MOLECULAR MODELING IN DRUG DISCOVERY CONTINUED

Computer-aided drug design

The most fundamental goal in drug design 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.

Ideally, the computational method will be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized, saving enormous time and cost. The reality is that present computational methods are imperfect and provide, at best, only qualitatively accurate estimates of affinity. In practice it still takes several iterations of

design, synthesis, and testing before an optimal drug is discovered. Computational methods have accelerated discovery by reducing the number of iterations required and have often provided novel structures.

Drug design with the help of computers may be used at any of the following stages of drug discovery:

1. Hit identification using virtual screening (structure- or ligand-based design)
2. Hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)

3. Lead optimization optimization of other pharmaceutical properties while maintaining affinity.

In order to overcome the insufficient prediction of binding affinity calculated by recent scoring functions, the protein-ligand interaction and compound 3D structure information are used for analysis. For structure-based drug design, several post-screening analyses focusing on protein-ligand interaction have been developed for improving enrichment and effectively mining potential candidates:

4. Consensus scoring
    1. Selecting candidates by voting of multiple scoring functions
    2. May lose the relationship between protein-ligand structural information and scoring criterion
5. Cluster analysis
    1. Represent and cluster candidates according to protein-ligand 3D information
    2. Needs meaningful representation of protein-ligand interactions.

Discovery and development of a new drug is generally known as a very complex process which takes a lot of time and resources. So now a day's computer aided drug design approaches are used very widely to increase the efficiency of the drug discovery and development course. Various approaches of CADD are evaluated as promising techniques according to their need, in between all these structure-based drug design and ligand-based drug design approaches are known as very efficient and powerful techniques in drug discovery and development. These both methods can be applied with molecular docking to virtual screening for lead identification and optimization. In the recent times computational tools are widely used in pharmaceutical industries and research areas to improve effectiveness and efficacy of drug discovery and development pipeline. In this article we give an overview of computational approaches, which is inventive process of finding novel leads and aid in the process of drug discovery and development research.

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.

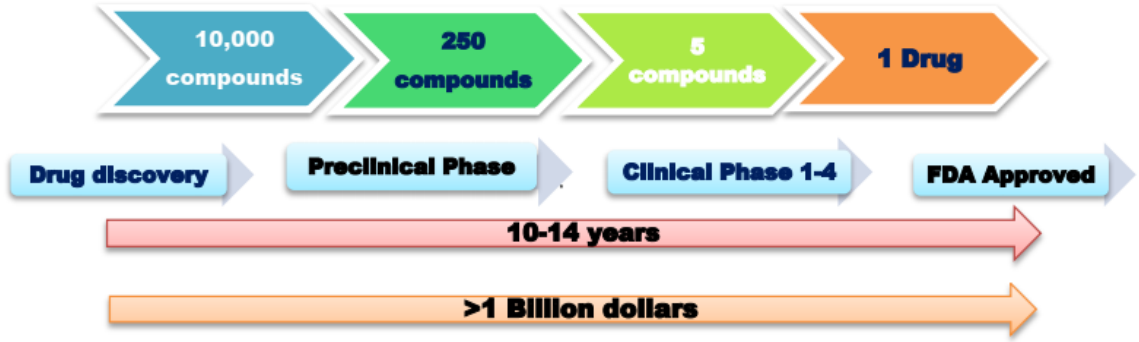

Figure 1: Traditional process of drug discovery and development.

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 reduce the cost of drug discovery and development up to 50% 2. CADD consist use of any software program-based process for establishing a standard to relate activity to structure.

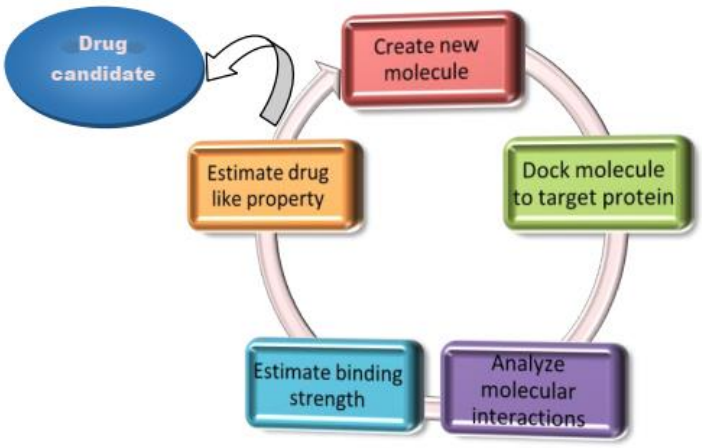

Figure 2: General Principle for Drug design through CADD.

