IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

QSAR-BASED VIRTUAL SCREENING & MOLECULAR DOCKING FOR NOVEL APPROACHES FOR DRUG DESIGN

A Brief Review

Mrs. Nehal Gandhi*[1], Dr. Vikram Pandya[*2], Ms. Urvi Bhanushali *[3] Ms. Mansi Bagul[*4]

[1]Assist. Professor, [2]Principal, [3,4]B.Pharm Scholar

[1]Pharmaceutical Chemistry,

[1]Tathya Pharmacy College, Chikhli ,Dist: Navsari, Gujarat India

Abstract: The search for new compounds with a given biological activity requires enormous effort in terms of manpower and cost. This effort arises from the large number of compounds that need to be synthesized and subsequently biologically evaluated. Virtual Screening (VS) has emerged in Drug discovery as a powerful Computational Approach to screen large no. Of small molecules for hits with desired properties. In the last years bioinformatics has experienced a great evolution due to the development of specialized software and to the increasing computer power. Through the computational approaches, speed up drug Discovery process & reduce the number of candidates to be tested experimentally, & to rationalize their choice.

The codification of the structural information of molecules through molecular descriptors and the subsequent data analysis allow establishing QSAR models (Quantitative Structure-Activity Relationship) that can be applied to the design and the virtual screening of new drugs. The development of sophisticated Docking methodologies also allows a more accurate predict of the biological activity of molecules. Moreover, through this type of computational techniques and theoretical approaches, it is possible to develop explanatory hypothesis on the mechanism of action of drugs. This work provides a brief description of a series of studies implemented in the software MOE (Molecular Operating Environment) with particular attention to the medicinal chemistry aspects.

Index Terms **- Virtual Screening, Drug Discovery, QSAR, Molecular Docking, Molecular Operating Environment (MOE)..**

I. INTRODUCTION

Virtual screening (VS) has emerged in drug discovery as a powerful computational approach to screen large libraries of small molecules for new hits with desired properties that can then be tested experimentally. Similar to other computational approaches, VS intention is not to replace in vitro or in vivo assays, but to speed up the discovery process, to reduce the number of candidates to be tested experimentally, and to rationalize their choice. Moreover, VS has become very popular in pharmaceutical companies and academic organizations due to its time- cost-, resources-, and labor saving. Among the VS approaches, quantitative structure–activity relationship (QSAR) analysis is the most powerful method due to its high and fast throughput and good hit rate. As the first preliminary step of a QSAR model development, relevant chemogenomic data are collected from databases and the literature.1,2

Quantitative structure–activity relationship (QSAR) analysis is a ligand-based drug design method developed more than 50 years ago by Hansch and Fujita (1964). Since then and until now, QSAR remains an efficient method for building mathematical models, which attempts to find a statistically significant correlation between the chemical structure and continuous (pIC50, pEC50, Ki, etc.) or categorical/binary (active, inactive, toxic, nontoxic, etc.) biological/toxicological property using regression and classification techniques, respectively.In the last decades, QSAR has undergone several transformations, ranging from the dimensionality of the molecular descriptors (from 1D to nD) and different methods for finding a correlation between the chemical structures and the biological property. Initially, QSAR modeling was limited to small series of congeneric compounds and simple regression methods. Nowadays, QSAR modeling has grown, diversified, and evolved

to the modeling molecular Docking and virtual screening (VS) of very large data sets comprising thousands of diverse chemical structures and using a wide variety of software learning techniques.3

QSAR has emerged and has evolved trying to fulfill the medicinal chemist' s need and desire to predict biological response. QSAR is the final result of computational processes that start with a suitable description of molecular structure and ends with some inference, hypothesis, and predictions on the behavior of molecules in environmental, physicochemical and biological system under analysis.
Multivariate QSAR analysis employs all the molecular descriptors from various representations of a molecule (1D, 2D and 3D representation) to compute a model, in a search for the best descriptors valid for the property in analysis.[4]

This review covers the concepts, the steps involved in the development of QSAR models & finally, the database is utilized to search or design new drug molecules, identifying molecules whose shape and physical and chemical properties match the receptor site, and these molecules are synthesized to test their biological activity. Novel lead compounds can be discovered after the above cycles in this way.

