Original Article

Computer Aided Drug Designing For Targeted Drug Delivery Systems

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DOI: 10.47750/pnr.2023.14.02.248

Abstract

Revelation and improvement of a modern sedate is generally known as an awfully complex handle which takes a parcel of time and assets. So presently a day computer helped medicate design approaches are used very broadly to extend the productivity of the drug discovery and improvement course. Various approaches of CADD are assessed as promising techniques concurring to their require, in between all these structure-based sedate plan and ligand-based drug plan approaches are known as exceptionally efficient and effective procedures in sedate revelation and development. These both strategies can be applied with atomic docking to virtual screening for lead recognizable proof and optimization. Within the recent times computational apparatuses are broadly utilized in pharmaceutical businesses and investigate ranges to improve viability and viability of drug discovery and advancement pipeline. In this article we deliver an outline of computational approaches, which is innovative prepare of finding novel leads and help within the prepare of medicate disclosure and development inquire about.

Keywords- Computer Aided Drug Discovery, Structure-Based Drug Design, Ligand-Based Drug Design, Virtual Screening, Molecular Docking.

INTRODUCTION

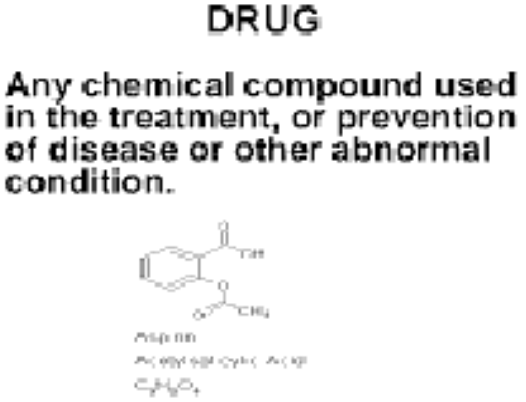
People in every civilization have used drugs of plant or animal origin to prevent and treat disease. The quest for substances to combat sickness and to alter mood and consciousness is nearly as basic as the search for food and shelter. Many drugs obtained from natural sources are highly valued, but most drugs used in modern medicine are the products of advances in synthetic organic chemistry and biotechnology. Thus a drug can be defined as a substance of either natural or synthetic origin that is used in the diagnosis, cure, relief, treatment, or prevention of disease or intended to affect the structure or function of the body. Thus a drug is a chemical that affects the body and its processes.

(i) Little History of Computer-Aided Drug Design

1960s Review the target-drug interaction
1980s Automation: High-throughput target/drug selection
1980s Databases (information technology):Combinatorial libraries
1980s Fast computers: Docking
1990s Fast computers: Genome assembly, genomic-based target selection
2000s Vast information handling: Pharmacogenomics

Drug- A chemical substance that affects the processes of the mind or body which is used in-
(a)Diagnosis-Medications for Diagnosis and Investigation refers to something that is used to determine the cause of an illness or disorder.
(b)Medication-your medical questions on prescription drugs, vitamins and Over the Counter medications. Find medical information, terminology and advice including.

(c)Treatment-Drug treatment can include behavioral therapy (such as cognitive-behavioral therapy or contingency management), medications, or their combination. The specific type of treatment or combination of treatments will vary depending on the patient's individual needs and, often, on the types of drugs they use.
(d)Prevantion of Disease or other Abnormal Condition- "Cancer" is the term given to a large group of diseases that vary in type and location but have one thing in common: abnormal cells growing out of control.



Drug design-Drug design, is the inventive process of finding new medications based on the knowledge of a biological target. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the molecular target with which they interact and bind. The drug is most commonly an organic small molecules that activates or inhibits the function of a biomolecules such as a proteins which in turn results in a therapeutic benefit to the patients.

Designed molecule should be

(a) Organic small molecule- A small molecule (or metabolite) is a low molecular weight organic compound, typically involved in a biological process as a substrate or product.
(b) Complementary in shape to the target- In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the bio-molecular target with which they interact and therefore will bind to it. A more accurate term is ligand design (i.e., design of a molecule that will bind tightly to its target).
(c) Oppositely charge to the bimolecular target-Drug design is an splendid inventive process of new medication on the basis of biological target. It is also known as rational drug design or rational design. That is the invention in medical history in order to yield significant therapeutic response. The drug is an organic molecule, when it is bind to target site it can either inhibit or activate the function of a biomolecule which results in therapeutic benefit. The drug design involves the design of such molecules that are similar to the bio molecular target site in shape and charge in order to bind to it. Drug design relies on the knowledge of the three dimensional structure of bimolecular targets.

