KAAV INTERNATIONAL JOURNAL OF SCIENCE, ENGINEERING & TECHNOLOGY
A REFEREED BLIND PEER REVIEW QUARTERLY JOURNAL
KIJSET/JUL-SEP (2017)/VOL-4/ISS-3/A3 PAGE NO.13-17
ISSN: 2348-5477 IMPACT FACTOR (2017) – 6.9101
WWW.KAAVPUBLICATIONS.ORG

AN EVALUATIVE ANALYSIS OF IMPORTANCE OF QSAR IN SYNTHETIC CHEMISTRY

[1]NARBIR SINGH
[1]Research Scholar

[2]YOGESH KUMAR

ABSTRACT
Quantitative structure-activity relationship (QSAR) modeling pertains to the construction of predictive models of biological activities as a function of structural and molecular information of a compound library. Over the last 20 years, extensive QSAR studies establish an attractive approach to the elucidation of the modern drug chemistry. In the recent years, constant increase in the performance of hardware and software transformed quantitative structure activity relationship (QSAR) and quantitative structure property relationship (QSPR) into powerful and widely used model for the prediction of many biological properties in the field of medicinal chemistry and bioinformatics. The aim of this article is to give an overview of the modern drug chemistry and the importance of various techniques used in the field of drug chemistry such as bioinformatics, QSAR/QSPR, cheminformatics. QSAR is an effective method in the field of medicinal research into rational drug design and mechanism of drug action. The review attempts to account the importance in synthetic chemistry and its related research while using different techniques i.e. QSAR.
KEYWORDS- *Synthetic Chemistry, QSAR, Drug Design, Drug Development. Quantitative Structure-Property Relationship.*

1. INTRODUCTION-

SAR stands for Structure Activity Relationship while the QSAR stands for Quantitative Structure Activity Relationship. SAR deals with the relationship of structure with biological activity while the QSAR accounts the relationship of magnitude of the various structural properties with the biological activity. Compounds with similar structures to a pharmacologically active drug are often themselves biologically active. This activity may be either similar to that of the original compound but different in potency and unwanted side effects or completely different to that exhibited by the original compound. These structurally related activities are commonly referred to as structure–activity relationship (SAR).Perhaps the historically most successful approach to such studies is to use so-called 2D-desceptors, which are based on bonding topology of the molecules. ***(Richet MC.,1893)*** A study of the structure–activity relationships of a lead compound and its analogues may be used to determine the parts of the structure of the lead compound that are responsible for both its beneficial biological activity, that is, its pharmacophore, and also its unwanted side effects. This information may be used to develop a new drug

that has increased activity, a different activity from an existing drug and fewer unwanted side effects. Structure–activity relationships are usually determined by making minor changes to the structure of a lead to produce analogues and assessing the effect these structural changes have on biological activity. The investigation of numerous lead compounds and their analogues has made it possible to make some broad generalizations about the biological effects of specific types of structural change. These changes may be conveniently classified as changing: (***Cristianini N, Shawe-Taylor J.,2000)***

1. The size, shape and branching of the parent structure
2. Types of substitution and their nature
3. The stereochemistry of the lead compound

The main assumption in the QSPR and QSAR approaches is that the all properties viz. physical, chemical and biological is purely depend on the molecular structure. QSAR is an attempt to remove the element of luck from drug design by establishing a mathematical relationship in the form of an equation between biological activity and measurable physicochemical parameters. These parameters are used to represent properties such as lipophilicity, shape and electron distribution, which are believed to have a major influence on the drug‘s activity. The structure of the compounds is represented in terms of numerical forms by various descriptors. They are normally defined so that they are in the form of numbers, which are derived from practical data that is thought to be related to the property the parameter represents. This makes it possible to either to measure or to calculate these parameters for a group of compounds and relate their values to the biological activity of these compounds by means of mathematical equations using statistical methods such as regression analysis. These equations may be used by the medicinal chemist to make a more informed choice as to which analogues to prepare. ***(Kendall RA, Aprà E, Bernholdt DE,2000)***

