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Research Paper

Quantitative structure activity relationship and drug design: A Review

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Abstract

The goal of QSAR (Quantitative Structure Activity Relationships) studies to find a mathematical relationship between the Biological activity and descriptors related to the structure of the molecule. In recent years, constant increase in the performance of hardware and software transformed quantitative structure activity relationship (QSAR) widely used model for the prediction of many biological properties in the field of medicinal chemistry. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the bio-molecular target with which they interact and therefore will bind it. QSAR studies more useful to use descriptors derived mathematically from either the 2D or 3D molecular structure.

Keywords: QSAR, 2D or 3D QSAR, CAD, Biological Activity, Drug design & Multiple Regression Analysis.

Introduction

Drug is most commonly an organic small molecule that activities or inhibits the function of a Bio molecule such as a protein, which in turn results in a therapeutic benefit to the patient Computer modelling techniques refer to as Computer-Aided Drug Design (CAD) finally, drug design that relies on the knowledge of the three-dimensional structure of the molecular target is known as structure of the bio-molecular target is known as structure based design[1]. In drug design experiments complemented with computation method are increasing used in early drug discovery to select compounds with more favourable ADME (Absorption, Distribution, Metabolism and Excretion) and toxicological profiles[2].

The objective of medicinal chemistry is the design and discovery of new compounds that are suitable for use as drugs. This process involves a team of workers from a wide range of disciplines such as chemistry, biology, biochemistry, pharmacology, mathematics, medicine and computing, amongst others. The discovery or design of a new drug not only requires a discovery or design process but also the synthesis of the drug, a method of administration, the development of tests and procedures to establish how it operates in the body and a safety assessment. Drug discovery may also require fundamental research into the biological and chemical nature of the diseased state. These and other aspects of drug design and discovery require input from specialists in many other fields and so medicinal chemists need to have outline knowledge of the relevant aspects of these fields. Drug design explain:

- Relationship between biological activity and structure.
- Modify the drug molecule according to the need.
- The effect of the drug towards the biological responds by various processes.

- Drug receptor interaction on the basis of various physico-chemical properties.

QSAR approach

Agrawalet.al.[3-12]have reported QSAR studies on different organic Drug compounds. 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 favourable to the concern activity, the latter can be optimized by choosing such substituent's which would enhance such physiochemical properties**.**

The mathematical and statistical analysis of QSAR data finally helps to reduce the number of educated success in molecular modification. During the mathematical and statistical and analysis one has to consider the description of the molecular structure, electrons, orbital reactivity and the role of structural and steric component. The ultimate objective of such QSAR studies is to understand the force governing the activity of a particular compound or a particular class of compounds. QSAR deals the relationship of magnitude of the various structural properties with the biological activity. Compound with the 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 the exhibited by the original compound. These structurally related activities are commonly referred to as structure-active relationship[13] (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.

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. While such descriptors can themselves be experimental properties of the molecule, it is generally more useful to use descriptors derived mathematically from either the 2D or the 3D molecular structure (ChemSketch Program[14]), since this allows any relationship so derived to be extended to the prediction of the property or activity for unavailable compounds.

Main descriptors used in QSAR topological modeling

We now discuss the main Molecular descriptors[15] derived from the molecular structure. Thus, we distinguish constitutional, topological, connectivity indices. These are given in Table 1.

Table 1: Main types of molecular descriptors used in QSAR

Constitutional descriptors
Molecular weight
Counts of atoms and bonds
Counts of rings
Topological descriptors
Weiner index (W)
Balaban index (J)
Xu index (Xu)
First Zagreb index (ZM_1)
Second Zagreb index (ZM_2)
Connectivity indices
Randic connectivity index ($^0\chi$, $^1\chi$, $^2\chi$, $^3\chi$, $^4\chi$, and $^5\chi$)
Valance Connectivity Indices ($^0\chi^V$, $^1\chi^V$, $^2\chi^V$, $^3\chi^V$, $^4\chi^V$, and $^5\chi^V$)

Constitutional descriptors depend fundamentally on the composition of the molecule rather than on the topology, geometry, or electronic structure. The counts of atoms of different elements and the molecular weight reflect the composition only, however numbers of rings or double bonds are also sensitive to the molecular topology. Constitutional descriptors whilst very simple in nature should be included in QSAR studies.