II. Importance Of QSAR as Virtual Screening:

QSAR methodologies have the potential of decreasing substantially the time and effort required for the discovery of new medicines. A major step in constructing the QSAR models is to find a set of molecular descriptors that represents variations of the structural properties of the molecule.
QSAR modeling has been playing a pivotal role in prioritizing compounds for synthesis and/or biological evaluation. The QSAR models can be used for both hits identification and hit-to lead optimization. In the latter, a favorable balance between potency, selectivity, and pharmacokinetic and toxicological parameters, which is required to develop a new, safe, and effective drug, could be achieved through several optimization cycles. As no compound need to be synthesized or tested before computational evaluation, QSAR represents a labor-, time-, and cost-effective method to obtain compounds with desired biological properties. Consequently, QSAR is widely practiced in industries, universities, and research centers around the world.

High-throughput screening (HTS) technologies resulted in the explosion of amount of data suitable for QSAR modeling.
The general scheme of QSAR-based VS approach is shown in Figure 1. Initially, the data sets collected from external sources are curated and integrated to remove or correct inconsistent data. Then, QSAR models are used to identify chemical compounds predicted to be active against selected endpoints from large chemical libraries. In principle, VS is often compared to a funnel, where a large chemical library (i.e., 10^5 to 10^7 chemical structures) is reduced by QSAR models to a smaller number of compounds, which then will be tested experimentally (i.e., 10^1 to 10^3 chemical structure). However, it is important to mention that modern VS workflows incorporate additional filtering steps, including: (i) sets of empirical rules [e.g., Lipinski's rules], (ii) chemical similarity cut-offs, (iii) other QSAR-based filters (e.g., toxicological and pharmacokinetic endpoints), and (iv) chemical feasibility and/or purchase ability. Although the experimental validation of computational hits does not represent part of the QSAR methodology, this should be performed as the final important step. After experimental validation, a multi-parameter optimization (MPO) with QSAR predictions of potency, selectivity, and pharmacokinetic parameters can be conducted. This information will be crucial during hit-to lead and lead optimization design of the compound series, to find the properties balance (potency, selectivity, and PK) related with the effect of different decoration patterns to establish a new series of target compounds for *in vivo* evaluation.[4,5,6,7]

