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QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS IN COMPUTER AIDED MOLECULAR DESIGN

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Graphical abstract

Abstract

The drug development process requires the complete evaluation and identification of the chosen substance as well as its properties. It involves extensive chemical examination to achieve the best therapeutic effects which demands huge expenditure both in terms of time and money. Computer aided molecular design (CAMD) allows the production of new substances with pre-decided properties. Additionally, in order to illustrate and determine the interrelationship between the chemical structure of a compound and its biological activity, Quantitative Structure Activity Relationship (QSAR) is applied by employing a mathematical model and arranging molecular descriptors. This paper presents review of CAMD and QSAR techniques. The most common chemometric techniques are also emphasized. CAMD and QSAR are considered to be extremely efficient instruments in molecular design and accelerate the initial steps of drug development process. Furthermore, they enhance the effectiveness and reduce the cost of newly developed drugs.

Keywords: Computer aided molecular design, CAMD, Quantitative Structure Activity Relationship, QSAR, Drug design, Chemical dataset, molecular design, and Biological activity

1.0 INTRODUCTION

There have been exciting developments in computational chemistry and computer aided molecular design (CAMD) and it has come up as a new branch of chemistry with tremendous potential. Investors have been lured back towards the field of theoretical research due to new technological methods that can deliver artificial compounds endowed with the required properties thus decreasing the amount of money that needs to be pumped in this field.

At present, development of new drugs and search for substances with the required pharmacokinetic properties has opened up new avenues for CAMD. A sub branch of CAMD [1] known as computer aided drug design (CADD) [2-4] specifically focuses on producing substances with a pre-decided set of properties. Various revolutionary technologies play an important role in this field and include simulation software, molecular modeling and Quantitative Structure Activity Relationship (QSAR) which has been restructured of late. CAMD works on the basis of certain processes which include determination of the structural framework which will confer the required property on a compound, initiating ligand receptor binding, in depth analysis of different biological mechanisms , studying the chemical reactivity of substances, development of novel substances with chemical action, determination of the presence of active lead compounds and laying down projections for compounds with structural similarities which are still in the pipeline. All these properties help CAMD to be an extremely efficient instrument in molecular design and specifically in development of new drugs.

The first step in development of any new drug is identification of a substance with the required properties. After the structural framework of the

candidate compound has been determined, various compounds with similar structure with the required properties are analyzed to achieve the best possible therapeutic effect and pharmacokinetic activity reducing the adverse effects to a minimum. The compounds undergo extensive testing in humans and animals covering aspects like therapeutic effect, mode of action, bio-availability, presence of side effects, market requirements, manufacturing set up needed and its space in the medical realm. The process of drug development has been conceived as a trial and error method which entails huge expenditure both in terms of time and money.

Of late, drug manufacturers have tried to use rational drug design and the existing drug development process in combination. So, the conventional trial and error method now have the support of sophisticated software programs, computerized measurement and analysis and other revolutionary technologies. The drug development process has also benefitted from the technological leaps in the field of combinatorial chemistry and biotechnological fields which focus on the study of proteins and genes. Various technologies work as a choir to enhance the effectiveness of the drug development process.

The basic mechanism that lies behind combinatorial chemistry is the use of High Throughput Screening (HTS) to analyze a mind –boggling number of compounds. All these compounds were analyzed by HTS Vis-a –Vis their effectiveness against any potential threatening agent which may be identified as an abnormal protein which may be behind the pathogenesis of a disease. In the next step, data mining software is used to separate the new arrangements that come up in the analysis that can then be used to study other combinations of data.

The field of computers has improved by leaps and bounds both in terms of the speed and the volume of information it can process and these developments over the past ten years have brought forward thousands of lead compounds in the scientific realm for further analysis. An avalanche of potential drug candidates has occurred due to advanced technology and the financial costs and the time involved in the drug development process have been cut down significantly thus making the entire process a more cost effective one.