Major types of approaches in CADD

There are mainly two types of approaches for drug design through CADD is the following:

1. Structure based drug design / direct approach
2. Ligand based drug design / indirect approach

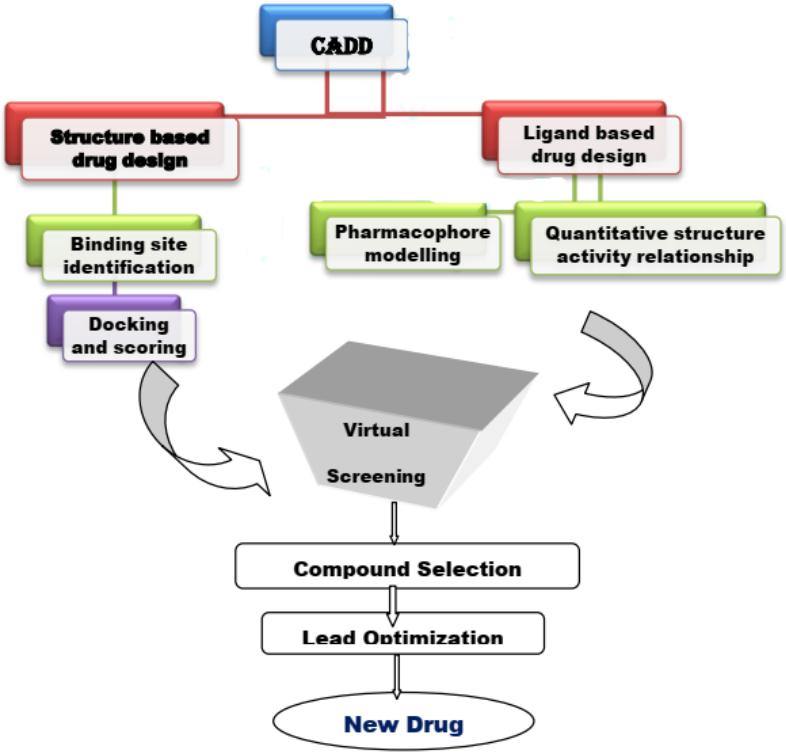

Figure 3: General Representation of workflow for CADD.

1. 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.

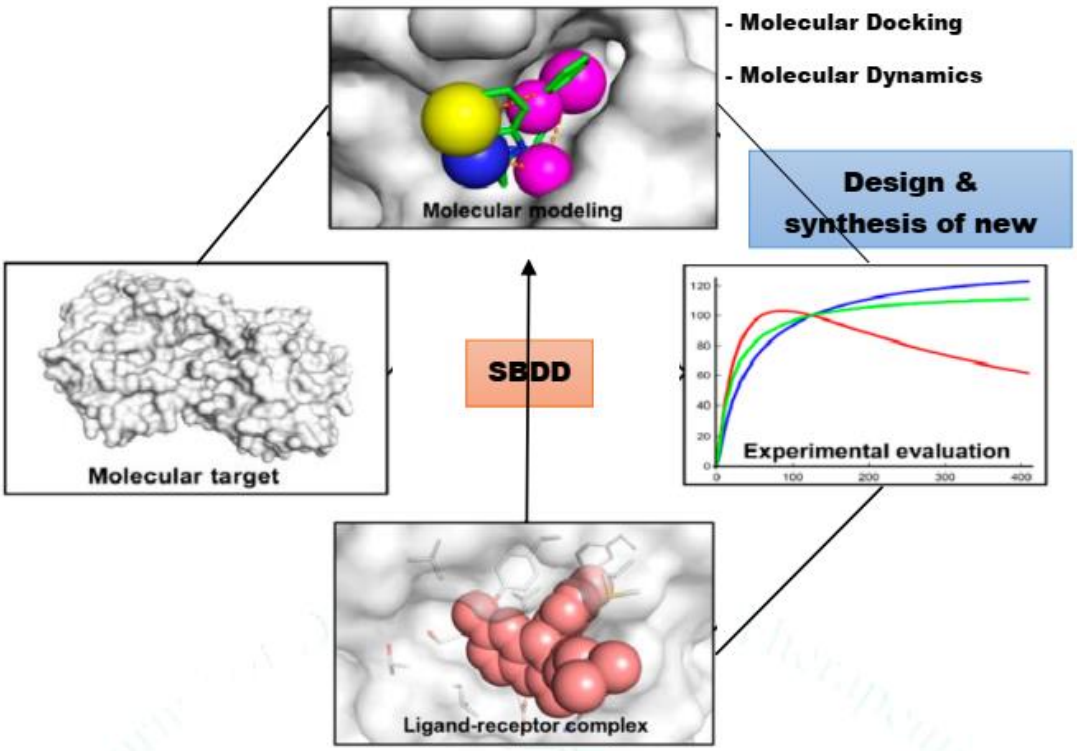

Figure 4: Layout of SBDD

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 modelling 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.

