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IMPORTANCE OF STRUCTURAL ACTIVITY RELATIONSHIP IN COMPUTER AIDED DRUG DESIGN - A REVIEW

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ABSTRACT

Quantitative structure-activity relationships (QSAR) represent an attempt to correlate structural or property descriptors of compounds with activities. These physicochemical descriptors, which include parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods. Activities used in QSAR include chemical measurements and biological assays. QSAR currently are being applied in many disciplines, with many pertaining to drug design and environmental risk assessment. Current Computer-Aided Drug Design aims to publish all the latest developments in drug design based on computational techniques. The field of computer-aided drug design has had extensive impact in the area of drug design. Current Computer-Aided Drug Design is an essential journal for all medicinal chemists who wish to be kept informed and up-to-date with all the latest and important developments in computer-aided methodologies and their applications in drug discovery. Each issue contains a series of timely, in-depth reviews written by leaders in the field, covering a range of computational techniques for drug design, screening, ADME studies, etc., providing excellent rationales for drug development.

INTRODUCTION

Structure–activity relationship (SAR)

The SAR is the relationship between the chemical or 3D structure of a molecule and its biological activity. The analysis of SAR enables the determination of the chemical groups responsible for evoking a target biological effect in the organism. This allows modification of the effect or the potency of a bioactive compound (typically a drug) by changing its chemical structure [1]. Medicinal chemists use the techniques of chemical synthesis to insert new chemical groups into the biomedical compound and test the modifications for their biological effects. This method was refined to build mathematical relationships between the chemical structure and the biological activity, known as quantitative structure - activity relationships (QSAR).A quantitative structural activity relationship is otherwise called as structure affinity relationship (SAFIR) [2].

Computer-aided drug design (CADD)

In the last few years, the paradigms of drug research have changed significantly. New technologies like Computer based drug design (CADD), Cheminformatics and high-throughput screening increase our chances to find new lead structures, with less effort than by dedicated synthesis and conventional screening. Computational methods can be used to predict or simulate how a particular compound interacts with a given protein target. They can be used to assist in building hypotheses about desirable chemical properties when designing the drug and moreover, they can be used to refine and modify drug

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candidates. You all are most welcome to share your experience/expertise as well as research problems regarding CADD and medicinal chemistry at this platform [3]. Computer-aided drug design methods are effective tools for drug discoveries. It is only small number of compounds that are required to be synthesized in practice, if the computer-aided drug design methods are used to predict the activities of the compounds. The methods are based on the interaction theory between drugs and their target proteins. Steric, electrostatic and hydrophobic complementarities are important in the interaction between the drug and the target protein. When three-dimensional structures of target proteins are known, the method is called as a structure-based drug design, while in case that the structures are unknown, a ligand-based drug design approach is employed for the computer-aided rational drug design. In the computer-aided structure-based drug design, it is important to build up the three-dimensional structure of drug-protein complex and to calculate a binding affinity of the drug to the protein [4, 5].

Importance of CADD

Computer-aided drug design (CADD) also called computer-assisted molecular design (CAMD), represents more recent applications of computers as tools in the drug design process [6-8]. In considering this topic, it is important to emphasize that computers cannot substitute for a clear understanding of the system being studied. That is, a computer is only an additional tool to gain better insight into the chemistry and biology of the problem at hand. In most current applications of CADD, attempts are made to find a ligand (the putative drug) that will interact favorably with a receptor that represents the target site. Binding of ligand to the receptor may include hydrophobic, electrostatic, and hydrogen-bonding interactions. In addition, solvation energies of the ligand and receptor site also are important because partial to complete desolvation must occur prior to binding. The binding of ligand with receptors was shown in Figure 1.

METHODOLOGY

DRUG & DRUG DESIGN

- A chemical substance that affects the processes of the mind or body.
- Any chemical compound used in the diagnosis, treatment or prevention of disease or other abnormal conditions.
- A substance used recreationally for its effects on the central nervous system, such as a narcotic.
- A small molecule which interacts with target.