Statistics show that around 5000 potential drug candidates have to be screened to get one genuine candidate. It also has to be kept in mind that all candidates have to clear the tests of safety, adverse effects, efficacy in clinical trials and the net result comes out to be that only one out of ten candidates manages to clear all these tests. So, it can be concluded that though the initial steps of the drug development process have been accelerated due to technological advances the stages of clinical trials have remained untouched by their benefits and are the stages that use the maximum amount of time and money in the entire drug development process. A study shows that by 2013, the total cost of finally delivering a drug to consumer came out to be 1000 million dollars [5].

The QSAR methods were applied in an effort to make the process more cost effective, these methods tried to find the interrelationship between the structural composition of a compound and its biological properties describing it by means of molecular structural descriptors.

There is a provision for actual quantitative measurement of descriptor variables in QSAR; they are calculated by computer programs so they hold good for a large number of compounds. The QSAR approach is based on the development of a model which will be applicable to a large number of compounds and can describe the interrelationship between structural framework and biological activity or therapeutic effect. Another technique that is used is that once the interrelationship between structural composition and biological activity is defined and understood then the biological activity of a new chemical substance can be predicted by using this model. As far as drug development is concerned the basic purpose served by QSAR is to screen all potential candidates in terms of side effects and clinical benefits in trials thus determining which chemical compound has the capability of acting like a drug.

The defining principle behind QSAR is that the structural composition of any compound is the determining factor of its biological properties [6, 7]. It also takes into account the similarity principle and considers compounds with similar structural configurations to have similar biological properties thus specific descriptors can be assigned to a specific structural composition. The similarity principle can only work if there is a provision of a technique that can analyze the similarities in the structural framework of different compounds; the Quantitative Structure Activity Relationships Theory provides a solution to this problem.

This paper presents the new CAMD advances and highlights the recent development of QSAR techniques. First, it introduces the historical birth and development of QSAR techniques. The QSAR field has significantly evolved since its qualitative origins, to the actual three-dimensional and higher dimensional models, going through the linear free energy relationships, the Hansch analysis, and the QSAR based on topological descriptors. In addition, this section also describes the generation of descriptors, the statistical treatment of Similarity Matrices (SM), and the validation of results. The most common chemometric techniques are also emphasised; among them. In any case, the objective is to build a mathematical model relating the molecular descriptors with the experimental data, namely the biological activity.

2.0 QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS (QSAR)

All the various methods used to determine the activity demonstrated by certain class of compounds either in practical situations or under theoretical conditions to achieve the optimum optical activity are included under the umbrella of QSAR. According to the QSAR method the biological properties of a compound and its structural composition are intricately linked and this approach tries to define the biological or chemical properties of a class of compounds under the purview of a mathematical model [8-10].

Generally compounds with similar structures to a chemically active compound are subjected to QSAR analysis. Such structurally similar compounds are generally developed by minor modifications in the original structures. In the next steps the molecular descriptors are arranged in a matrix framework and are used to describe the characteristic features of any molecule. The correlation equation that defines the interrelationship between the amount of biological activity and the column variables of the matrix utilizes these very column variables as independent variables.

Both the statistical methods that are used to analyze molecular descriptors and the criteria for defining molecular descriptors are included in the QSAR technique. In contrast, the field of chemometrics only deals with different statistical methods that helps in defining mathematical interrelationship and making them more accurate [11-13]. Any mathematical model thus derived is tested by scientists who did not participate in the development process and the results derived from the model are compared with the actual results. In the next step an estimate of the biological activity of experimental compounds is done so that they can be separated on the basis of their activity and the net yield of the process is improved.

3.0 ORIGINS AND EVALUATION OF QSAR

3.1 The Birth of QSAR

About 2500 years ago it was Plato who for the first time attempted to associate features of chemical and physical behavior with structures. According to Plato, gasification is a reaction that takes place with the conversion of fire into air present in an aqueous solution. He made this assumption on the basis of reactants structure.

Even Mendeleev is often considered as an ancestor of QSAR because it was his predictions about new elements and their characteristics that helped him in forming the periodic table of elements. In 1869 the periodic table was prepared [14].

However it was found that in the nineteenth century the first experiments relating a biological response or a physicochemical feature of a chain of compounds with a structural property were conducted. The previous experiments were qualitative in nature. It was later on that the quantitative evaluations were conducted, where statistical considerations are used for relating the bioactivity and a set of parameters mathematically.

