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REVIEW ARTICLE ON DRUG DESIGN

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ABSTRACT
Pharmaceutical drug discovery is an expensive and time consuming process. The development of a drug from an initial idea to its entry into the market is a very complex process which can take around 5-10 yrs. and cost is very high upto billion. It is an development process involves use of variety of computational techniques, such as structure activity relationship, quantitative structure activity relationship, molecular mechanics, quantam mechanics, molecular dynamics and drug protein docking. The idea for a new development can come from a variety of sources which include the current necessities of the market, new emerging diseases, academic and clinical research, commercial sector. The pharmaceutical industry is under pressure in developing cost effectiveness drug molecule from the previous knowledge and established Quantitative Structure Activity Relationship. The structure based design is one of reliable and promising techniques used in drug designing. In drug design, the main aim is to find out the three dimensional structure of pharmacologically significant receptor ligand complexes. The aim of this review is to give an overview on the rational drug design approaches with a case study on drug discovery for influenza A virus, HER2 Receptor, targeting dopamine D3 receptor, purpose, and applications of QSAR. This article highlight the benefits and promises of developing tools for drug discovery.

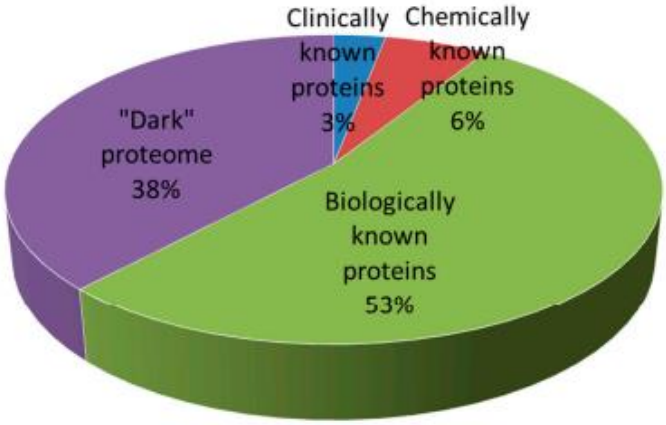
KEYWORDS: OSAR, docking, pharmacore.

INTRODUCTION
Drug design is an integrated developing discipline which portends an era of "Tailored drug". It is an development process involves use of variety of computational techniques, such as structure activity relationship, quantitative structure activity relationship(QSAR), molecular mechanics, quantam mechanics, molecular dynamics and drug protein docking. The QSAR establish a statistical relationship between biological activity or environmental behaviour of the chemicals of interest and their structural properties. QSAR predict chemical behaviour of directly from chemical structure and stimulate adverse effect in cells, tissues and lab animals minimizing the need to use animals test to comply with regulatory requirements for human health and ecotoxicology.[1]

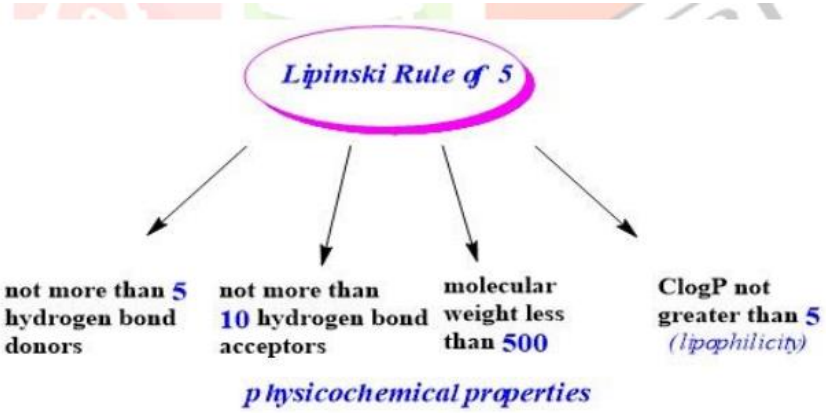
The biological activity may be "Positive" as in drug design or "Negative" as in toxicology. Drug design frequently but not necessarily relies on computer modelling is often referred to as "Computer aided drug design". Drug design that relies on the knowledge of three dimensional structure of the biomolecular target is known as structure based drug design. Drug design is the intensive process of finding new medications based on the knowledge of a biological target. despite advances in biotechnology and understanding of biological systems, drug discovery is still lengthy, costly, difficult, and inefficient process with a high attrition rate of new therapeutic discovery.[2]

DRUG DESIGN- Historical notes There were several major achievements in the science of drug design that made it the main approach in the current and the future drug discovery. The first of them is the understanding of