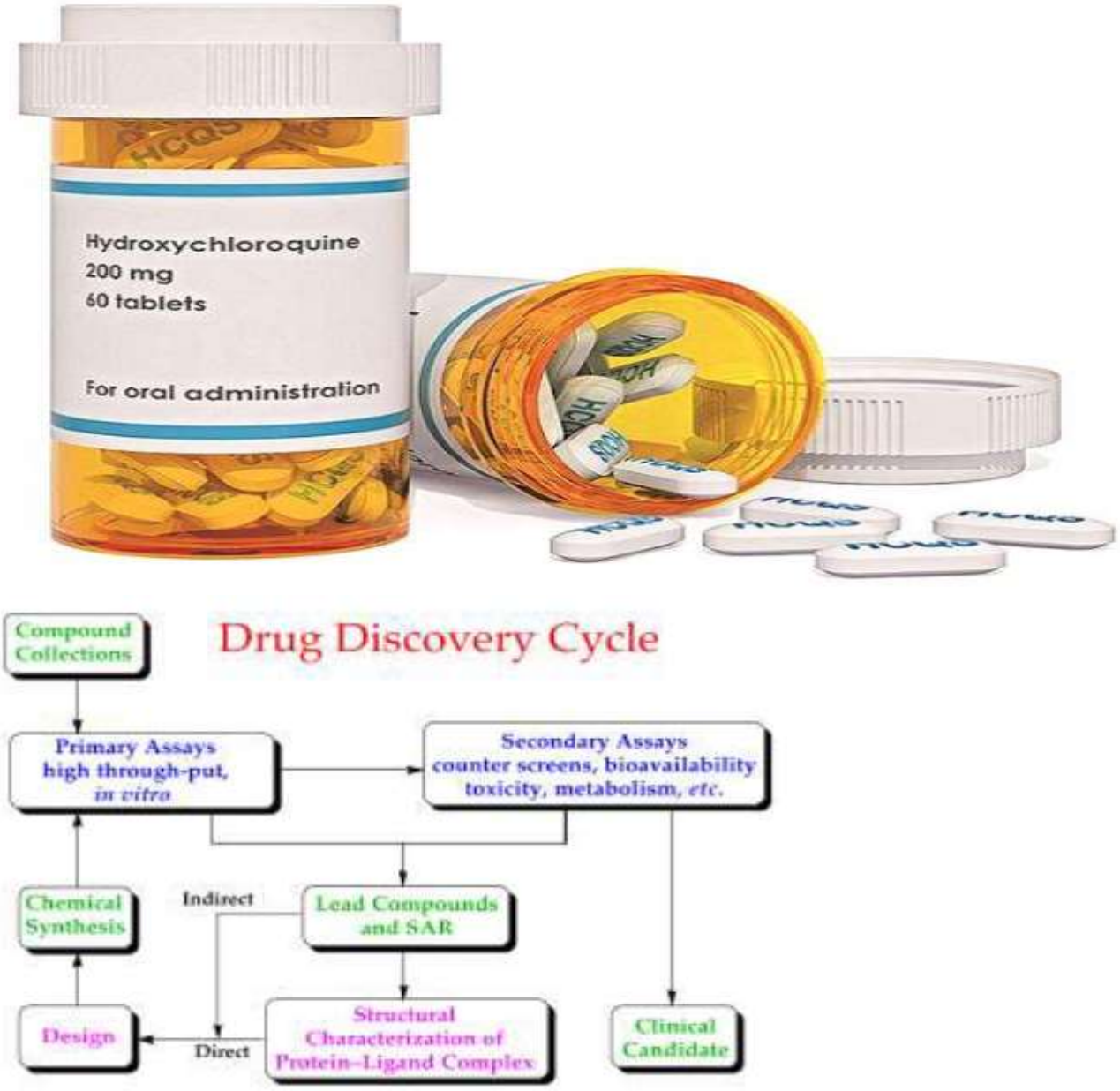


Fig- Drug Discovery Cycle

Types of drug design

(a)Ligand Based Drug Design-In LBDD, 3D structure of the target protein is not known but the knowledge of ligands which binds to the desired target site is known. These ligands can be used to develop a pharmacophore model or molecule which possesses all necessary structural features for bind to a target active site. Generally ligand-based techniques are pharmacophore based approach and quantitative- structure activity relationships (QSARs). In LBDD it is assumed that compounds which having similarity in their structure also having the same biological action and interaction with the target protein.

