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RESEARCH ARTICLE

APPLICATION OF QSAR IN DRUG DESIGN AND DRUG DISCOVERY

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ABSTRACT

Over past twenty years a large number of ligands, both agonists and antagonists have been developed by computational methodologies which are used to increase the efficiency of drug discovery process by rendering the design of new drug candidates. Both 2D and 3D-quantitative structure activity relation (QSAR) studies have been carried out using topological parameters along with thermodynamic and structural descriptors. The scope of this review is to highlight the use of pharmacophoric models and QSAR studies for identification and optimization of new ligands having potential to develop as drug candidates.

INTRODUCTION

The QSAR is based on structure activity relation (SAR) approach. It uses physicochemical properties (parameters) to represent drug properties that are believed to have a major influence on drug action. Some of the common pharmacophoric features include hydrophobic, aromatic, hydrogen bond acceptor, hydrogen bond donor, positive ionizable, and negative ionizable groups.

These parameters are properties that are capable of being represented by a numerical value which are used to produce a general equation correlating activity with relevant physicochemical properties. Many applications of QSAR and 3D QSAR methods have proved their utility in drug discovery. Once a 3D QSAR model is generated for a group of compounds having desired activity, it is further optimized by molecular docking to predict the interaction mode between the high/low potent ligands and protein (enzyme/receptor) [1].

Parameters

Lipophilic parameters

Two parameters are commonly used to relate drug absorption and distribution with biological activity, namely, the partition coefficient (P) and the lipophilic substituent Constant (p). The former parameter refers to the whole molecule whilst the latter is related to substituent groups. A drug has to pass through a number of biological membranes in order to reach its site of action. Partition coefficients were the obvious parameter to use as a measure of the movement of the drug through these membranes. The nature of the relationship obtained depends on the range of P values for the compounds used. If this range is small the results may, by the use of regression analysis, be expressed as a straight line equation having the general form:

$$\text{Log } (1/C) = k1\log P + k2 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where k1 and k2 are constants. This equation indicates a linear relationship between the activity of the drug and its partition coefficient.

Electronic parameters

The distribution of the electrons in a drug molecule will have an influence on the activity of a drug. In order to reach its target a drug normally has to pass through a number of biological membranes. As a general rule, non-polar and polar drugs in their unionized form are usually more readily transported through membranes than polar drugs and drugs in their ionized forms. Furthermore, once the drug reaches its target site the distribution of electrons in its structure will control the type of bonds it forms with that target, which in turn

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affects its biological activity. In other words, the electron distribution in a drug molecule will have an effect on how strongly that drug binds to its target site, which in turn affects its activity.

The distribution of electrons within a molecule depends on the nature of the electron withdrawing and donating groups found in that structure. For example, benzoic acid is weakly ionized in water. Substitution of a ring hydrogen by an electron withdrawing substituent (X), such as a nitro group, will weaken the O–H bond of the carboxyl group and stabilize the carboxyl ate anion. This will move the equilibrium to the right which means that the substituted compound is a stronger acid than benzoic acid (KX>K). It also means that at equilibrium more of the nitro benzoic acid will exist as anions, which could make its transfer through membranes more difficult than that of the weaker less ionized benzoic acid. Conversely, the introduction of an electron donor substituent (X) such as a methyl group into the ring strengthens the acidic O–H group and reduces the stability of the carboxylate anion.

Table 1 Development Status of Site Directed Thrombin Inhibitors, Taken from Literature [8]

Agents	Chemical name	Developmental status
Hirudin PEG-Hirudin and related variants	Recombinant analogues of natural Hirudin and their derivatives.	Various clinical phases of development. Additional derivatives are being developed. One product is available in Europe.
Hirulogs	Synthetic bifunctional oligopeptides	Phase II and III clinical studies completed. Additional studies are carried out at this time.
Peptidomimetics	Synthetic heterocyclic derivatives	Phase II and III clinical development in the U.S

Steric parameters

In order for a drug to bind effectively to its target site the dimensions of the pharmacophore of the drug must be complementary to those of the target site. The Taft steric parameter (Es) was the first attempt to show the relationship between a measurable parameter related to the shape and size (bulk) of a drug and the dimensions of the target site and a drug's activity. This has been followed by Charton's steric parameter, Verloop's steric parameters and the molar refractivity (MR), amongst others. The most used of these additional parameters is probably the molar refractivity. However, in all cases the required parameter is calculated for a set of related analogues and correlated with their activity using a suitable statistical method such as regression analysis. The results of individual investigations have shown varying degrees of success in relating the biological activity to the parameter. This is probably because little is known about the finer details of the three-dimensional structures of the target sites.

