QSAR: Application, Limitations and Purposes for Drug Design

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Abstract: Quantitative Structure Activity Relationship (QSAR) revolutionized drug research by converting qualitative relationships into quantitative structures. (QSPR) is useful in study the methods for rational drug design, aiming to optimize existing leads, improve biological activities and physio-chemical properties, and enquire the biological activities of untested and sometimes unavailable compounds. QSAR studies are effective in study of drug activity or binding mode on specific receptors. It is a statistical model used to establish relationships between chemical substances and their biological activities, providing a reliable predictor for new chemical entities. It enhance method for building computational and mathematical methods. It approach ligand based designing. It focus on study of error less method for synthesising, compound activity. QSAR helps in study on hazardous compound before synthesis of investigated molecule. QSAR deals with 2D structure of molecules and biomolecule deals with 3D structure. Hansch's studies involve the application of QSAR in medicinal chemistry, including its capability and role in understanding mechanism action of various drugs. Its process involve the analysing the combined effect of molecule and mixture present in compound. Its application gives information from intercept values, bioisosterism, information on receptor site, drug research, application of free- Wilson model, quantitative structure toxicity relationship. Cramer's study utilizes methodology to develop antiallergic pyrene-amines. In future QSAR further developes in many sectors of drug design and its application will be enhanced.

Keywords: Bioisosterism, QSAR, QSPR, Drug design, PCA-inhibitor

INTRODUCTION

Drug discovery and development is a complex, time-consuming, and resource-intensive process requiring multidisciplinary expertise and innovative approaches. With rapid technological advancements, biomedical engineering has become essential in solving medical problems. Rational drug design methods, such as QSAR/QSPR studies, have been used to simplify the process. Drug design can be divided into Structure-based drug design (SBDD) and Ligand-based drug design (LBDD), which use structural information to develop inhibitors and rely on molecules binding to the biological target. (1)

Quantitative structure-activity relationships (QSAR) are crucial in drug design and drug discovery due to their cost-effectiveness and scientific credibility. QSAR models predict biological activities, drug resistance, toxicity, and physicochemical properties. They use molecular structure differences to correlate biological activity with specific descriptors, allowing for specific regression techniques to estimate biological effects.

Drug design and discovery have been the primary focus of pharmaceutical sciences, particularly medicinal chemistry. This field has evolved from pharmaceutical chemistry, with structure-activity relationship studies being crucial. Computational technology has the potential to reduce hit and trial methods in drug discovery and development, making it a modern and productive science.

Despite advancements in medical and pharmaceutical sciences, many incurable diseases remain untreated due to the lack of appropriate therapeutic agents. Only one-third of the 30000 known diseases can be treated with drugs, and incurable maladies like viral diseases, CNS disorders, cancer, and autoimmune disorders can be fatal or cause significant suffering. There is a need for better drugs with active, selective, fewer undesired side-effects, and minimal environmental contamination. Medicinal chemistry focuses on designing and discovering new drugs, involving a team from various disciplines. This process involves

synthesis, administration, tests, procedures, and safety assessments. (2)

Quantitative Structure-activity relationship (QSAR) is a method for building computational or mathematical models which attempts to find a statistically significant correlation technique between structure and function using a chemo metric technique. The objectives of QSAR include:

1: To quantitatively correlate the relationship between trends in chemical
structure alterations and changes in biological end point for their biological
activities.

2: To optimize the existing leads to improve their biological
activities.

3: To predict the biological activities of untested and yet
unavailable compounds. (3)

SAR DEFINATION AND DEVELOPMENT:

Quantitative structure activity relationship (QSAR) is one of the widely used approaches in ligand based drug designing processes. In QSAR/QSPR studies quantitatively correlate and recapitulate the relationships between trends in chemical structure alterations and respective changes in biological endpoint for comprehending which chemical properties are most likely determinants for their biological activities or physicochemical properties [4].

Quantitative Structure Activity Relationships (QSARs) & DEVLOPMENT:

Means 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. 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. In QSAR, the structure of a molecule must contain the features and properties responsible for its physical, chemical, and biological activities [5,6].

PURPOSE OF QSAR

QSAR focuses on developing the best drug model to overcome trial and error methods, reducing costs and time in drug synthesis and improving biological activity. By analysing relationships, models can be developed, and their validity and predictability can be tested using statistical tools. QSAR techniques are widely used in various situations and have practical purposes, such as improving drug molecule biological activity.