(b)Structure-based drug design- In SBDD, structure of the target protein is known and interaction or bio-affinity for all tested compounds calculate after the process of docking; to design a new drug molecule, which shows better interaction with target protein.

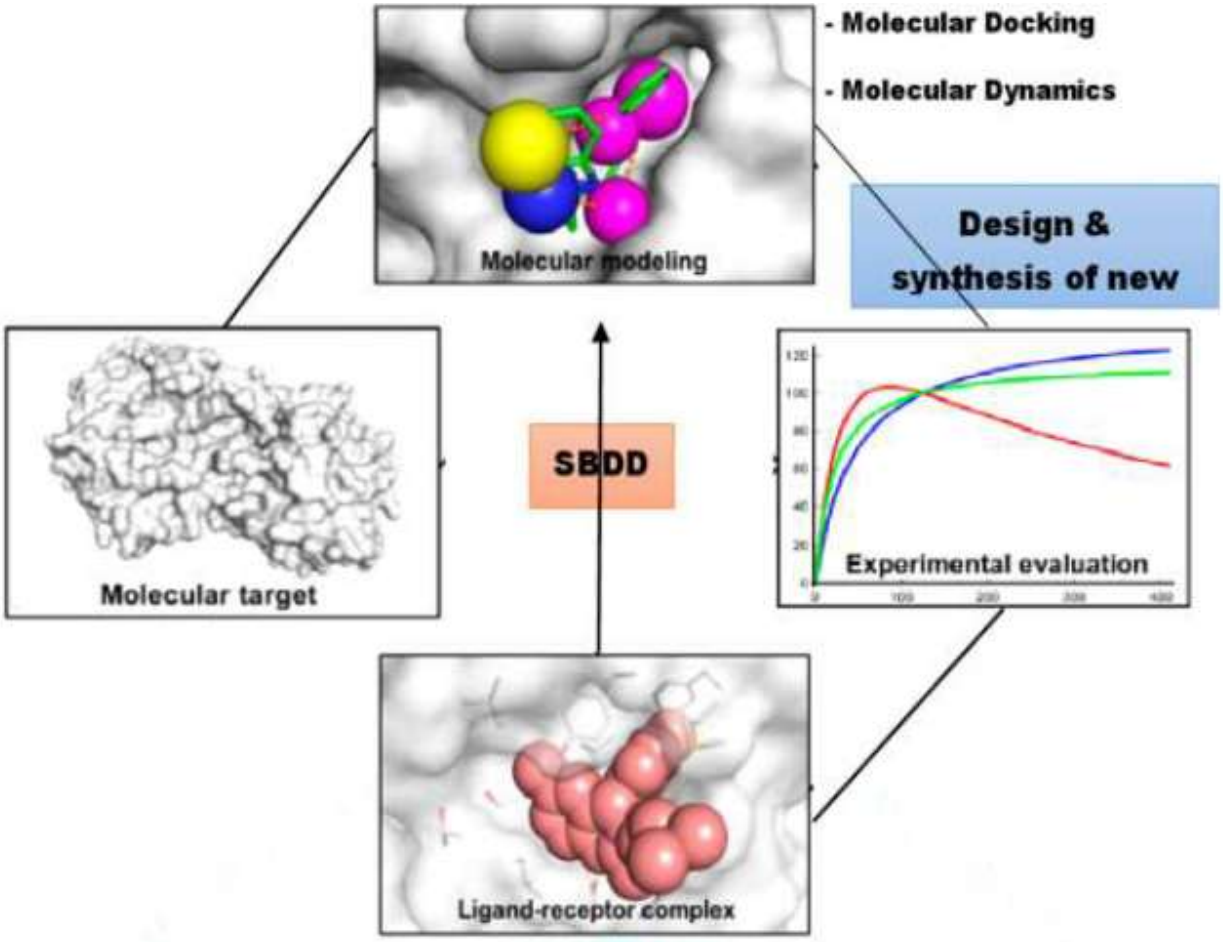


Fig- Layout of SBDD

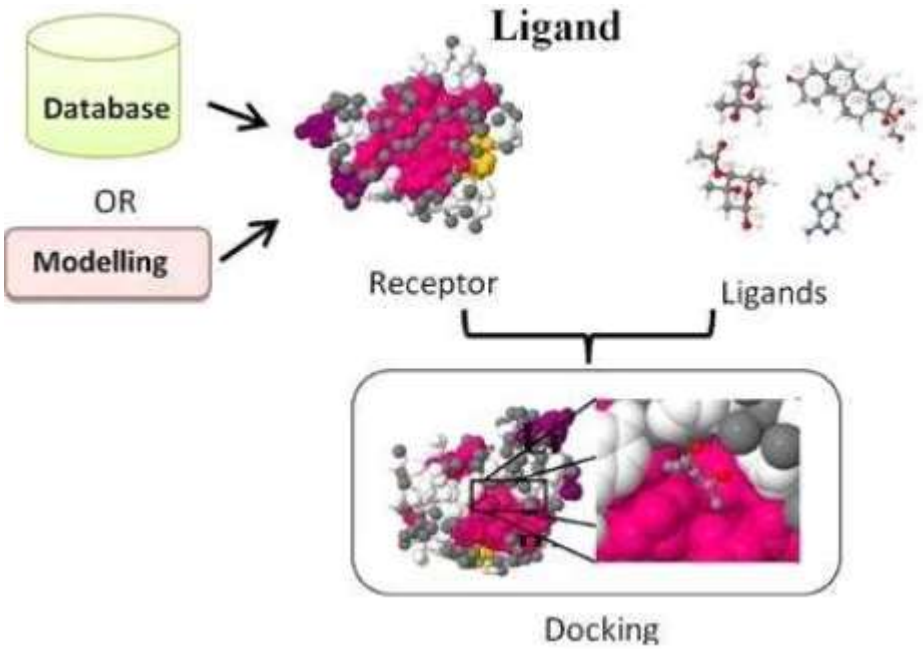


Fig- Outline of process involved in LBDD

OVERVIEW OF THE PROCESS INVOLVED IN SBDD

SBDD runs through multiple cycles before the optimized lead reached into clinical trials. The first cycle comprises isolation, purification and structure determination of the target protein by one of three key methods: like X-ray crystallography, homology modeling or NMR. Using compounds

comes through virtual screening of different databases are placed into a selected region (active site) of the protein. These compounds are scored and ranked on the bases of steric, hydrophobic, electrostatic interaction of these molecules with the active site of target protein. Top ranked compounds are tested with biochemical assays. Second cycle comprises structure determination of the protein in complex with the most optimistic lead of the first cycle, the one with minimum micro-molar inhibition in-vitro, and shows sites of the compound which can be optimized for further
increment in the potency. After several additional cycles like synthesis of lead, further optimization of lead through complex structure of protein with lead compound, the optimized compounds generally show marked increment in the target specificity and binding affinity

Fig-Steps involved in SBDD

Modern drug design

(a)High Throughput Screening-

- Fast and automatic, Very expensive, High Success Rate.
- Diversity of chemical compounds: Combinatorial Chemistry.

(b)PubChem Bioassay-

- 231 M bio-actives (leads) and in-actives/1.22M AID depositions/>10636 drug targets and 4771 human drug targets 22M CID‟s and 35M SID‟s

(c)Chem EMBL Bioassay-

- 14.67 Lakh bio- actives/Leads/1.3M AID -11538 drug targets, 67000 publications.