Cros in 1863 found that with decreasing solubility of the alcohols in water, there was an increase in the toxicity of alcohols in mammals [14]. A theory stating about an association between physiological activities and chemical structures was presented by Crum-Brown and Fraser in 1968 [14]. An equation connecting changes in both biological activity and chemical structure was proposed by them, however methods of exemplifying chemical structure on quantitative basis was not revealed by them. Based on this, the chemical structure as a solubility function was proposed by Richardson [14].

A Quantitative Structure Property Relationships (QSPR) to predict the melting and boiling points in homologous series was produced in 1884 by Mills. Improved by one degree this prediction was quite precise [15]. Afterward, the empirical principle "Plus ilssontsolubles, moinsilssonttoxiques", was determined by Richet who connected toxicities of a set of alcohols, ethers and ketones with aqueous solubility [15]. According to "Plus ilssontsolubles, moinsilssonttoxiques" « more solubility means less toxity ». Meyer and Overton from University of Marburg and University of Zurich respectively in the 1900's worked independently and found that it was lipophilicity of the organic compounds that determined their narcotic abilities [14]. They linked partition coefficients to anaesthetic potencies on the basis of biological experiments. Moreover, the functional groups effecting the increase or decrease of partition coefficients were even established by Overton. Later, in St. Petersburg Lazarev used partition coefficients for developing standards of industrial hygiene. Using a log scale he stated the correlations, and also produced a system that calculates the partition coefficients using structure of chemical [14].

But the earliest mathematical formulation is attributed to Ferguson, who announced a principle for toxicity. He observed the increase in anaesthetic potency when ascending in a homologous series of either n-alkanes or alkanols to a point where a loss of potency, or at least no further increase occurred, using physical properties such as solubility in water, distribution between phases, capillarity and steam pressure[15].

Prior to the work of Louis P. Hammett in the field of organic chemistry, not much development of QSAR had happened [16]. Hammett is considered as the father of Linear Free Energy Relationships (LFER). Indeed, the free modern publications of the Free-Wilson model [16] and the model of Hansch [17] is to

be accredited for the utilization of QSAR approach used these days.

3.2 Linear Free-Energy Relationships (LFER)

Hammett in the mid-1930s found that a logical and quantitative impact was been applied on the dissociation constant by adding substituents to the benzoic acid's aromatic ring of. Also, an equivalent impact on the dissociation of other organic acids and bases was observed by him [16]. The following linear relationship was derived by Hammett from the empirical observation. This is also known as the Hammett equation (1953):

Here, a proportionality reaction constant that is related to a given equilibrium is signified by the slope ρ. This slope links the elements impact on the equilibrium with the impact on the benzoic acid equilibrium. A factor describing the electronic features of aromatic elements, i.e. electron-withdrawing or donating capability is expressed by σ.

As these associations evoke the equation connecting the free energy, ΔG, with an equilibrium constant, K, or rate constant, k, they are known as linear free energy relationships. The logarithmic relationships connect the reaction energetics with the measurements of concentration.

In the late 1960s, as an order by Hansch and his colleagues the Hammett's correlation describing the aromatic systems reactivity was involved with the QSAR's unexplored derivation. Moreover, for the first time the molecule was divided and its action was explained considering its fragments and not by its totality. Taft derived the Taft equation [16] by working on the steric effects (ES).

Besides, the influence of field and resonance was researched by Swain. The deviation of reactivity of a certain electrophilic substrate towards a chain of nucleophilic reagents was studied by him. As a result the linear free-energy relation also called Swain-Scott equation was derived [16].

Here, the nucleophilicity feature of the reagent is measured by n and the sensitivity to the nucleophilicity of the reagent feature of the substrate is measured by s. Moreover, the Swain-Lupton equation was derived by him. This equation involves a field constant (F) and a resonance constant (R), hence it is a dual factor approach to the correlation study of elements impacts [16]. Molecular partition method of Free and Wilson and Hammett were different. According to Free and Wilson considering the number, kind and location in the parent skeleton, a molecular set biological activity could be correlated by adding substituents. Hence, a stabilizer model discretizing the activity as a simple sum of contributions was formed by them.

