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A REVIEW ON Drug Design

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Abstract:- Drug design is applied in the discovery of novel lead drugs. Its rapid development is mainly attributed to the tremendous advancements in the computer science, statistics, molecular biology, biophysics, biochemistry, medicinal chemistry, pharmacokinetics and pharmacodynamics experienced in the last few decades. The promising feature that characterizes the application of rational drug design is that it uses for developing potential leads in drug discovery all known theoretical and experimental knowledge of the system under study. The utilization of the knowledge of the molecular basis of the system ultimately aims to reduce human power cost, time saving and laboratory expenses in the drug discovery. In this review paper various strategies applied for systems which include:

(i) Absence of knowledge of the receptor active site;
(ii) The knowledge of a homology model of a receptor,
(iii) The knowledge of the experimentally determined (i.e. X-ray crystallography, nmr spectroscopy) coordinates of the active site of the protein in absence and
(iv) The presence of the ligand will be analyzed.

Key words :- Principle of drug design , ligand based drug design, structure based drug design, rational drug design , computer aided drug design.

Introduction:

According to FDA (Food and Drug Administration), a drug is any substance (other than a food or device), which is used in the diagnosis, cure, relief, treatment or prevention of disease, or intended to affect the structure or function of the body. This definition is used for legal purposes, but in a lay man's term 'drug' is a pharmaceutical biomolecule or a combination of molecules that affect the body and its processes. Drug discovery starts by studying the biochemistry of the disease and the possible ways to develop a therapeutic molecule for curing the disease. So the initial outcome from the study would be the identification and analysis of specific receptors (targets) in the specialized area. Then the identified targets must be modulated to alter their activity by performing protein receptor/target activity.

Finally, drug scientist identifies the therapeutic compound in order to interact with the receptor, and the therapeutic compound could be either synthetic or naturally available.

Objectives of Drug design

- To improved the activity and properties of the lead compound
- It is time saved techniques.
- There strategies to overcome toxic side effects.

Purpose Of Drug Design…….

- To Improve The Selectivity Of Action.
- To Improve ADME Profile (Absorption, Distribution, Metabolism or Elimination)
- To Obtain Drug Having Most Desirable Properties Than The Lead Compound in Potency, Toxicity And Specificity.
- To Reduce The Cost Of Production.
- Exploitation Of Side Effects Of Existing Drug.

PRINCIPLE OF DRUG DESIGN :

Lipinski's Rule of Fives :

The rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most medication Lipinski's rule of five also known as the Pfizer's rule of five or simply the Rule of five (RO5) is a rule of thumb to evaluate drug drugs are relatively small and lipophilic molecules The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion("ADME"). However, the rule does not predict if a compound is pharmacologically active The rule is important to keep in mind during drug discovery when a pharmacologically active lead structure is optimized step-wise to increase the activity and selectivity of the compound as well as to insure drug-like physicochemical properties are maintained as described by Lipinski's rule. Candidate drugs that conform to the RO5 tend to have lower attrition rates during clinical trials and hence have an increased chance of reaching the market.

Components of the rule :

Lipinski's rule states that, in general, an orally active drug has no more than one violation of Jithe following criteria:

1.Not more than 5 hydrogen bond donors (nitrogen or oxygenatoms with one or more hydrogenatoms.

2.Not more than 10 hydrogen bond acceptors (nitrogen or oxygenatoms)

A molecular mass less than 500 daltons.

3.Molecular weight Less than 500.

4.An octanol-water partition coefficient log P not greater than 5.

Pharmacokinetics of drug design

- ❖ Drugs must be polar – to be soluble in aqueous conditions
- ❖ To interact with molecular targets
- ❖ Drugs must be 'fatty' – to cross cell membranes to avoid rapid excretion
- ❖ Drugs must have both hydrophilic and lipophilic characteristics
- ❖ Many drugs are weak bases with pKa 's 6-8.

Approaches for drug design

The various approaches used in drug design include the following..

1) Random screening of synthetic compounds or chemicals and natural products by bioassay procedures.
2) Novel compounds preparation based on the known structures of biologically active, natural substances of plant and animal origin, i.e., lead skeleton.
3) Preparation of structural analogs of lead with increasing biological activity and

Application of bioisosteric principle.