1. The goal is to decrease trial and error in drug synthesis, thereby reducing the time and cost of the drug's laboratory synthesis.
2. The goal is to enhance the significance of greener chemistry, particularly for environmental purposes, by reducing waste and utilizing less toxic compounds.
3. The goal is to minimize time and effort in clinical trials, particularly animal trials and preclinical trials.
4. Advanced drug mechanisms with specific enzymes and proteins are being developed to create more potent drugs for various diseases.
5. The objective is to comprehend and rationalize the mechanisms of action within a series of chemicals.

LIMITATION OF CLASSICAL QSAR

Classical QSAR methods are simpler and faster than 3D-QSAR approaches, allowing for the analysis of large compounds and computational screening of molecular databases. However, they still face limitations in drug design due to the increasing challenges in the field.

1. Classical QSAR primarily deals with 2D structures, while biomolecules are primarily complex three-dimensional structures.
2. The traditional method has limitations due to the limited number of descriptors considered when using 2D descriptors.

3. Regardless of the availability of molecule representations, there is no representation of stereochemistry or 3D-structure.
4. The generated model lacks predictivity, making it challenging to synthesize for the 2D model.
5. 2D QSAR models are based on chance correlation rather than actual prediction.
6. Designing a molecule requires extensive knowledge of substituent constants in physical organic chemistry, as classical QSAR equations do not directly suggest new compounds to synthesize.

APPLICATION OF QSAR

QSAR applications in drug design and medicinal chemistry have expanded to various fields, including rationalizing new compounds with enhanced biological activity, identifying toxic chemicals, optimizing pharmacological and pesticidal activity, selecting compounds for optimal biological responses, rationalizing products like surface-active agents, perfumes, dyes, and fine chemicals, and identifying properties for drug molecule design and improved biological activity. (7)

CHEMICAL APPLICATIONS

Predicting biological activity is valuable in various industries, including chemical, biological, and regulatory agencies. Chemical applications include predicting boiling points, as there is a strong correlation between structure and observed properties. (8)

BIOLOGICAL APPLICATION

Biological applications involve measuring a molecule's biological activity in assays to determine its inhibitory effect on specific pathways.

1. QSAR is utilized in drug discovery to identify new leads with pharmacological, biocidal, or pesticidal activity and enhance their efficacy.
2. The rational design of various products, including surface active agents, perfumes dyes, and fine chemicals.
3. The process involves identifying hazardous compounds early in product development or screening existing compound inventories.
4. The design of a new compound involves assessing its toxicity and potential side effects.
5. The study focuses on predicting the toxicity to humans due to deliberate, occasional, and occupational exposure.
6. The study focuses on predicting the toxicity of various environmental species.
7. The selection of a compound with optimal pharmacokinetic properties, including stability and availability in the biological system.
8. The prediction of various physicochemical properties of molecules, including pharmaceuticals, pesticides, personal products, and fine chemicals, is crucial.
9. The prediction of the fate of molecules released in the environment is crucial for understanding their potential impact.
10. The process involves analysing and predicting the combined effects of molecules, whether they are mixtures or formulations. (9)

STRUCTURAL APPLICATION

QSAR models' application relies on their statistical significance and predictive ability. Valid predictions require the compound to be within the applicability domain, defined by model descriptors and training set molecules. The leverage approach can check if a new compound is within this domain. Other approaches include training set interpolation and cluster-based approaches. (10,11)

APPLICATION FOR DRUG DESIGN

Since Hansch's publication, there's a surge in literature discussing its application in medicinal chemistry, including its predictive capabilities and its role in understanding the mechanism of action of numerous drugs.

1. Information from the intercept values

The intercepts in the QSAR equation represent the activity of an unsubstituted compound in a series, which increases or decreases depending on the substitution, as reflected in the slope or regression coefficient. High intercepts and low slopes indicate high activity in the basic nucleus or parent compound, with no significant contribution of substituents. Further position variations may not result in significant changes in activity, making the intercept a measure of intrinsic activity.

2.Bioisosterism

Biososterism has been applied in drug design for years, but it remains qualitative and intuitive. With the advent of Quantitative Structural Analysis (QSAR), it is now possible to quantify similarities and classify them based on physicochemical properties. This allows for the replacement of one group with another with similar properties both qualitatively and quantitatively. One interesting application of biososterism is the discovery of cyanoguanidine as the bioisostere of thiourea, leading to the development of H2 antagonists. Two derivatives (metiamide and burimamide) with a thiourea [NHC(S)NHR] group in the side chain underwent extensive clinical trials but were abandoned due to side effects. To replace thiourea with another bioisosteric group, a guanidine.