Here, the molar dose is expressed by C, the substituent Xi's group contribution is indicated by ai and the biological activity of the parent structure is indicated by μ. The presence or absence of specific features of the structure is codified by the descriptors, or indicator variables, in this stabilizer model. Accordingly the binary values of 1 and 0 are assigned to them.

However Bruice *et al*. in 1956 had already reported the first usage of the Free-Wilson type study [16]. Even for considering the possible relations among close elements, Free-Wilson models along with crossed terms were developed by Bocek and Kopecký [16].

Later, the Free-Wilson equation was simplified by calculating the non-substituted compound activity by Fujita and Ban. For quantifying the participation of some particular bonds in an activity that initiates the beginning of a carcinogenic result, Daudels, Pullmans, and Coulson used valence bond theory and molecular orbital theory in their study. The theory showing the regions of K and L having a possible mechanism of the hydrocarbons was developed on the basis of descriptors having theoretical structure 16].

As descriptors of the structure electronic features are used by Hammett's relationships on the basis of QSAR. When researchers tried to use Hammett-type relationships to biological systems they faced problem, which showed that it was important to have alternative structural descriptors. For predicting regularities Hansch and Fujita set up their model on empirical searches present among the various descriptors and techniques of data analysis, this was basically done for dealing with the problems of biological systems, free from analysis of Free-Wilson. It was for the first time that computers were used instead of pencil and paper.

3.3 Hansch Analysis

The research conducted by Robert Muir marked the origins of QSAR as applied nowadays. Researching on the biological activity of plant growth regulators, Robert Muir was a botanist at Pomona College. He took help of Corwin Hansch, his colleague in chemistry for relating the compounds structures to their activities. Afterward, a LFER related model which was considered as the formal start for QSAR was published by Hansch and Fujita. Two more information and application was being added by their fragment and additive group contribution theory. The first one was using estimated features for relating to biological activities, and second was acknowledging that the biological action might be affected by the various different features. Hence, considering this purpose, the use of computer was implemented so that it fits in the equation of QSAR equations [17].

The substituents on a parent molecule in this theory from the very beginning have a quantities relationship with biological activity. For considering the electronic impact of substituents so that it does not lead to meaningful QSAR, Hammett sigma parameters was used by them. However, the significance of the lipophilicity was understood by Hansch, which on biological activity was expressed as the octanol-water partition coefficient. A measure of the bioavailability of compounds determining the

amount of the compound that reaches to the site of the target partially is provided by this factor. For relating physicochemical features to biological activities, the Hansch equation was developed, which is in the following manner:

Here, the molar concentration producing the biological impact is represented by C; the partition coefficient of octanol/water is expressed by P and the electronic Hammett constant by σ.

For the first time a parabolic model's definition and the blend of diverse physicochemical features were allowed in one model, this helped to describe SAR which using a single term could not be connected. A lipophilicity parameter π could be applied as a substitute to values of log P. The Lipophilicity parameter π and the Hammett's electronic parameter σ are described in a similar manner. Moreover, Hansch-type associations were created by Rudolf Zahradnik quite ahead of its time [17].

The utility of both QSAR techniques are broadened by the mixed approach of the amalgamation of Free-Wilson analysis and Hansch. Several parameters are used as descriptors of the structural molecular features in order to develop SAR.

3.4 Spatial Methods: 3D-QSAR

Lately, the three-dimensional field of QSAR has been introduced due to the need of including the effect of the conformations and stereochemistry in studies of QSAR. The three-dimensional factors for describing compounds are introduced by these new methods; this allows computations to the space that is found near the molecules. It even needs the molecules' position to a pharmacophore found in general. The interaction research of a ligand along with a receptor is an application of such QSAR methods; in such case in three dimensions the molecules are evaluated. Parameters such as electrostatic and steric govern these interactions. Stereoisomers, enantiomers, and diastereomers are the various conformations of the compounds, which are considered in this technique.

The Comparative Molecular Field Analysis, CoMFA [18, 19] was the first technique that is about the electrostatic and steric molecules interactions with their environment. In order to function it considered 3D shape. Even today in the field of receptor and ligand's modeling this method is commonly used. Afterward, the CoMFA superposition method was used by Good and Richards [20-22] to compare the electronic resemblance between molecules, and also they used Neural Networks and Partial Least Squares technique to correlate the topological indices.