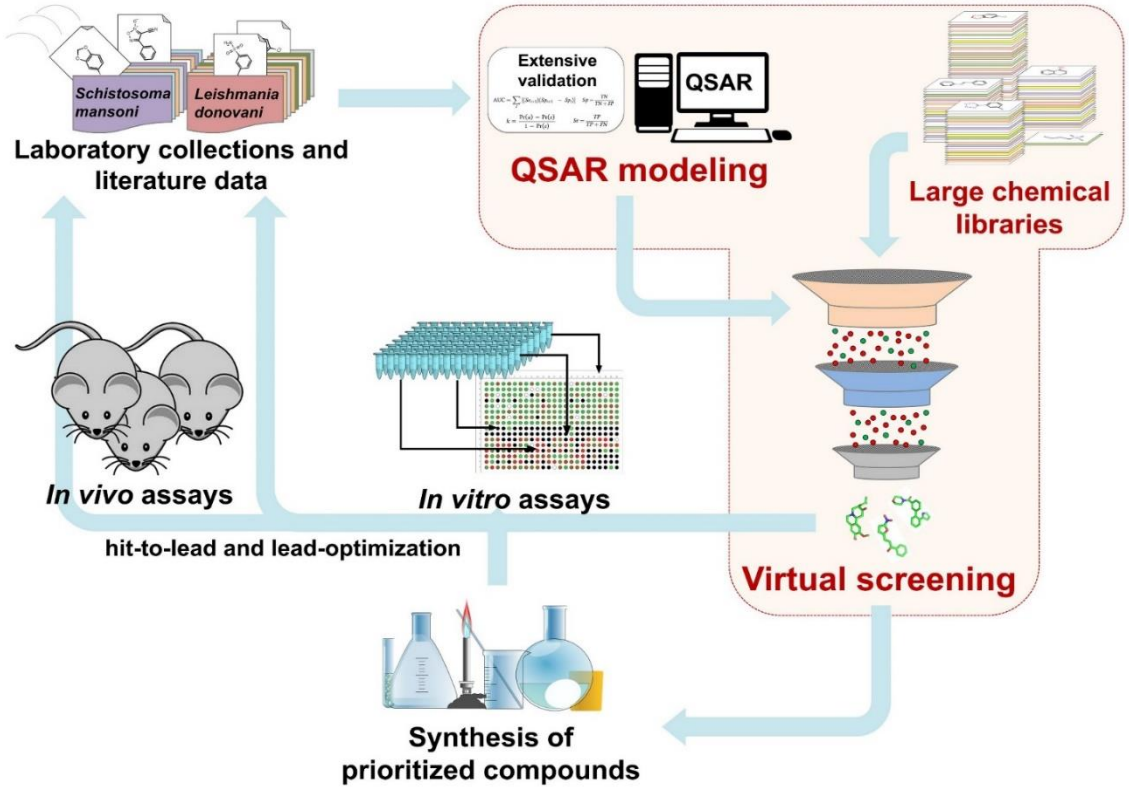

Figure: Flow chart of QSAR Modelling

Molecular docking simulation to study the interactions between small molecules and their target protein or predict the binding affinity between them. Docking technique to dock drug candidates into macromolecules in which scoring binding affinity of two molecules or association to spatial orientation is applied to predict protein-ligand or protein-protein interaction when an agent is bound to a receptor (protein or enzyme). [8,9,10]

The main steps of docking simulation are as follows:

1) Accurate ligand insertion at the receptor binding site.
2) Estimation of the ligand affinity by a scoring function[11,12]

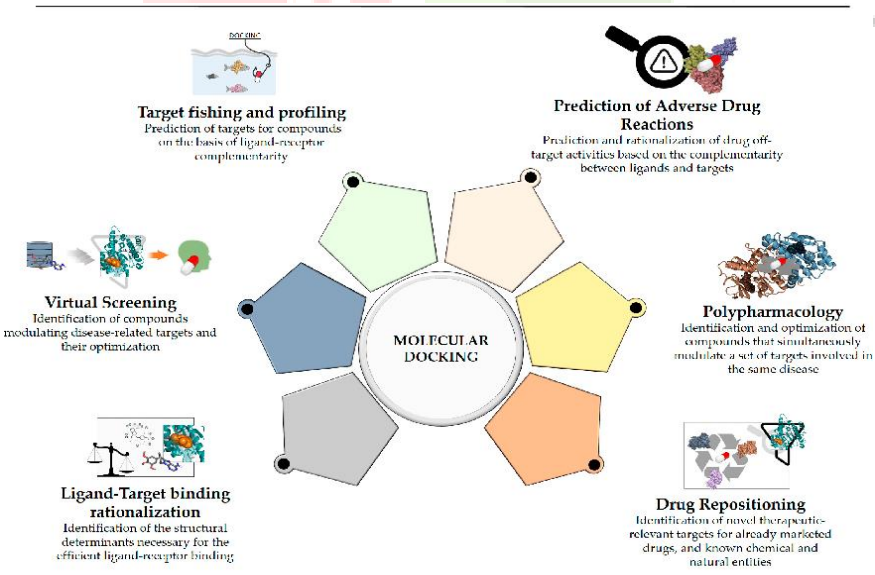

Figure: Importance Of Molecular Docking

III. Significance:

The current pipeline to discover hit compounds in early stages of drug discovery is a data driven process, which relies on bioactivity data obtained from HTS campaigns The QSAR models can be used for both hits identification and hit-to-lead optimization. In the latter, a favorable balance between potency, selectivity, and pharmacokinetic and toxicological parameters, which is required to develop a new, safe, and effective drug, could be achieved through several optimization cycle.[14,15]

IV. Conclusion:

To summarize, we would like to emphasize that QSAR modeling represents a time-, labor-, and cost-effective tool to discover hit compounds and lead candidates in the early stages of drug discovery process. Analyzing the examples of QSAR-based VS available in the literature, one can see that many of them led to the identification of promising lead candidates.