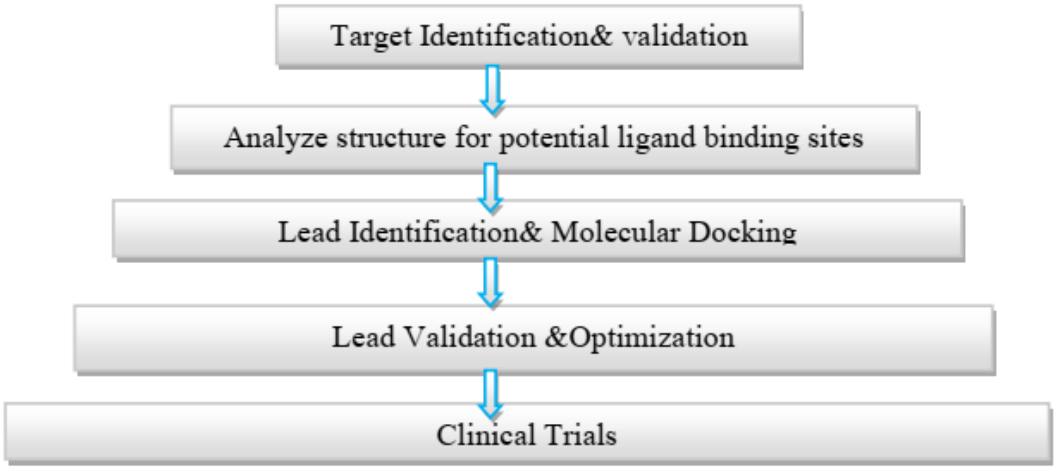

Figure 5: Steps involved in SBDD.

2. 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.

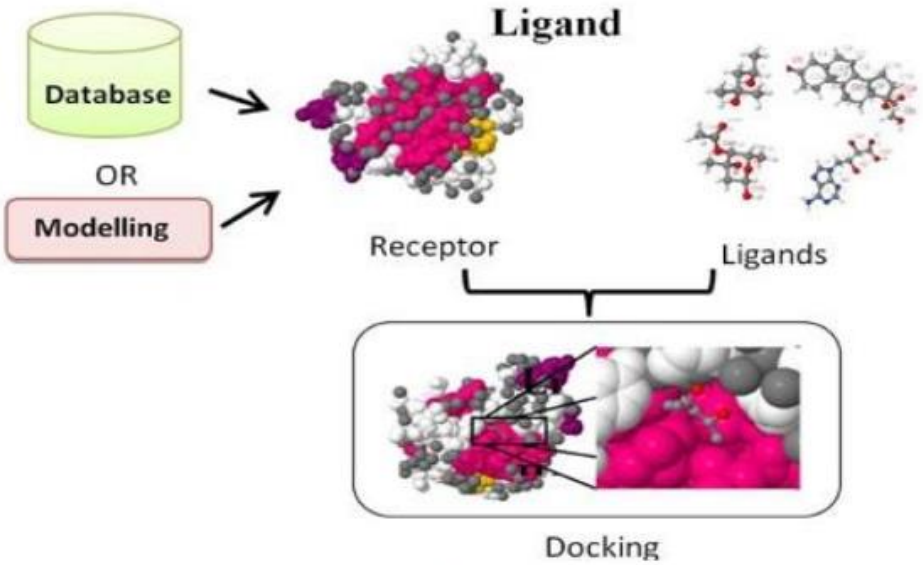

Figure 6: Outline of process involved in LBDD

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.

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.