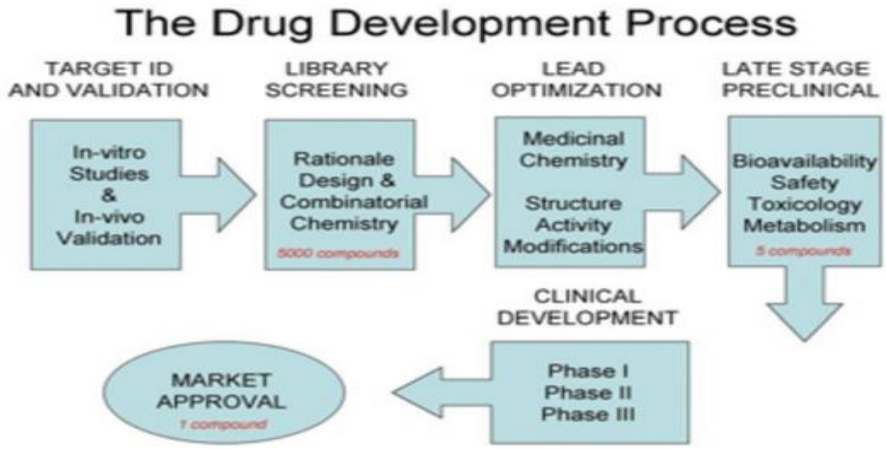
drug–receptor recognition. In the early 1890s, Emil Fisher compared the drug–receptor interaction to the key and lock interplay. He considered that both the drug and the receptor interact as solid bodies without changing their conformations.[3] Lately, Daniel Koshaland suggested that both molecules do undergo conformational changes during interaction and adopt the most suitable conformation in order to connect each other.



Principles of Drug design: Lipinski's Rule of Fives: Lipinski's rule also known as the Pfizer rule of five or simply the rule of five is a rule of thumb to evaluate drug likeness or determine chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans .The rule was formulated by Christoper in 1997, based on the observation that most medication drugs are relatively small and lipophilic molecules.[4] The rule describes molecular properties for drugs pharmacokinetics in the human body including their ADME.



DRUG DEVELOPMENT

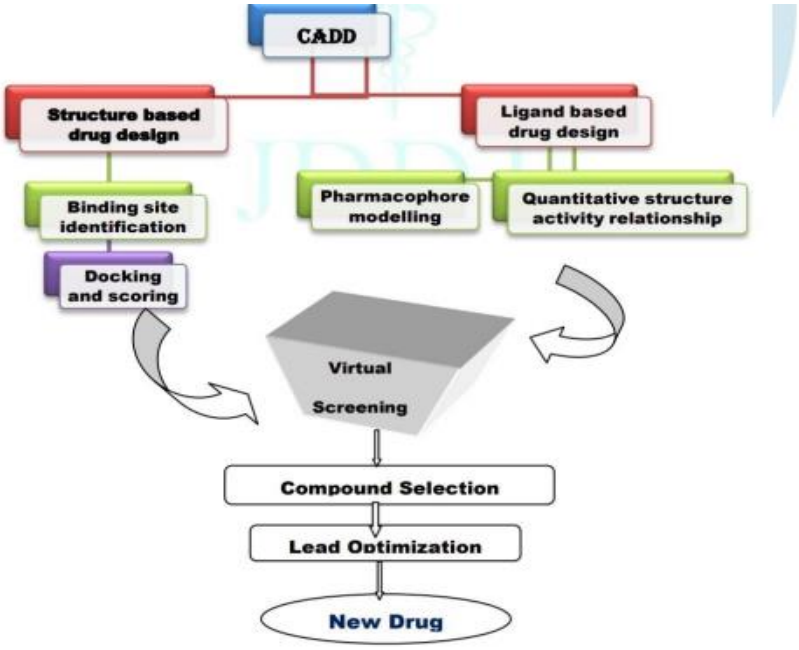


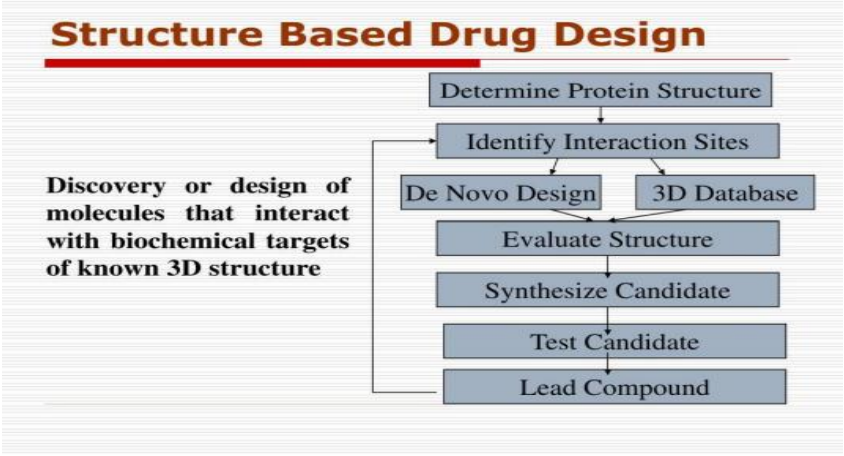
CADD: Computer Aidded Drug Design

The main categories of CADD techniques are: CAD Computer-aided design is the process of creating and documenting a product utilising software. Engineering drawings need the use of visual symbols such point lines, curves, planes, and shapes. In essence, it gives a detailed graphical depiction of each component's explanation. The following are the two basic methodologies for drug design with CADD: Direct or structure-based medication design 2. Ligand based drug design / indirect approach.[5]