3.Information on receptor site

QSAR studies have significantly improved our understanding of receptor sites, particularly in the inhibition of dihydro folate reductase (DHFR) by benzyl pyrimidines and other compounds. A QSAR equation was obtained for a series of Trimethoprim type benzyl pyrimidines from bovine liver and E.coli.

QSAR studies on Quinazolines have provided a map of the binding site of dihydrofolate on DHFR. A hydrophobic parameter for the substituent at five positions of Quinazolines appears with a large positive coefficient, defining a hydrophobic pocket. This hydrophobic pocket is inferred for both mammalian and bacterial DHFR. Triazines have shown that this pocket is larger in bacterial enzymes than mammalian ones. A similar study for papain suggested that the amide part of substrate binds with the hydrophobic cleft of the enzyme.

QSAR studies were utilized to develop hypotheses for centrally acting α- receptor agonists, revealing that the receptor accepts electrons for the donor protonated drug, with clonidine type requiring an electron deficient phenyl, with one side dominating steric requirements.

4.Importance in drug research

QSAR analysis indicates that anti-inflammatory agents have reached their maximum activity in a series, indicating no need for further analogs. Nitroimidazole's carcinogenic potential has led to attempts for non-nitro derivatives, but QSAR studies show these efforts are futile. Diphenhydramine analogs show a negative contribution from the partition coefficient for antihistaminic activity, suggesting increased hydrophilicity leads to enhanced activity and the possibility of finding a good antihistaminic agent without CNS side effects.

- Success story of PCA inhibitor

Cramer's study at Smith Kline and French Laboratories utilized QSAR methodology to develop anti-allergic pyranen-amines. The study started with 19 compounds selected using the Topliss scheme. However, the Topliss scheme did not significantly increase activity, leading to the synthesis of bioisosters with similar activities. The most active compound was the 4-OH derivative.

5.Application of free - Wilson model

The Free-Wilson method is a quantitative analysis technique that uses indicator variables without any physico-chemical parameters. It has been used in numerous cases to obtain useful information, such as predicting the antimicrobial activity of Quinoxaline 1,4-dioxider and analysing the analgesic activity of semi-synthetic opioid narcotics, morphinan-6. The analysis revealed that phenolic and nonphenolic members of this series must bind at different sites or act in alternative mechanisms.

In the case of erythromycin esters, the Free-Wilson method was more useful than the Hansch method due to the type substituents being various combinations of OH, OCOH, OCOCH3, and OCOC2 H5. The Free-Wilson analysis resulted in an equation with r2 of 0.986 and s of 0.072, which was larger than the Hansch analysis, indicating that the physicochemical properties accurately reflect the activity.

The Free-Wilson method is suitable for peptide analysis, as the only variation is the individual amino-acid, and the activity of each amino acid is not influenced by any other amino-acid. The method has been applied to ACTH related peptides, bradykinin potentiating peptides, and other peptides. Despite its limitations, the Free-Wilson method has proven useful in obtaining valuable information in various cases.

6.Quantitative structure pharmacokinetic relationship

The study of physical chemical properties in absorption, distribution, metabolism, and excretion (ADME) has been extensively researched using QSAR methodologies. It is known that absorption, penetration into the brain, and liver metabolism increase with increasing log P, while urinary excretion decreases with increasing log P. However, QSAR analysis reveals many deviations from linear relationships. Lipophilicity is crucial for protein binding, but structural features also influence it. A plot

of binding constant against log P for various drugs shows multiple parallel lines.

7.Quantitative structure toxicity relationship

QSAR methods are increasingly used in toxicology and ecological sciences to predict mutagenicity of compounds. Hansch's study showed hydrophobicity is the most important determinant of mutagenicity, with steric and electronic parameters secondary. QSAR was also useful in studying carcinogenicity and mutagenicity of various amines, with a significant correlation between mutagenic and carcinogenic potencies. Lipophilicity influences the bio-concentration of pesticides in the food chain. (12)

CONCLUSION

Quantitative Structural Analysis (QSAR), particularly Hansch analysis, and its application in drug design. QSAR is often seen as a predictive tool, but its importance extends beyond its predictive potential. This has helped in assimilating more sophisticated computer-aided drug design techniques like molecular graphics, 3D QSAR, and multivariate analysis. QSAR's importance will be appreciated more in the years to come. Despite attempts to study chiral drugs using QSAR, results have varied. Descriptors with the best correlation provide information about functional groups in tested compounds' structures, suggesting that altering these groups can enhance pharmacological activity or physico-chemical properties. This study focuses on understanding the biological activities of drug molecules by examining the properties associated with their structures.

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