Topological descriptors are probably the most widely used class of descriptors and include such well-known classical molecule parameters as the Randic index[16] and the Kier and Hall[17], Balaban index[18] molecular connectivity index. These descriptors are obviously most sensitive to the molecular topology (i.e. molecular connectivity), and in particular to the branching of the molecule.

3D Optimization and Calculation of molecular descriptors

Shape of molecule and conformation are often of great important for the prediction and description of biological activities and molecular properties. In such cases a 2D 3D optimization is required. For this DRAGON[19] software is used. Molecular structures are drawn by ChemSketch /ACD labs software.

Multiple linear Regression Analysis

Multiple regression analysis[20], which involves finding the best fit of the independent variables to a linear combination of independent variable, was performed using the least squares method, correlation equations were obtained by stepwise regression procedure. These statistical analyses were carried out using the Regression-1 program supplied by Professor Istavan Lukovits (Central Research Institute for Chemistry, Hungarian Academy of Sciences, Budapest, Hungary).The multiple linear regression method is used to screen the appropriate descriptor from a large pool of descriptor. Multiple linear regressions (MLR) is a method used to model the relationship between two or more explanatory variables and a response variable by fitting a linear equation to the observed was employed to correlate the binding affinity and molecular descriptors. It has given below in Figure 1 shows the graphical representation of the observed and calculated activity for any data set using multiple linear regression analysis. I have published a research paper on Lipophilicity of some Alkanes by using MLR[21].

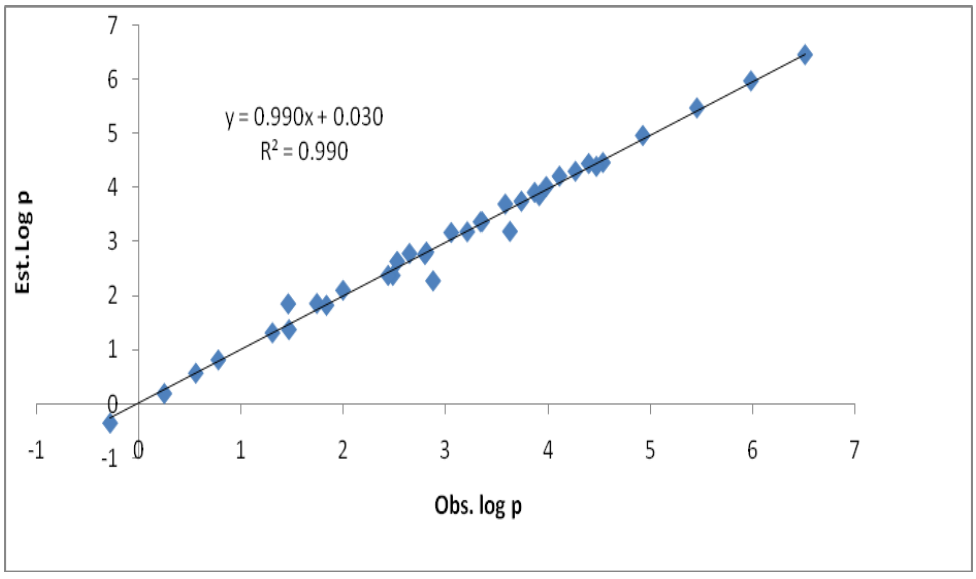

Figure 1: Graphical representation of MLR between observed and calculated Biological activity

Applications of QSAR

In the field of drug design and medicinal chemistry the application of QSARs are given below:

- To rationalization of new leads compound with enhance biological activity.
- 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.
- The optimization of pharmacological and pesticidal activity.
- The identification and selection of the compound in order to get the best biological responds with better and optimal pharmacokinetics properties.

- To identify the role of various properties to design the drug molecule and to know the better properties to improve the biological activity.

Conclusion

QSAR can be expected that the 3D QSAR will continue to impact the analysis of high throughput screening structure-activity data. The field of chem.-informatics is newly introduced and gains the importance for the researcher in development of new drugs. Different software packages play vital role in this direction. QSPR studies are an important tool for research and knowledge of chemical compounds and it has been frequently used in medicinal chemistry and molecular design to investigate new drugs. It is especially useful when the experimental determination of properties is very complex, the handling of materials may involve some risk, or determinations may not be easy in cases where compounds can quickly degrade. 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.

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