2. BRIF HISTORY (LITERATURE) ABOUT QSAR

QSAR has its origins in the field of toxicology whereby Cros in 1863 proposed a relationship which existed between the toxicity of primary aliphatic alcohols with their water solubility ***(Cros, 1863).*** Likewise, Crum-Brown and Fraser (Crum- Brown and Fraser, 1868-1869) postulated the linkage between chemical constitution and physiological action in their pioneering investigation in 1868 as follows:

“performing upon a substance a chemical operation which shall introduce a known change into its constitution, and then examining and comparing the physiological action of the substance before and after the change” Shortly after, Richet (1893), Meyer (1899), and Overton (1901) separately discovered a linear correlation between lipophilicity (e. g. oil-water partition coefficients) and biological effects (e. g. narcotic effects and toxicity). By 1935, Hammett (1935, 1937) introduced a method to account for substituent effects on reaction mechanisms through the use of an equation which took two parameters into consideration namely the (i) substituent constant and the (ii) reaction constant. Complementing the Hammett’s model, Taft proposed in 1956 an approach for separating polar, static, and resonance effects of substituent's in aliphatic compounds (Taft, 1956). The contributions from Hammett and Taft set forth the mechanistic basis for QSAR/QSPR development by Hansch and Fujita (1964) in their seminal development of the linear Hansch equation which integrated hydrophobic parameters with Hammett’s electronic constants. An insightful account on the development of QSAR/QSPR can be found in the excellent book by Hansch and Leo (1995).

3. ROLE & IMPORTNACE OF QSAR IN SYNTHETIC CHEMISTRY

- Quantitative structure-activity relationship (QSAR) and quantitative structure-property relationship (QSPR) studies are undoubtedly of great importance in modern chemistry and biochemistry. To obtain a significant correlation, it is essential that appropriate descriptors be used, regardless of whether they are theoretical, empirical or derived from readily available experimental characteristics of structures. Many descriptors reflect simple molecular properties and can thus provide insight into the physicochemical nature of the activity/property under consideration.

- Quantitative structure activity and structure property relationships (QSAR/QSPR) are of great importance in medicinal chemistry and biochemistry, because they can accelerate the development of new compounds for use as drugs, materials or additives by computer screening of molecular structures that can predict the desired properties prior to laboratory tests.
- Activities used in QSAR include chemical measurements and biological assays. For example, biological activity can be expressed quantitatively as in the concentration of a substance required to give a certain biological response. Additionally, when physicochemical properties of structures are expressed by numbers, one can find a quantitative structure-activity relationship between properties and structures. The mathematical expression can then be used to predict the biological response of other chemical structures.
- QSAR are currently being applied in many disciplines, such as drug design and environmental risk assessment. Using QSAR, an estimate of the activity of a chemical from its molecular structure can be obtained; QSAR offers the possibility for screening a large number of chemicals in a short time and at low cost.

The basic idea behind the QSAR/QSPR is to find the appropriate function i.e. physio- chemical, topological and other properties by using the information which given in the structure of the molecule. In fact QSAR, as a technique attempting to summarize chemical and biological information in order to generate relationships between structure and biological activity, hastens the drug design and aims to develop these compounds.

Property= F (Structure)

So, we can say that the biological properties of any molecule are the function of the structure i.e. any change in structure will definitely affect the biological activity.

3.2 CLASSIFICATION OF QSAR METHODOLOGIES

Based on dimensionality

Most often the QSAR methods are categorized into following classes, based on the structural representation or the way by which the descriptor values are derived:

- 1D-QSAR Correlation of fundamental molecular properties viz. pKa, log P with biological activity.
- 2D-QSAR Correlation of various 2D properties i.e. physio-chemical properties with biological activity.
- 3D-QSAR Correlation of various 3D properties which surrounding the molecule.
- 4D-QSAR Introducing the ligand receptor interaction of the drug molecule with the 3D properties.
- 5D-QSAR explicitly representing different induced-fit models in 4D-QSAR
- 6D-QSAR further incorporating different salvation models in 5D-QSAR.

