Drug Design and Strategies in Drug Design

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***Abstract*: Drug design is a crucial stage in drug discovery and drug development. It is the method of designing a medication in a manner that there is maximum interaction between the drug and the target with least side effects. The paper begins with giving a brief introduction of drug design. Furthermore, the paper will delve into the various types of drug designs. Then, it will look at the strategies of drug design that improve the drug-target interactions.**

***Index Terms*: Drug design, Target, Receptor, Drug-Target Interaction, Drug, Target, Ligand, CADD**

I. INTRODUCTION

Development in the field of medicine and advancement in biosciences, helped the scientist to understand the functions of the human body at molecular level. This led the pharmaceutical industry to design a therapeutic drug which can interact with the target or receptor with high binding capacity resulting in minimum side effects. Drug design is the innovative method of discovering new medicines based on the knowledge of a target. In simple words, it involves the designing of molecules in such a manner that it complements the shape and charge of the target with which it interacts and binds. In today's times, there is frequent reliance on computer modelling techniques and bioinformatics approaches. There are various objectives to be considered while designing a drug namely, ease of synthesis, maximum interaction between the lead compound and target molecule, minimum side effects and safety and effectiveness of the drug. The steps involved in drug design are complex and involve several tedious years of unending experiments performed by the scientist. The estimated cost for designing of the drug is exorbitant. It takes approximately 1 billion dollars for drug synthesis and 7-12 years for the drug to be marketed. The ways of designing the drug include Ligand based drug design, structure-based drug design and computer aided drug design (CADD). Apart from this, there exist multiple strategies to improve the interactions between the drug and the respective target.

II. TYPES OF DRUG DESIGN

Drug design can be classified into the following types:

Ligand Based Drug Design

Ligand based drug design is the indirect method for the designing of the therapeutic drugs. It is based on the understanding of ligand that binds with the target and makes use of pharmacophore model. Under pharmacophore model, the model of biological target is made based on the knowledge of the binding site. This model is used to design new ligands that interact with the target to give maximum ligand-target interaction. The potential ligands thus obtained are screened based on those fitted in the active site of the biological target. Ligand based drug design makes use of Quantitative Structure Activity Relationship (QSAR) that gives the mathematical relationship between the chemical structure of ligand molecule and its biological activity which is further used to know the activity of the new drug analogues. Ligand based drug design makes use of the molecular structure of the ligands where the structure of the target is not known.

Structure Based Drug Design

Structure based drug design is also referred to as direct drug design. It is based on the knowledge of the 3D structure of the receptor molecule obtained through Nuclear Magnetic Resonance (NMR) or X-ray crystallography. It deals with the known target molecules. Thus, the understanding of the structure of the target, the drug can be designed based on the selective binding sites of the target which results in maximum drug target interaction.

Computer Aided Drug Design (CADD)

The process of drug design is challenging, time consuming and costly. Recent years have witnessed the development of new computer techniques that have helped in speeding up of drug design. CADD is also known as silico screening. It makes use of molecular mechanics which identifies the conformation of small molecule and models the conformational changes in the biological target. This results in maximum interaction between the molecule and the target. The different approaches used under CADD are:

- *Target with known 3D structure:* It begins with the 3D structure of the target molecule being identified by NMR technique or x-ray crystallography. Then, High Throughout Screening (HTS) is used for further identification of the target molecule and data analysis. This helps in the recognition of the probable drug molecule. The data base collected leads to the formation of a drug bank where the potential drugs are collected. Finally, the structure of the drug is modified using CADD to ensure effective and selective interaction with the target. Stronger the drug target interaction, higher the biological potency of the same.

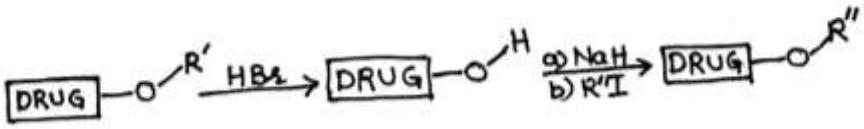
- *Target with unknown 3D structure:* Biological screening is carried out to identify the potent molecules which can be probable potential drug. This is followed by target identification through docking. Docking accounts for one of the most applied virtual methods for screening. It is the identification of receptor for a given ligand molecule among last number of receptors. Furthermore, evaluation is carried out wherein assesses binding affinity between the drug and the target through docking. The knowledge of CADD looks into the therapeutic activity of the drug on molecular basis and finally the 3D structure of the drug is evaluated through CADD technique. However, it must be noted that in practice the computational chemistry is not accurate. As a result, the design and synthesis must be carried out several times before a potential drug is designed. An example of a drug designed through CADD is carbonic anhydrase inhibitor, dorzolamide. Another example is Imatinib.