There are two major types of CADD

1) Structure based drug design
2) Ligand based drug design





Pharmacophore modeling

- Ehrlich initially used the term "pharmacophore" in 1909, defining it as "A molecular framework that transmits (phoros) the main features important for a drug's (pharmacon) biological effect." Pharmacophore modelling:
- The Pharmacophore technique hasn't altered in decades, but computer technologies have enabled it to develop concurrently.[6]
- This study lightens the strain on medicinal chemists by aiding in the selection and improvement of the lead molecule. There are further programmes, such as DS visualizer® and ligand scoutR. A vital computational technique that supports drug development in the absence of a macromolecular target structure is ligand-based pharmacophore modelling.
- The pharmacophore concept was soon used for rational drug design procedures and has since been regularly applied to virtual screening.
- Even in the lack of a 3D molecular structure for a particular receptor of therapeutic relevance, the concept is quite powerful.
- Scopes of Pharmacophore Modeling Making ligands and finding novel medications are basic jobs for a medicinal chemist.

Ligand: • The idea of similarity, which states that if ligand structures are similar, they may display comparable physical, chemical, and biological properties, is the foundation for drug design.[7]

There are two ways to conclude a pharmacophore:
1. Direct styles
2. Circular styles

Combinatorial chemistry
Combinatorial chemistry is a powerful approach used in drug design and discovery, in which large numbers of molecules are synthesized simultaneously or in a rapid sequence to identify compounds with desirable biological properties.
A.) Solid-phase synthesis: In this method, the starting material is attached to a solid support, and various reagents are added to create a library of molecules.[8] After synthesis, the compounds are cleaved from the support and screened for their biological activity.
B.) Solution-phase synthesis: In this method, the synthesis is carried out in a solution, and various reagents are added to create a library of molecules. The resulting mixture of compounds is then screened for biological activity

DOCKING
Instruction of docking: Molecular docking is a technique for computationally determining the architecture of compounds made up of two or more different molecules.

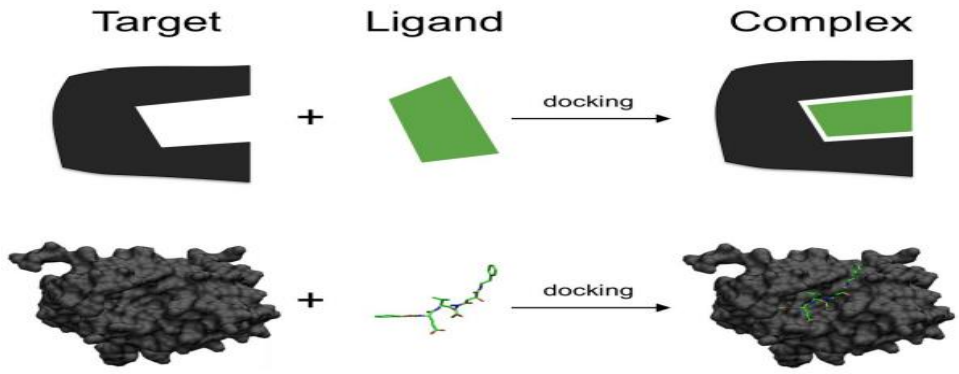
Predicting intended three-dimensional structures is the goal of docking investigations. Only appropriate incentive structures are generated by docking in and of themselves.

The structures that are most likely to exist in nature are sorted using scoring systems from among these possibilities.[9]

Definition of Docking
Reconstruction of the ligand structure, as well as its placement and orientation inside these sites (often referred to as pose), and evaluation of the binding affinity.[10]

Types of docking
1. Rigid docking: We are looking for a three-dimensional rearrangement of one of the compounds that produces the best match to the other compounds in terms of a scoring system, assuming that the compounds are rigid.

2. Flexible docking
Further advances in computing power made it feasible to simulate potential changes in the interior geometry of the interacting partners that may take place during the formation of a complex.



ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity.)
ADMET Evaluation function module is composed of a series of high-quality prediction models trained by multi-task graph attention framework. It enables the users to conveniently and efficiently implement the calculation and prediction of 17 physicochemical properties, 13 medicinal chemistry measures, 23 ADME endpoints, and 27 toxicity endpoints and 8 toxicophore rules (751 substructures), thereby selecting promising lead compounds for further exploration.[11]

Acyclic diene metathesis polymerization (ADMET) is a step growth polycondensation reaction which releases ethylene as a by product. Elimination of ethylene by applying vacuum to the reaction vessel is the driving force of the reaction. Polymerization occurs either in bulk at high temperature up to 190 °C or with the use of solvents at considerably lower temperatures via metathesis using an appropriate catalyst.

➢ QSAR
(Quantitative structure- activity relationship)
- A correlation between quantitative structure and activity Is a mathematical connection that uses an equation to relate measurable or calculable chemical attributes to a certain biological activity In order to apply these rules to assess the biological activity of novel compounds, QSAR seeks to establish a reliable link between molecular characteristics and biological activity.

- Acquiring knowledge of electronic effect, steric effect, and lipophilicity in QSAR.
- By changing the lead compound's chemical structure, it may be possible to create a more effective therapeutic agent by retaining or enhancing the desired pharmacologic impact while reducing undesirable pharmacological, physical, and chemical features.[12]

❖ **Steps**

1. Selection of Data set and extraction of structural/empirical descriptors
2. Variable selection,
3. Model construction and
4. Validation evaluation.

❖ **Parameter**

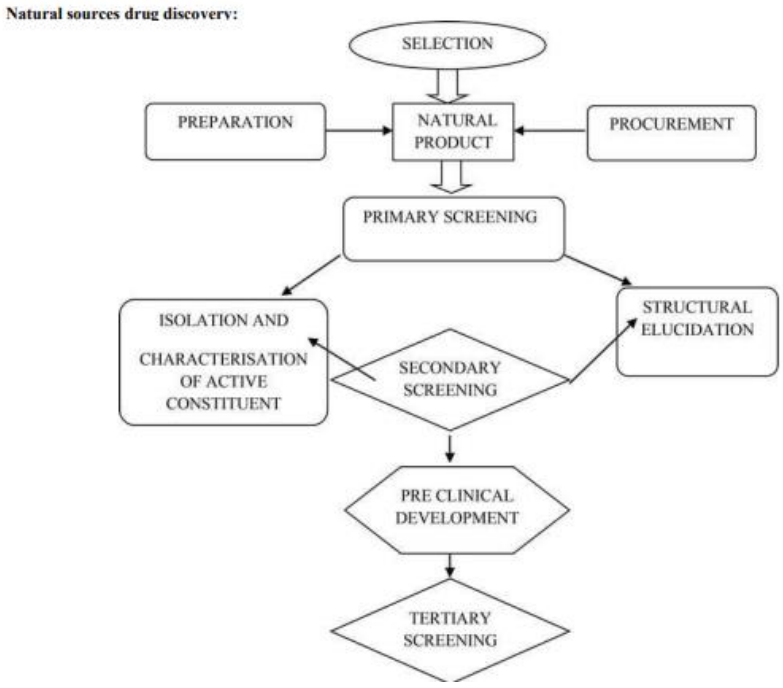
Various parameter uses in QSAR parameter

1. Lipophilic parameter – Partition coefficient molar refractivity.
2. Electronic parameter- Hammet constant
3. Steric parameter – Taft's constant verloop steric parameter.[13]

DRUGS FROM NATURAL SOURCES

A natural product is a chemical compound or substance produced by a living organism – found in nature. Natural sources of drug are –plant, animal, mineral, microorganisms. Plant sources are leaf, bark, fruit, seeds. Drugs obtained from animal sources are heparin, insulin, thyroxin, cod liver oil, antitoxic cera. Microorganism sources are bacterial, fungi, molds etc. mineral sources are ferrous sulphate, magnesium sulphate, sodium bi carbonate, aluminium hydroxide.

Animal sources are In the broadest sense, natural products include any substance produced by life. the field of organic chemistry, the definition of natural products is usually restricted to mean purified organic compounds isolated from natural sources that are produced by the pathways of primary or secondary metabolism.[14] Many secondary metabolites are cytotoxic and have been selected and optimized through evolution for use as "chemical warfare" agents against prey, predators, and competing organisms. synthetic analogs of natural products with improved potency and safety can be prepared and therefore natural products are often used as starting points for drug discovery.



CONCLUSION

Drug design is the process of coming up with novel treatments based on an understanding of a biological target. This review talks about several forms of drug discovery, lead discovery, lead modification, and drug design principles. An essential method of lead modification known as bioisosterism has been found to be effective in reducing toxicity or altering the activity of a lead. It may also play a key part in changing the pharmakinetics of a lead. When compared to computational approaches, the process of discovering new drugs through laboratory experimentation takes a long time and costs a lot of money.

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