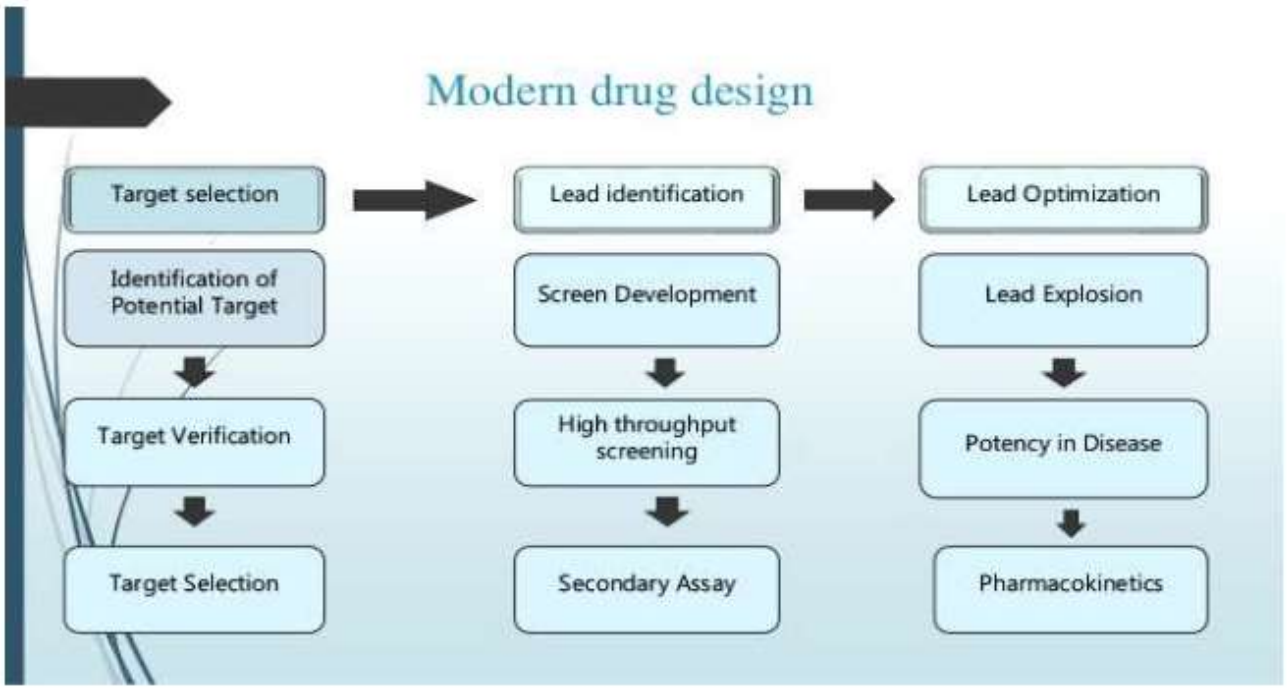


Fig- Modern drug design

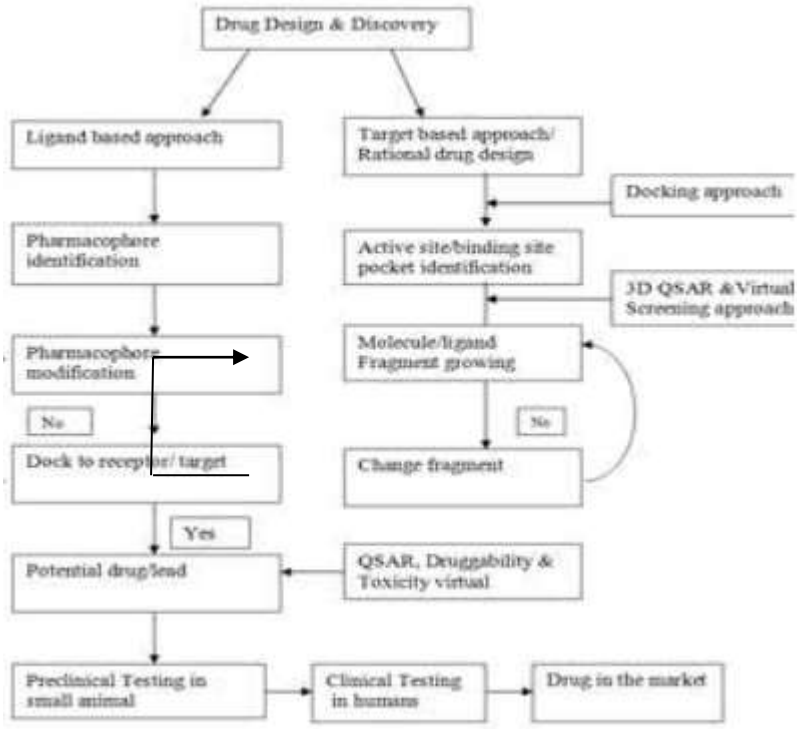


Fig- Modern drug design cycle

COMPUTER AIDED DRUG DESIGN (CADD)