III. STRATEGIES IN DRUG DESIGN

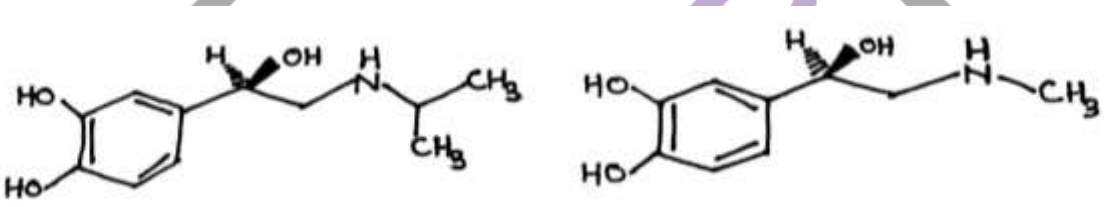
Drug design strategies are used to improve the binding interactions between the drug and its target. Such improvements increase the activity of the drug and may reduce side effects if the interactions between the drug and the target are selective. The strategies are as follows:

Variation of Substituents

If certain alkyl groups in the drugs are substituted by other substituents, these might increase the drug target interaction and increase the activity of the drug.



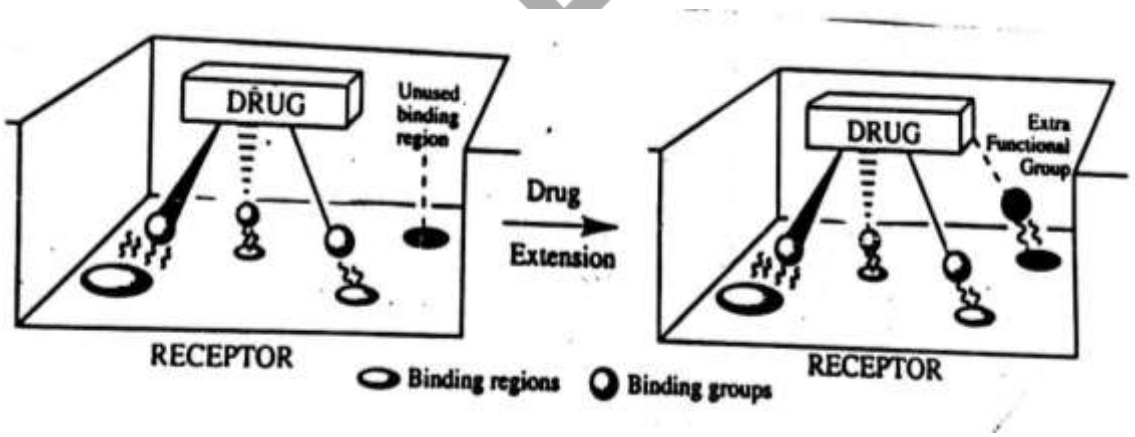
For example, isoprenaline is an analogue of adrenaline where a methyl group in adrenaline has been replaced by an isopropyl group resulting in selectivity of adrenergic β-receptors over adrenergic a-receptors.



Isoprenaline *Adrenaline*

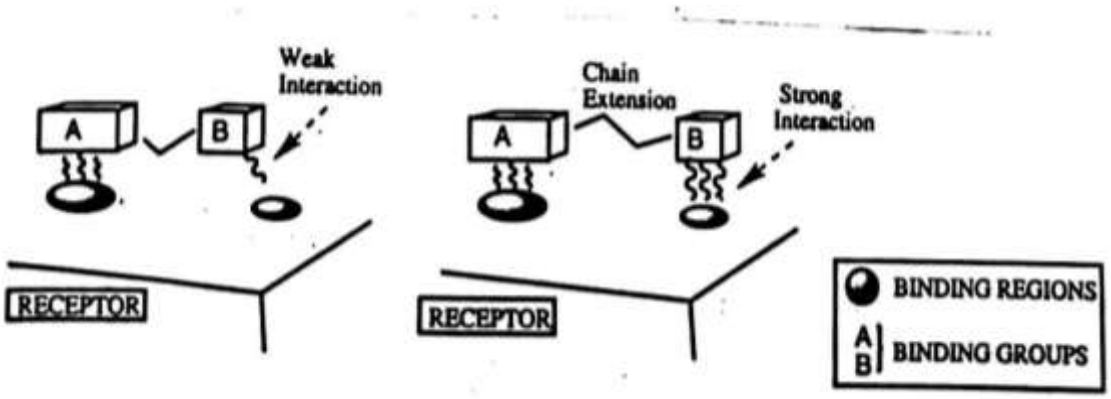
Extension of the Structure

The strategy of extension involves the addition of another functional group to the lead compound for extra binding interaction with the target. Lead compound may bind with all the functional group present in it with the available binding groups in the receptor. However, it is possible that they do not interact with all the binding groups that are available. For example, a lead compound may bind with three binding sites but fail to interact with fourth binding site. In this case an extra functional group can be added for the fourth interaction.