Moreover, for representing a group of conformations there have been the development of 4D-QSAR [23, 24] and 5D-QSAR [25, 26]. Various conformations, states of protonation and orientation are presented by this.

4.0 MOLECULAR DESCRIPTORS

Describing the molecules and their features is a usual problem of QSAR. A very important element of a QSAR study is the used descriptors behavior and the degree to which the properties of structure associated with the biological action are encoded by them [27]. Today availability of molecular descriptors is more than 3,000 in number [28-30]. Commercial software packages like ADAPT [31], OASIS [32], and DRAGON [29] can be used to calculate these descriptors in theory.

The topostructural, topochemical, geometrical, relativistic, and biodescriptors are among the most widely used bibliography available extensivley, and stated in increasing complexity order. In different manner the important descriptors are categorized, these descriptors are used for exemplifying chemical compounds. They are classified into three groups:

i. In the standard models of QSAR the empirical factors obtained from organic chemistry, are used, for instance the analysis of Hansch. Firstly, these models were categorized into electronic, hydrophobic, and steric on the basis of numerous physicochemical descriptors. However later more different descriptors such as solubility, boiling point, spectroscopic descriptors, melting point, etc were included.

ii. Characteristics determined theoretically: Topological descriptors, factors obtained from computational chemistry are included in this group. Even the chemicals that are not yet synthesized are assessable by these theoretical descriptors.

iii. Lately, from the eighties, the tridimensional descriptors have come into existence. The three-dimensional molecular structure is considered by these factors and is applied in the3D-QSAR methods and they may require a molecular super position procedure. Molecular similarity indices as well as topological quantum similarity indices are included in this group.

Moreover, in the activity the structural features effect could be localized to a part of a molecule or it might be universal as well. This is another categorization of descriptors used commonly.

4.1 Whole Molecule Representations

Complete structures of molecule are used to obtain few of these descriptors. Though the molecular structures are obtained from the extensions of the substituent constant approach, yet many of them are entirely new.

4.1.1 Electronic Whole Molecule Descriptors

Obtained from a three-dimensional conformation of the molecule, these descriptors, depend on the used modeling program. The experimental to semi-empirical and to quantum mechanical values shows the variation in the range of value. Moreover

thermodynamics is also the reason behind some of these. The commons aspects of the whole molecule or local aspects of a particular site are encoded by them [33-35]. Polar and energetic descriptors are among the electronic descriptors.

4.1.2 Polar Descriptors

The force fields applied on the molecule are described by these descriptors. Hence the influence or potential of various intermolecular interactions can be encoded by them.

Intermolecular forces. The potential of polar-type interactions [35] are encoded by these forces. Quantum mechanical methods are used to determine it experimentally and calculated theoretically. Ion-ion, ion-dipole, dipole-dipole, dipole-induced dipole, dispersion forces, hydrogen bonding are the interactions by which the intermolecular forces arise.

Molecular polarizability and molar refractivity are a measure of a molecule that is polarized. The refractive index [36] and the molar volume are used to calculate these descriptors.

Ionization constants. The ionic interactions are encoded by these constants and information related to the absorption and distribution of a drug are provided by them [36].

4.1.3 Energetic Descriptors

These descriptors are derived from the calculations of molecular orbital and electronic interaction is defined by them. Electrostatic potentials, bond order, atomic charges, number of hydrogen bond donors and acceptors, measures of the π-πdonor-acceptor ability of molecules, and, specially, reactivity indices are few types of such descriptors.

Reactivity indices. EHOMO or energy of the highest occupied molecular orbital is a quantitative measure of the chemical reaction of the compound-ionization potential of a molecule. ELUMO or energy of the lowest unoccupied molecular orbital is the electron affinity [37]. However, also the HOMO-LUMO band gap energy could be used.

4.1.4 Geometric Descriptors

Information related to the shape and size of active compounds, along with the extent of complementarity of a ligand and the receptor are provided by them. The three-dimensional molecules models help in their development, and the computations of molecular surface area help to obtain them.