Computational approaches in drug design, discovery and development process gaining very rapid exploration, implementation and admiration. Introducing a new drug in a market is a very complex, risky and costly process in terms of time, money and manpower. Generally it is found that drug discovery and development process takes around 10-14 years and more than 1 billion dollars capital in total. So for reducing time, cost and risk borne factors computer aided drug design (CADD) method is widely used as a new drug design approach. It has been seen that by the use of CADD approaches we can reduced the cost of drug discovery and development up to 50%. CADD consist use of any software program based process for establishing a standard to relate activity to structure.

Drug design with the help of computers using

(i)Molecular docking- Molecular docking is in-silico method which predicts the placement of small molecules or ligands within the active site of their target protein (receptor). It is mainly used to accurate estimation of most favorable binding modes and bio-affinities of ligands with their receptor, presently it has been broadly applied to virtual screening for the optimization of the lead compounds. Molecular docking methodology comprises mainly three goals which are interconnected to each other like: prediction of binding pose, bio affinity and virtual screening. In the molecular docking method the basis tools are search algorithm and scoring functions for creating and analyzing conformations of the ligand.

(ii) Virtual screening-Virtual screening has been worked as a most convenient tool now a day to find out the most favorable bioactive compounds with the help of information about the protein target or known active ligands. In the recent time virtual screening is known as a mind blowing alternative of high-throughput screening mainly in terms of cost effectiveness and probability of finding most appropriate novel hit through filter the large of libraries of compounds. There are generally two types of virtual screening approaches like structure-based virtual screening (SBVS) and ligand-based virtual screening (LBVS), SBVS method rely on the structure of target protein active site and LBVS method is based on estimation of calculated similarity between the known active and compound come from databases.