4. PURPOSE OF QSAR

Primary focus of any QSAR is to develop the best drug model to overcome the difficulty of the trial and error methods. This is the only way to reduce the cost and time of the synthesis of the drug, so as to improve the biological activity of the drug molecule. From these relationships we can develop models, and the validity and predictiivty of the model can also tested with various statistical tools. There are many practical purposes of a QSAR and these techniques are utilized widely in many situations. Some of them given below-

1. To reduce the trial and error synthesis drugs, which also reduce the time and cost of the synthesis of the drug in the laboratory.
2. To enhancing the importance and role of greener chemistry specially for environmental purposes with the elimination of waste and less toxic compounds.
3. To save time and effort in clinical trial specially the animal trial and preclinical trial.
4. with the help of advanced mechanism of the drug with the specific enzymes and proteins, the idea to synthesis the more potent drug for the diseases.

5. To comprehend and rationalize the mechanisms of action within a series of chemicals.

5. APPLICATIONS OF QSAR

With the advancement in the field of drug design and medicinal chemistry the applications of QSAR spread on the various filed of drug discovery. Few of them is given below-

1. To rationalization of new leads compound with enhance biological activity.
2. To identify the toxic chemicals and toxicity of the drug molecule before the synthesis. This will reduce the toxicity for environmental species and other biological system.
3. The optimization of pharmacological and pesticidal activity.
4. The identification and selection of the compound in order to get the best biological responds with better and optimal pharmacokinetics properties.
5. The rational design of numerous other products such as surface-active agents, perfumes, dyes, and fine chemicals.
6. To identify the role of various properties to design the drug molecule and to know the better properties to improve the biological activity.

LIMITATIONS OF CLASSICAL QSAR

Although the classical QSAR methods are much simpler and faster than 3D-QSAR approaches. They include clearly-defined physio-chemical descriptors and are best suited for the analysis of large number of compounds and computational screening of molecular databases. But still the day by day challenges in the field of drug design shows that this one also has some limitations. Few of them given below-

1. The biomolecules mainly are in complicated three dimensional structure while the classical QSAR only deals with the 2D-structures.
2. While using 2D descriptor only limited number of descriptor taken into account, which has the limitation of the traditional method.
3. No representation of stereochemistry or 3D-structure of molecules, regardless of their availability.
4. No predictivity of generated model, so it is difficult of go for the synthesis on behalf of the 2D model.
5. 2D QSAR models of better by the chance correlation rather than the actual prediction.
6. Requires considerable knowledge of substituent constants in physical organic chemistry to design a molecule, since classical QSAR equation do not directly suggest new compounds to synthesize

6. CONCLUSION

The past few decades have witnessed many advances in the development of computational models for the prediction of a wide span of biological and chemical activities that are beneficial for screening promising compounds with robust properties. In this review article, we have provided a brief introduction to the concepts of QSAR along investigations on diverse biological and chemical systems. It should be noted that the applicability of QSAR models are only useful in the domains that they were trained and validated. The review attempts to account the importance in synthetic chemistry and its related research while using different techniques i.e. QSAR. It was found interesting to note that there are many paths for researchers in the field of QSAR/QSPR in their quest of establishing relationships between structure and activities/properties. Such abstract nature holds the beauty of the field as there are endless possibilities in reaching the same destination of designing novel molecules with desirable properties.

REFERENCES

- ***Angeli C, Bak KL, Bakken V, et al.*** DALTON, a molecular electronic structure program. Release 2.0; 2005.
- ***Bosse E, Roy J, Wark S.*** Concepts, models, and tools for information fusion. Norwood, MA: Artech House, Inc., 2007.
- ***Chen N, Lu W, Yang J, Li G***. Support vector machine in chemistry. Singapore: World Scientific Publishing, 2004.