Applications

1. Malaria, caused by the plasmodium parasite, is a major threat in the developing world, infecting 247 million people annually, and causing one million deaths. Resistance to anti- malarial drugs is a major public health problem to the control of malaria. Molecular docking is used to study how ligands are interacting with its biological target. Murray *et al* reported QSAR, pharmacophore and docking studies of dihydrofolate reductase thymidylate syntheses inhibitors [2, 3]
2. Thrombotic disorders remain the major cause of death and disability in the western society and are projected to be the leading cause of death worldwide within last twenty years [4]. The use of anticoagulants in the treatment and prevention of both acute and chronic thrombosis-related disorders is growing at a rapid pace, in part due to an increasing geriatric population and the recognition of intravascular diseases such as myocardial infarction, unstable angina, deep vein thrombosis, pulmonary embolism and ischemic stroke [5]. The significant role of thrombin makes it an attractive target in the design of new drugs for the treatment of cardiovascular and other diseases [6, 7]. Scientists [8] reported a development Status of Site Directed Thrombin Inhibitors (Table 1).
3. Cancer is a group of diseases characterized by the proliferation of cells without normal cellular controls over these events. These diseases are the second leading cause of death in the USA with approximately 1.2 million new cases diagnosed each year. With the revolutionary discoveries in molecular biology it became obvious that specific targets can be identified in tumors cells, the functions of which are necessary prerequisites for their replication. These targets might be specifically blocked by molecules designed and synthesized for this purpose. The advances in QSAR studies have widened the scope of rationalizing the drug design and, even finding the mechanisms of drug actions. QSARs have proved their worth in the interpretation of mechanisms of inhibition of a number of enzyme systems and a variety of anticancer drugs [9, 10].
4. Tyrosine kinase have emerged as new promising targets for cancer therapy [11].Tyrosine kinase plays a central role in transformation of cells. This can be achieved in several ways; gene amplification and/or over expression of protein tyrosine kinase (PTKs) example, EGFR and erbB over expression that is commonly observed in several cancers, causes enhanced tyrosine kinase activity with quantitatively and qualitatively altered downstream signaling [12]. erbB-2 is involved in development and progression of several human cancers including lung and breast. The erbB family of receptors transmembrane receptor tyrosine kinase is involved in a wide range signal transduction and cellular functions, and has become a very fruitful area for the successful development of drugs to treat cancer [13]. erbB-2 is found to be significantly overexpressed in 20-30% of human breast cancer and is associated with poor prognosis [14]. The development of tyrosine kinase inhibitors has therefore become an active area of research in pharmaceutical science. One could not, however, confirm that the compounds designed would always possess good inhibitory activity to tyrosine kinase erbB-2, while experimental assessments of inhibitory activity of these compounds are time-consuming and expensive. Consequently, it is interesting to develop a prediction method for biological activities before the synthesis. QSAR searches information relating chemical structure tobiological and other activities by developing a

QSAR model. Using such an approach one could predict the activities of newly designed compounds before a decision is being made whether these compounds should be really synthesized and tested.

5. The Epidermal Growth Factor (EGF) and its receptor have been identified as key drivers in the process of cell growth and replication. The kinase domain of EGFR is known [15] and provides a basis for structure based design; ligands based approach also provides an effective way for designing new inhibitors. There are few core structures which can be used for designing the best molecule. There are several EGFR, QSAR models published in the literature [16, 17]. The models are based on Hansch analysis or 3D-QSAR techniques [14, 15].
6. Adenosine receptors (ARs) are a family of G-protein coupled receptors (GPCRs) of great interest as targets for therapeutic intervention. There is a lack of reliable adenosine receptor structures. So, adenosine ligands, agonists and antagonists, have been developed by homology modeling of GPCR. Homology modeling is a computational method for constructing a three-dimensional model of a protein from its amino acid sequence by means of the alignment with one or more known protein structures, namely templates, likely to resemble the structure of the query sequence [18, 19]. Once generated, a homology model could be used with structure-based techniques.

DISCUSSION

Various compounds have occupied researchers in recent years and numerous computational models have been drawn up. Many of these models have been generated by means of Ligand-based approaches, mainly pharmacophore modeling and 3D QSAR studies. Such models were capable to predict a potent drug for new drug discovery. Most of these models have also been successfully applied to the design of new ligands or to the optimization of known active compounds [20-24]. But the problems with the industrial application of QSAR stem from difficulties that arise in the following stages of modeling:

- Data collection and accessibility
- Determination of the error level of data
- Presentation of molecular structure
- Choice of the appropriate QSAR model
- Optimization of model architecture
- Identifying the optimal subset of variables
- Robustness of model and the size of external
- validation effort.

There are many problems but there are also many recommendations which were given in 1973, by Unger and Hansch. They are:

- Independent parameters should use.
- Parameters should be validated.

Now a day, there are more recommendations for 3D QSAR. They are:

- Select rationalized startingϖ geometries.
- Cross validation should be done.
- Prediction of biological activity values depend on training set.
- Observed value and predicted value should be summarized.[25,26]

CONCLUSION

Many more approaches like metabolomics, genomics, proteomics also compliment well with the other techniques so that more target specific agents can be discovered with more accuracy. Drug discovery is yet more to be explored, even more than that explored till date. The findings of the human genome project have added more understanding to the target identification. Nature has made all the provisions for curing a disease or disorder, human efforts of finding is what is required. Exploring natural sources which is ill-explored should be effective done as nature is source of countless chemicals which could lead to a successful drug candidate.

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