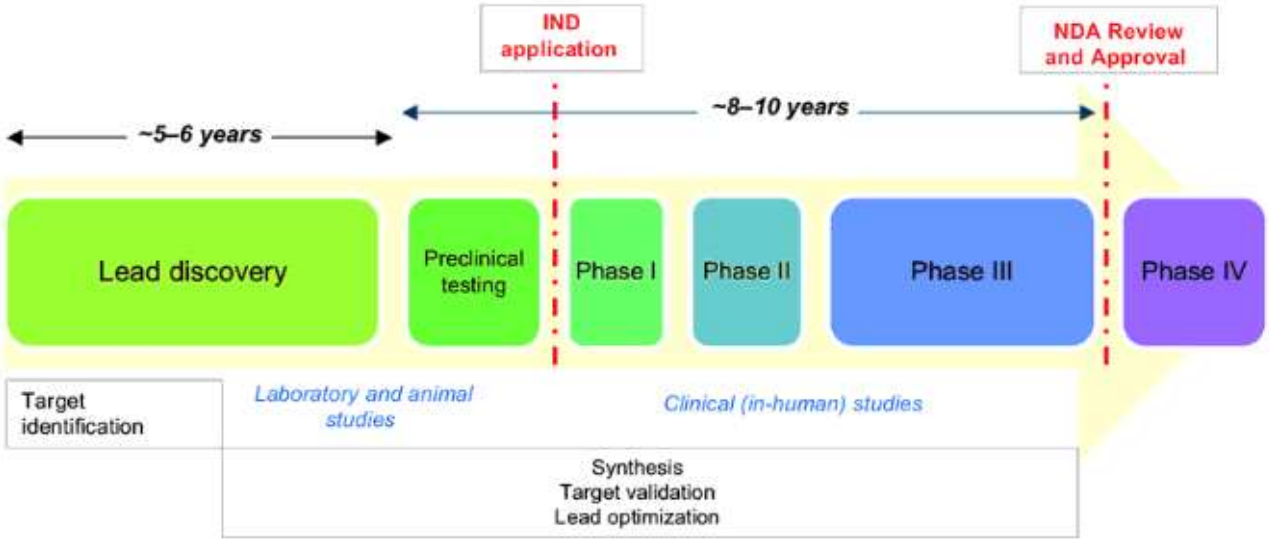


Fig- Traditional process of drug discovery and development

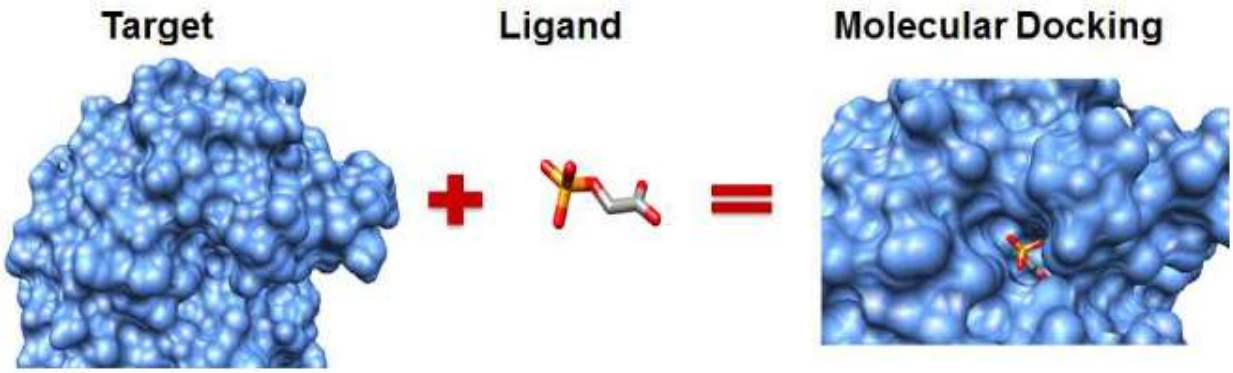


Fig-Process of Docking

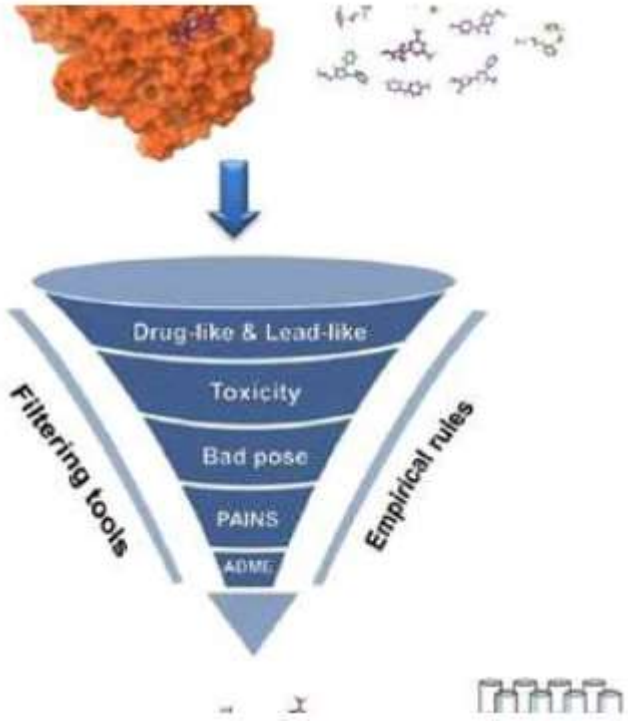


Fig-Overview of Virtual screening process

(iii) QSAR: (Quantitative structure–activity relationship) - Models (QSAR models) are regression or classification models used in the chemical and biological sciences and engineering.

Like other regression models, QSAR regression models relate a set of "predictor" variables (X) to the potency of the response variable(Y), while classification QSAR models relate the predictor variables to a categorical value of the response variable. In QSAR modeling, the predictors consist of physic-chemical properties or theoretical molecular descriptors of chemicals; the QSAR response-variable could be a biological activity of the chemicals. QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals. Second, QSAR models predict the activities of new chemicals

