals volume	0.713	0.654	0.06
[40]	Comparative Molecular Field Analysis (CoMFA) of a Series of Selective Adenosine Receptor A2A Antagonists	Electrostatic and steric field	0.970	0.840	0.13
[41]	QSAR and docking studies on xanthone derivatives for anticancer activity targeting DNA topoisomerase II α	Dielectric energy, group count, LogP, shape index basic (order 3), solvent-accessible surface area	0.840	Not detected	/

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
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Some applications of QSAR study in drug design are described in table 1. QSAR study was a predictive tool for investigations antidiabetic drugs based on sitagliptin as potential antioxidant agents. Hydrophobicity, counts of rotatable bonds, hydrogen bond donor and acceptor atoms, and topological polar surface area were used as descriptors in this research. Based on the established QSAR equations, new sitagliptin derivatives with possibly improved pharmacological effect as DPP4 inhibitors are proposed to investigate [35].

Also, by using QSAR study can be predict Antioxidant Activity of Coumarin Type Compounds. In this study the best correlation between activity and structure has shown van der Waals volume, that was used as molecular descriptor [39].

In silico methods can be good predictive tool for evaluation inhibitory activity of molecules. In this investigations, QSAR studies often combine with other methods as docking studies and neural network. For predict 3,5-dipyridyl-1,2,4-triazole derivatives as xanthine oxidoreductase inhibitors, QSAR study was used. The results suggested that the steric, electrostatic, and hydrophobic fields played an important role in the models [36].

A QSAR study was performed on a series of 1,3-dioxo-4-methyl-2,3-dihydro-1H-pyrrolo[3,4-c] quinolones in pursuit of better caspase-3 inhibitors. The study reveals that when increasing the conformational minimum energy while decreasing the lowest unoccupied molecular orbital energy (LUMO) and highest occupied molecular orbital energy (HOMO), the biological activity can be increased. On the basis of a selected QSAR model, a new series of 1,3-dioxo-4-methyl-2,3-dihydro-1H-pyrrolo[3,4-c]quinolines compounds, calculated their caspases inhibitory activity and found that the designed compounds were more potent than the existing compounds [37].

QSAR model was carried out to predict HIV-1 protease receptors inhibitors activity. In this study Radial Distribution Function (RDF) was used as molecular descriptor that has shown the best correlation with HIV-1 protease inhibition. The QSAR model also indicates that the descriptors (RDF010u, RDF010m, TPSA (NO), F04[C–N]) play an important role in enzyme binding [38].

The CoMFA approach to studies of 3D-QSAR for series of compounds has proven to be a valuable technique for building predictive model. In this study electrostatic and steric field were used as descriptors [41].

A QSAR model was developed to explore the anticancer compounds from xanthone derivatives by the multiple linear regression method. A high activity–descriptors relationship accuracy are obtained referred by regression coefficient and a high activity prediction accuracy. Molecular descriptors: dielectric energy, group count (hydroxyl), LogP (the logarithm of the partition coefficient between n-octanol and water), shape index basic, and the solvent-accessible surface area – were found to correlate with anticancer activity [40].

IV. CONCLUSION

In all described articles QSAR study were good prediction tool for investigation drug activity or binding mode on specific receptors. Descriptors that have shown the best correlation in this investigation gives information about important functional groups in the structures of tested compounds. According to this, by changing some groups in the structure of drugs, we can increase their pharmacological activity or physico-chemical properties.

In general, the experimental determinations are very expensive and the QSPR studies allow a reduction of this cost. It is basically used to study the biological activities with various properties associated with the structures, which is helpful to explain how structural features in a drug molecule influence the biological activities. QSPR/QSAR methods can be used to build models that can predict properties or activities for organic compounds. However, an effective way to encode the structures with calculated molecular structure descriptors are required for accurate models development. The descriptors incorporated in models development can provide an opportunity to focus on specific features account for the property or activity of interest in the compounds.

QSAR should not replace experimental values, but it is useful predictive tool and might be usable if no data were available.

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