The QSAR models are useful for various purposes including the prediction of activities of untested chemicals. It helps in the rational design of drugs by computer aided tools via molecular modeling, simulation and virtual screening of promising candidates prior to synthesis. In this review article the concept, brief history and components involved in modeling were discussed.

References:

1) Cherkasov, A., Muratov, E. N., Fourches, D., Varnek, A., Baskin, I. I., Cronin, M., et al. (2014). QSAR modeling.
2) Colley, D. G., Bustinduy, A. L., Secor, W. E., and King, C. H. (2014). Human schistosomiasis. Lancet 383, 2253–2264. doi: 10.1016/S0140-6736(13)61949-2
3) Bajorath, J. (2012). Computational chemistry in pharmaceutical research: at the crossroads. J. Comput. Aided. Mol. Des. 26, 11–12. doi: 10.1007/s10822-011- 9488-2.
4) C. D., et al. (2013). Benchmarking ligand-based virtual high-throughput screening with the pubchem database. Molecules 18, 735–756. doi: 10.3390/ molecules18010735
5) Fourches, D., Muratov, E., and Tropsha, A. (2010). Trust, but verify: on the importance of chemical structure curation in cheminformatics and QSAR modeling research. J. Chem. Inf. Model. 50, 1189–1204. doi: 10.1021/ci100176x Fourches, D., Muratov, E., and Tropsha, A. (2015). Curation of chemogenomics data. Nat. Chem. Biol. 11, 535–535. doi: 10.1038/nchembio.1881.
6) Hansch C, Sinclair JF, Sinclair PR. Induction of Cytochrome P450 by Barbiturates in Chick Embryo Hepatocytes: A Quantitative Structure- Activity Analysis. Quantitative Structure-Activity Relationships. 1990;9(3):223–226.
7) Bajorath, J. (2012). Computational chemistry in pharmaceutical research: at the crossroads. *J. Comput. Aided. Mol. Des.* 26, 11–12. doi: 10.1007/s10822-011-9488-z
8) Butkiewicz, M., Lowe, E. W., Mueller, R., Mendenhall, J. L., Teixeira, P. L., Weaver, C. D., et al. (2013). Benchmarking ligand-based virtual high-throughput screening with the pubchem database. *Molecules* 18, 735–756. doi: 10.3390/molecules18010735
9) Eriksson L, Jaworska J, Worth AP, et al. Methods for reliability and uncertainty assessment and for applicability evaluations of classification–and regression–based QSARs. Environ Health Perspect. 2003;111(10):1361–1375
10) AlMatar, M., AlMandeal, H., Var, I., Kayar, B., and Köksal, F. (2017). New drugs for the treatment of *Mycobacterium tuberculosis* infection. *Biomed. Pharmacother.* 91, 546–558. doi: 10.1016/j.biopha.2017.04.105
11) Ekins, S., Lage de Siqueira-Neto, J., McCall, L.-I., Sarker, M., Yadav, M., Ponder, E. L., et al. (2015). Machine learning models and pathway genome data base for *Trypanosoma cruzi* drug discovery. *PLoS Negl. Trop. Dis.* 9:e0003878. doi: 10.1371/journal.pntd.0003878
12) Fourches, D., Muratov, E., and Tropsha, A. (2010). Trust, but verify: on the importance of chemical structure curation in cheminformatics and QSAR modeling research. *J. Chem. Inf. Model.* 50, 1189–1204. doi: 10.1021/ci100176x
13) Fourches, D., Muratov, E., and Tropsha, A. (2015). Curation of chemogenomics data. *Nat. Chem. Biol.* 11, 535–535. doi: 10.1038/nchembio.1881
14) Goh, G. B., Hodas, N. O., and Vishnu, A. (2017). Deep learning for computational chemistry. *J. Comput. Chem.* 38, 1291–1307. doi: 10.1002/jcc.24764
15) Lipinski, C. A., Lombardo, F., Dominy, B. W., and Feeney, P. J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 23, 3–25. doi: 10.1016/S0169-409X(96)00423-1