Drug design

Design is more rational and targeted and discovery. But design and discovery share a lot of information regarding pharmaceutical aids [9, 10].

Types of Drug Design

Ligand based drug design, Structure based drug design.

LIGAND BASED DRUG DESIGN

- These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target.
- Ligand based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interet.
- In other words, a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target [11].
- Alternatively a quantitative structure-activity relationship (QSAR) in which a correlation between calculated properties of molecules and their experimentally determined biological activity may be derived. The QSAR relationships in turn may be used to predict the activity of new analogs.

Fig 1. Ligand binding with receptor

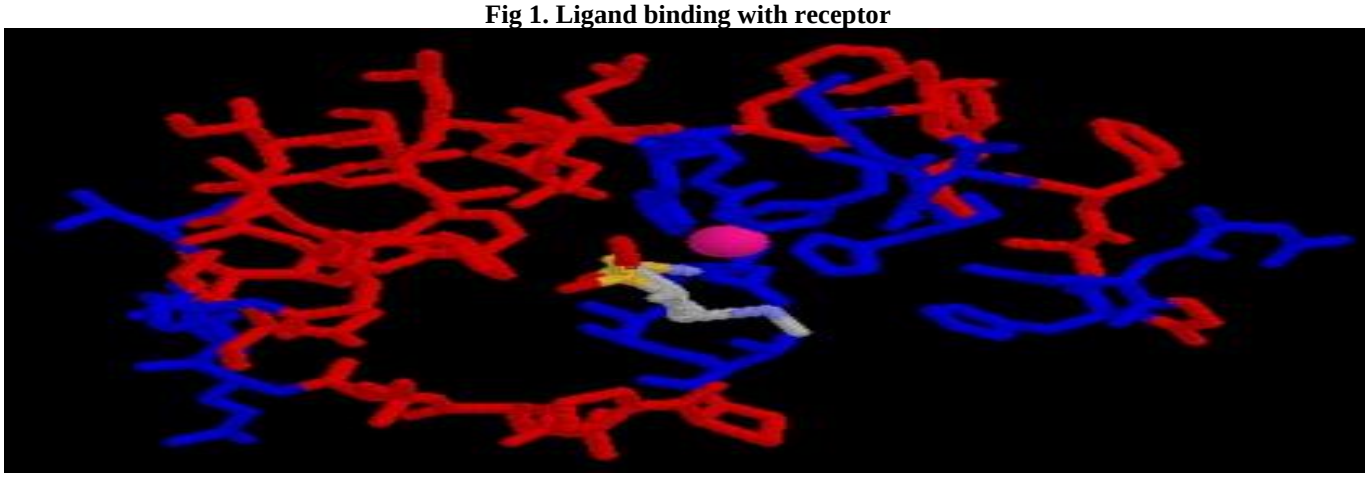


Fig 2. Two pathway to drug discovery and drug design

Structure based known receptor **Structure based unknow receptor**

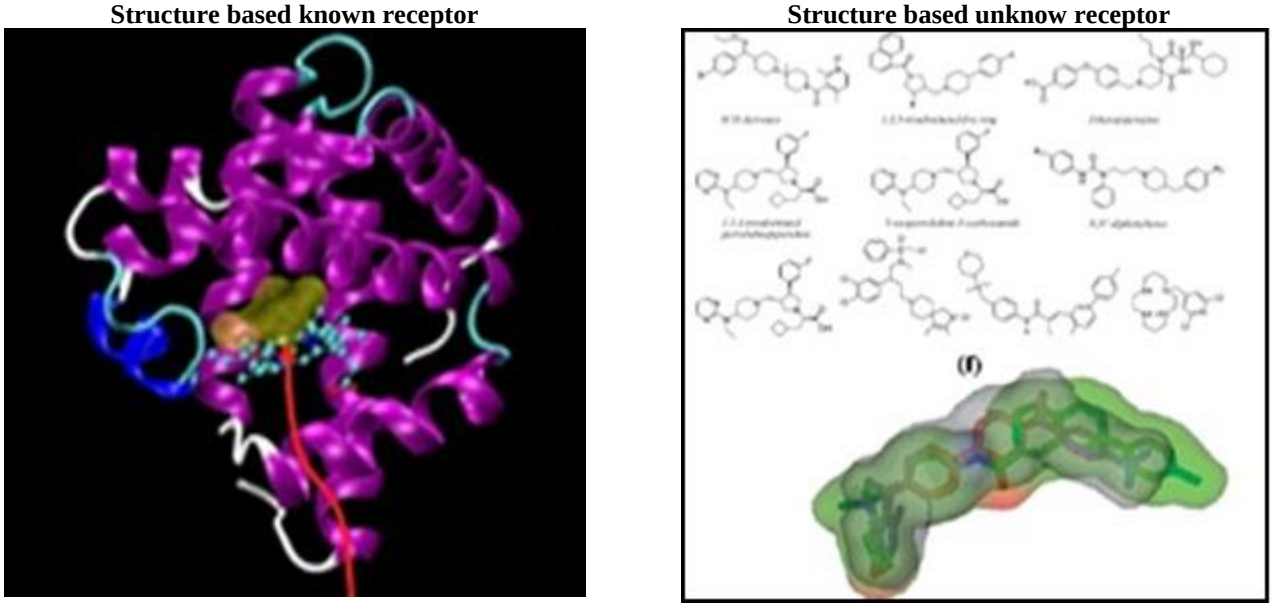
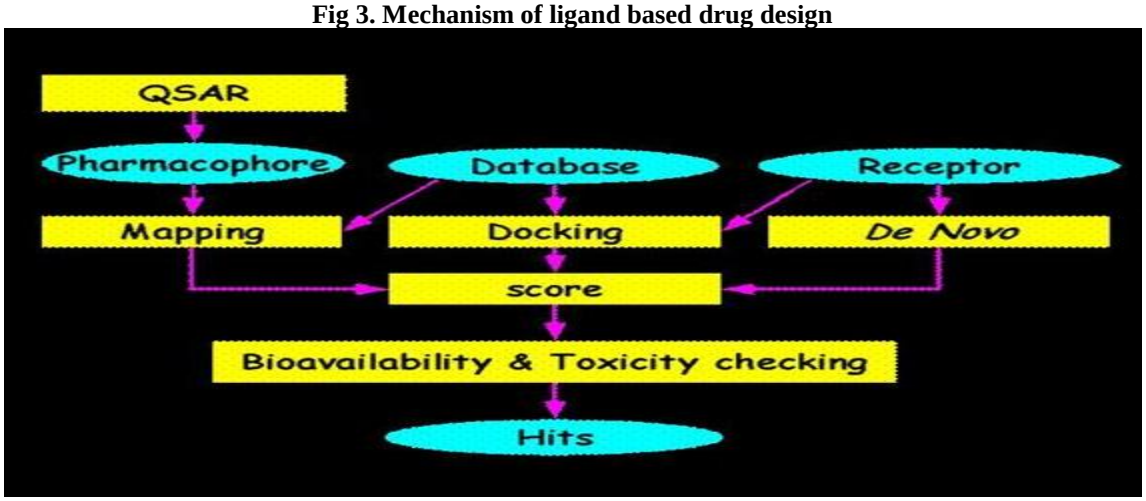


Fig 3. Mechanism of ligand based drug design



SUMMARY AND CONCLUSION

SAR believes that the biological activity of a compound is a result of its chemical structure. Within the SAR approach, the descriptor variable is not physically measured. Computed, therefore, they are easy and cheap to generate even for large molecular sets.In computational structure-based drug design, the scoring functions are the cornerstones to the success of design, discovery. Many approaches have been explored to improve their reliability and accuracy, leading to three families of scoring functions: force-field-based, knowledge-based, and empirical. SAR is a way of finding a simple equation that can be used to calculate some property from the molecular structure of a compound. SAR attempt to correlate structural molecular features (descriptors) with physicochemical properties such as biological activities for a set of compounds, by means of statistical methods, as a result, a simple mathematical relationship is established.

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