- ***Cristianini N, Shawe-Taylor J***. An introduction to support vector machines and other kernel-based learning methods. Cambridge: Cambridge University Press, 2000.
- ***Cros AFA*.** Action de l'alcohol amylique sur l'organisme. Strasbourg, University of Strasbourg, Thesis, 1863.
- ***Hansch C, Fujita*** T. p-σ-π analysis. A method for the correlation of biological activity and chemical structure. J Am Chem Soc 1964;86:1616-26.
- ***Hansch C, Leo*** A. Exploring QSAR. Washington, DC: American Chemical Society, 1995.
- ***Helguera AM, Combes RD, Gonzalez MP, Cordeiro MN***. Applications of 2D descriptors in drug design: a DRAGON tale. Curr Top Med Chem 2008;8:1628-55.
- ***Höskuldsson A. PLS regression methods. J Chemometr*** 1988;2:211-28.
- ***Karelson M, Lobanov VS, Katritzky AR***. Quantum-chemical descriptors in QSAR/ QSPR studies. Chem Rev 1996;96: 1027- 44.
- ***Karlström G, Lindh R, Malmqvist P-Å***, et al. MOLCAS: a program package for computational
- chemistry. Comput Mater Sci 2003;28:222-39.
- ***Katritzky AR, Gordeeva EV*.** Traditional topological indices vs electronic, geometrical, and combined molecular descriptors in QSAR/QSPR research. J Chem Inf Comput Sci 1993;33:835-57.
- ***Katritzky AR, Karelson M, Petrukhin R***. CODESSA PRO, Florida, U.S.A., 2005.
- ***Kendall RA, Aprà E, Bernholdt DE***, et al. High performance computational chemistry: An overview of N W Chem a distributed parallel application. Comput Phys Commun 2000;128:260-83.
- ***Kim K. Outliers in SAR and QSAR***: 2. Is a flexible binding site a possible source of outliers? J Comput Aid Mol Des 2007a;21: 421-35.
- ***Nantasenamat C, Isarankura-Na-Ayudhya C, Naenna T, Prachayasittikul V*.** Prediction of bond dissociation enthalpy of antioxidant phenols by support vector machine. J Mol Graph Model 2008;27:188-96.
- ***Overton CE. Studien über die Narkose. Jena:*** Fischer, 1901. Randić M. The nature of chemical structure.
- ***J Math*** Chem 1990;4:157-84. Randić M, Razinger M. On characterization of 3D molecular structure. In: Balaban AT (ed.): From chemical topology to threedimensional geometry. New York: Plenum Press, 1997.
- ***Richet MC***. Note sur le rapport entre la toxicité et les propriétes physiques des corps. Compt Rend Soc Biol (Paris) 1893;45:775-6.
- ***Schmidt MW,*** Baldridge KK, Boatz JA, et al. General atomic and molecular electronic structure system. J Comput Chem 1993;14: 1347-63.
- ***Schrödinger, Inc. Jaguar,*** Version 7.5207; Portland, OR, 2008. Shao Y, Molnar LF, Jung Y, et al. Advances in methods and algorithms in a modern quantum chemistry program package. Phys Chem Chem Phys 2006;8:3172- 91.
- ***Stewart J***. MOPAC2009, Colorado, USA, 2009.
- ***Sukumar N, Breneman*** CM. RECON, Version 5.5; New York, USA, 2002.
- ***Taft RW*.** Separation of polar, steric and resonance effects in reactivity. In: Newman MS (ed.): Steric effects in organic chemistry (pp 556-675). New York: Wiley, 1956.
- ***Wold S, Trygg J, Berglund A, Antti H*.** Some recent developments in PLS modeling. Chemometr Intell Lab 2001;58:131-50.
- ***Worachartcheewan A, Nantasenamat C, Naenna T, Isarankura-Na-Ayudhya C, Prachayasittikul V***. Modeling the activity of furin inhibitors using artificial neural network. Eur J Med Chem 2009;44:1664-73.
- ***Xue L, Bajorath J*.** Molecular descriptors in chemoinformatics, computational combinatorial chemistry, and virtual screening. Comb Chem High Throughput Screening 2000; 3:363-72.