Molecular volume is an overall measure of size of molecule. A sphere is placed on each atom having radius obtained from the Van der Waals radius of the atom to calculate it. Pearlman developed the volume estimation method which is used commonly [38].

Molecular surface area: Lee and Richards [35], Herman [35], and Pearlman [36] gave some estimation that is used to calculate the molecular surface area.

Charged partial surface area: For understanding the features that are affected by polar molecules interactions, certain information about surface area and charge information are provided charged partial surface area [36].

4.1.5 Topological Descriptors

These descriptors depend on a molecule's connection table and on a molecule's compressed representation of connectivity. However, their values might or might not be free of conformation present in three-dimension.

Structure-based descriptors or information-content indices

The occurrence frequency of a substituent or substructures found inside molecules as indicator variables are counted by these descriptors. These variables are bonds and atoms number [35, 36].

Topological Indices

These are obtained from the graphical representation of chemical structures and by manipulating the graph-theoretical features of the structures [39] they try to encode the size, shape, or branching in the compound. The molecular connectivity indices[35, 36], Wiener index (sum of the chemical bonds found between pairs of heavy atoms), Zagreb index (sum of the squares of vertex valences), Hosoya index, Kier and Hall molecular connectivity index (a chain of numbers chosen by order and subgraph focusing on several features of atom connectivity) are the most significant indices. There are even others such as Molecularflexibility index, Kier & Hall valence-modified connectivity index, Balaban indices, Kier's alpha-modified shape indices and Kier & Hall subgraph count index that are equally important.

Electrotopological Descriptors

The electrotopological state indices are numerical values computed for each atom in a molecule, which encode information about both the topological environment of the atom and the electronic interactions due to all other atoms in the molecule. The topological relationship is based on the graph distance to each other atom.

Kappa Indices

Kier developed Kappa indices that are formed by a chain of graph theoretical indices. These are associated with the shape of the molecule [35] .

4.2 Other Descriptors

4.2.1 Receptor Surface Analysis (RSA) Descriptors

The interaction energy found between every point on the receptor surface and each model to the study table is calculated by these descriptors [35, 36].

4.2.2 Molecular Field Analysis (MFA) Descriptors

The energy between a probe and a molecular model found at a chain of points and described with the help of a rectangular or spherical grid is calculated by these descriptors [35, 36].

4.2.3 Molecular Shape Analysis (MSA) Descriptors

These are even known as pharmacophoric descriptors or 3DKeys, and are formed by a combinations assortment having three properties (triplets) and four properties (quadruplets) in the 3D space for all conformers. The aspects could be negative and positive charges, hydrogen bond donors and acceptors, negative and positive ionisable groups, aromatic rings and hydrophobic groups etc [35, 36].
Absorption-Distribution-Metabolism-Excretion (ADME) Descriptors: On the basis of profiles such as stability of potency, pharmacokinetics, selectivity, and toxicity that are need for an ideal drug and the reduction of powerful side effects, these descriptors help to understand and calculate the responses of drug. The cost of drug detection are reduced, the development and time of assessment of successful candidates are minimized by predicting the difficult new chemical bodies at an early stage of development, which is done by these ADME descriptors [35, 36].

5.0 CONCLUSIONS

It was demonstrated by the Quantitative Structure Activity Relationships (QSAR) that the biological properties of any compound is determined by its structural composition. Therefore, specific molecular descriptors were selected to encode the association's degree between the physical and chemical structure of a compound and its biological action. While the tridimensional descriptors evaluate the molecule in a three dimensions, the topological descriptors that can determine and assess theoretically the characteristics of any studied molecule even if it's not synthesized. All the various methods used to determine the activity demonstrated by certain class of compounds either in practical situations or under theoretical conditions to achieve the optimum optical activity are included under the umbrella of QSAR. Thus, QSAR has matured over the last few decades in terms of the descriptors, models, methods of analysis, and choice of substituents and compounds. Embarking on a QSAR project may be a daunting and confusing task to a novice. However, there are many excellent reviews and tomes [2, 4, 6, 15, 35, 36] on this subject that can aid in the elucidation of the paradigm. Dealing with biological systems is not a simple problem and in attempting to develop a QSAR, one must always be cognizant of the biochemistry of the system analyzed and the limitations of the approach used

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