The current trend in the drug design is to develop new clinically effective agents through the structural modification of lead nucleus. The lead is a prototype compound that has the desired biological or pharmacological activity but may have many undesirable charachteristics, like high toxicity, other biological activity, insolubility or metabolism problems. Such organic leads once identified, are easy to exploit. This process is rathe straightforward. The real test resides with the identiication of such lead real test resides with the identification of such lead bioactive positions on the basic skeleton of such leads.

Types of drug design

- Ligand based drug design
- Structure based drug design
- Rational drug design
- Computer aided drug design

1) Ligand based drug design

Ligand-based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest. 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. 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. 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. These QSAR relationships in turn may be used to predict the activity of new analogs..

2) Structure-based Drug Design:

Structure-based drug design (or direct drug design) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy.[5]If an experimental structure of a target is not available, it may be possible to create a homology modelof the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist. Alternatively various automated computational procedures may be used to suggest new drug candidates.

As experimental methods such as X-ray crystallography and NMR develop, the amount of information concerning 3D structures of biomolecular targets has increased dramatically. In parallel, information about the structural dynamics and electronic properties about ligands has also increased. This has encouraged the rapid development of the structure-based drug design. Current methods for structure-based drug design can be divided roughly into two categories. The first category is about “finding” ligands for a given receptor, which is usually referred as database searching. In this case, a

large number of potential ligand molecules are screened to find those fitting the binding pocket of the receptor. This method is usually referred as ligand-based drug design. The key advantage of database searching is that it saves synthetic effort to obtain new lead compounds. Another category of structure-based drug design methods is about "building" ligands, which is usually referred as receptor-based drug design. In this case, ligand molecules are built up within the constraints of the binding pocket by assembling small pieces in a stepwise manner. These pieces can be either individual atoms or molecular fragments. The key advantage of such a method is that novel structures, not contained in any database, can be suggested.

2) **Rational drug design :**

In contrast to traditional methods of drug discovery, which rely on trial-and-error testing of chemical substances on cultured cells or animals, and matching the apparent effects to treatments, rational drug design begins with a hypothesis that modulation of a specific biological target may have therapeutic value. In order for a biomolecule to be selected as a drug target, two essential pieces of information are required. The first is evidence that modulation of the target will have therapeutic value. This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states. The second is that the target is "drugable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule.

Once a suitable target has been identified, the target is normally cloned and expressed. The expressed target is then used to establish a screening assay. In addition, the three-dimensional structure of the target may be determined.

The search for small molecules that bind to the target is begun by screening libraries of potential drug compounds. This may be done by using the screening assay (a "wet screen"). In addition, if the structure of the target is available, a virtual screen may be performed of candidate drugs. Ideally the candidate drug compounds should be "drug-like", that is they should possess properties that are predicted to lead to oral bioavailability, adequate chemical and metabolic stability, and minimal toxic effects. Several methods are available to estimate druglikeness such as Lipinski's Rule of Five and a range of scoring methods such as Lipophilic efficiency. Several methods for predicting drug metabolism have been proposed in the scientific literature, and a recent example is SPORCalc. Due to the complexity of the drug design process, two terms of interest are still serendipity and bounded rationality. Those challenges are caused by the large chemical space describing potential new drugs without side-effects.

4) Computer-Aided drug design

Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically active molecules. The most fundamental goal is to predict whether a given molecule will bind to a target and if so how strongly. Molecular mechanics or molecular dynamics are most often used to predict the conformation of the small molecule and to model conformational changes in the biological target that may occur when the small molecule binds to it. Semi-empirical, ab initio quantum chemistry methods, or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability, etc.) of the drug candidate that will influence binding affinity.

Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge-based scoring function may be used to provide binding affinity estimates. These methods use linear regression, machine learning, neural nets or other statistical

techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target.[15][16]

Ideally the computational method should be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to synthesized. The reality however is that present computational methods are imperfect and provide at best only qualitatively accurate estimates of affinity. Therefore in practice it still takes several iterations of design, synthesis, and testing before an optimal molecule is discovered. On the other hand, computational methods have accelerated discovery by reducing the number of iterations required and in addition have often provided more novel small molecule structures.

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