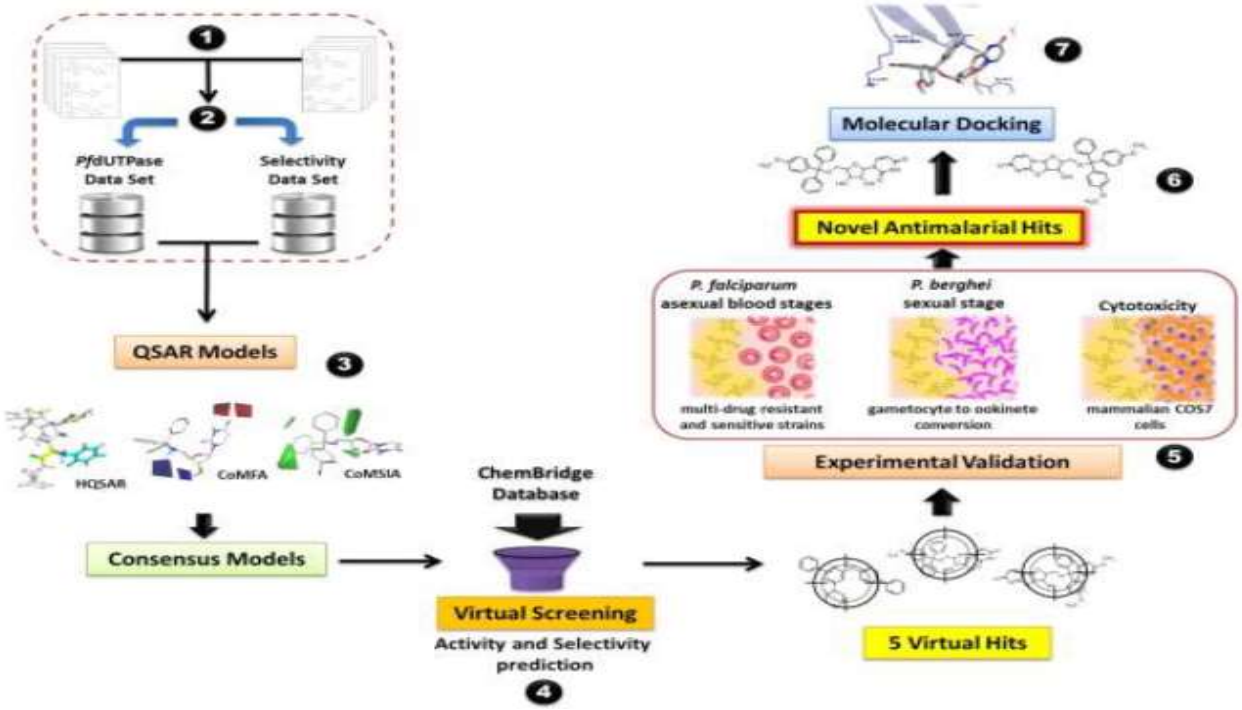


Fig- QSAR driven design

CONCLUSION

In the early 1990s, there was a great deal of optimism that CADD would revolutionize the way in which drugs are developed. The enduring exponential increase in computing power progressed to such a point that rudimentary estimations of ligand-receptor complementarities could be performed. Through computer graphics technology, scientists acquired the ability to generate vector models of chemical structures and manipulate them in real time. By using computers, computational chemists believed that they could circumvent much of the time and effort required for drug synthesis and testing simply by generating novel compounds with the help of computers. The concept of generating virtual lead compounds entirely through the computer simulation was termed de novo design. The world's largest pharmaceutical firms spent millions of dollars on hardware and software to turn de novo design into a reality. Unfortunately, success is rare, and except for few cases, de novo design proved to be an utter failure. De novo design could not prove itself to be an effective method to discover lead compounds. The main reasons behind are limitations in computing power and a lack of useful software functions. In scientific computing accuracy and processing time are very important. Thus, to make calculations run in a finite period of time, assumptions, algorithms, approximations, and other shortcuts are necessary. This greatly diminished the calculated accuracy of any ligand receptor interactions. Even though chemists postulated numerous chemical structures that potentially could complement the active site based on computer simulations, the calculated binding had no correlation with reality. This remains the most significant challenge in de novo design. Although computers have become exponentially faster, the sheer number of calculations needed to accurately predict the binding of a de novo generated ligand to its receptor in a useful time frame still requires significant approximations. In de novo design, attempts are being made to generate whole ligands from scratch and dock them within their receptors. However, the problem remains how the pre dicted structure behaves in real life. The second significant problem in computer-aided denovo design is the generation of undesired chemical structures that are of no use.

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