Chain Extension / Contraction

Some drugs have two binding groups, which are equally important and are linked by a chain and the length of the chain is not ideal for best interaction between the drug and the target. Shortening or lengthening the chain length can increase the interaction.



Ring Expansion / Contractions

If a drug has a ring, we can synthesize its analogues where one of the rings can be expanded or contracted by one unit, to increase the drug-target interaction. For example, in the development of anti-hypertensive agent Cilazaprilat, by carrying out its ring expansion it has better interaction with the binding site.

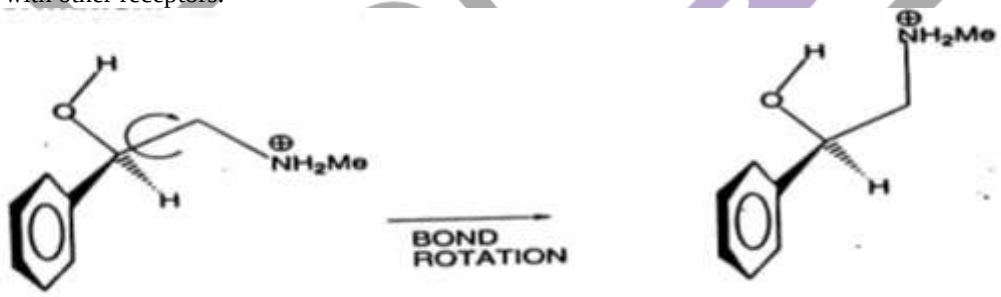
Isosteres

Isosteres have been used in drug design to vary the character of the molecule with respect to features like polarity, and electronic distribution and that results in better drug-target interaction. For example, if we replace hydrogen by fluorine in anti-tumor drug to get 5 fluorouracil the presence of fluorine in the drug makes it to have better drug-target interaction.

Rigidification of the Structure

Rigidification of the structure is used to increase the activity of a drug or to reduce its side effects. If we take any lead compound, bond rotation can lead to large number of conformation or shapes, confirmation I is accepted by the receptor (target). Other conformation II may interact with other receptors present in the body and this produces side effects. The strategy of rigidification is to lock the drug molecule into rigid conformation such that it cannot take up other shapes or conformations. Consequently, other receptor interactions and side effects are eliminated.

By locking the drug into active conformation, the drug is ready to fit its target receptor site and doesn't change its conformation and thus cannot interact with other receptors.



Conformation I

To lock conformation I which interacts with target receptor, a ring is incorporated in the structure.

Conformation I

Molecular

So far, we have discussed the different steps/strategies involved in drug design, where we have binding groups of the drug and binding site of enzymes in the target molecule which interact to give maximum drug-target interaction. We can obtain an X-ray structure of the protein by crystallography with the ligands bound to the binding site. This structure can be downloaded into a computer and the complex can be studied by molecular modelling to see how ligands bind. Once the important binding groups are

identified modeling software are used to remove these groups and potential drugs can be fit in using various permutations and combinations. For example, Oxamniquine is a third world drug for the treatment of Schistosomiasis, this disease is transmitted by swimming in infected water. The disease is carried by a snail whose flukes can penetrate the human skin. The development and design were done by the carrying out the steps mentioned above.

IV. CONCLUSION

Drug design is a complex process involving various steps. It involves several continuous and challenging experiments. The costs for designing a drug are excessive and considering that there is no guarantee of successful results, the price might be seen to be unreasonable. The methods involved at each step are laborious and time-consuming resulting in many years before the drug is marketed. It may appear that with the development of technology, the process may have become extremely short. Despite immense advancement in technological innovation and usage of computers including CADD, the drug design is still a very long process in order to ensure the safety and effectiveness of the drug. To improve the interaction between the drug and the target, there exists a variety of strategies. Thus, it can be concluded that though drug design is an extensive process but at the same time it is facilitated by several strategies, technologies and methods that speed up the process.

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