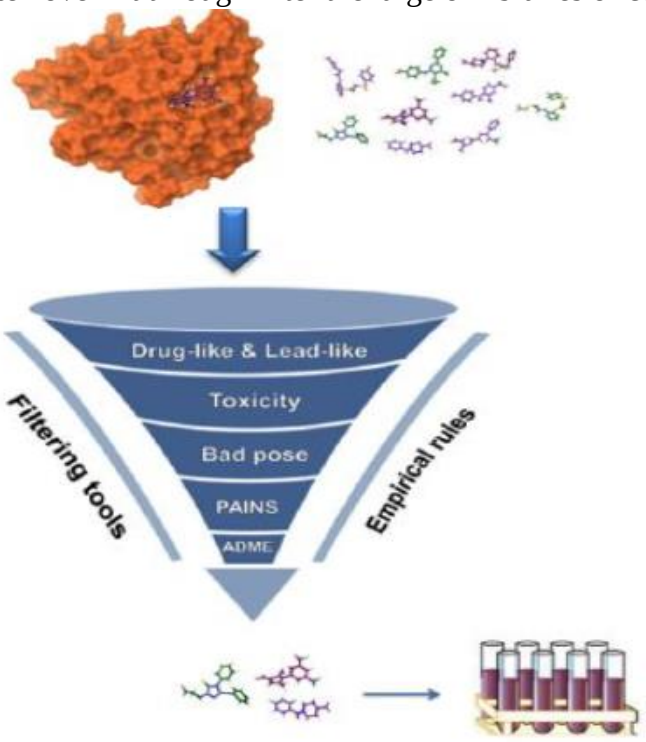

Figure 7: Overview of Virtual screening process

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.

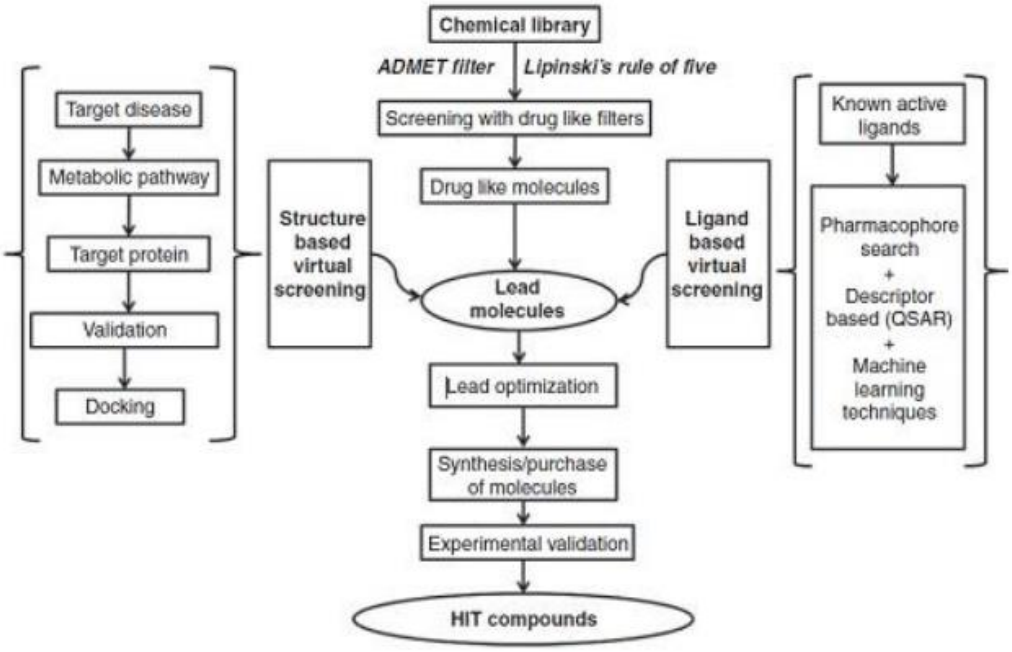

Figure 8: Schematic diagram of VS process for SBDD & LBDD

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.

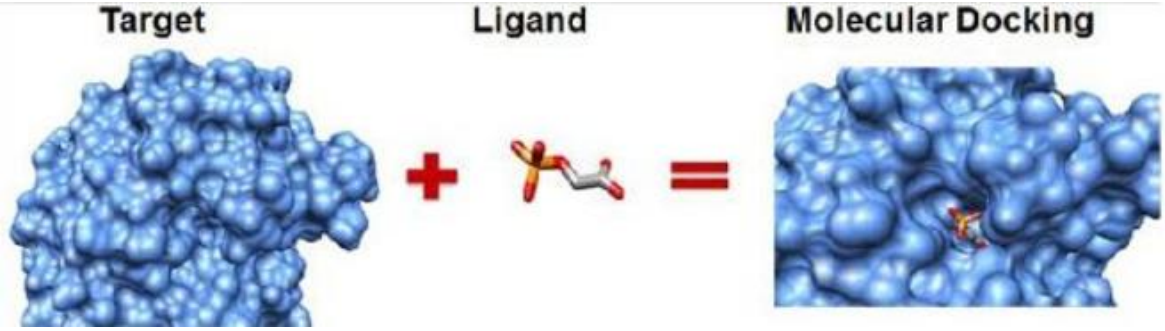

Figure 9: Process of Docking

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 analysing conformations of the ligand.

ADVANTAGES OF CADD (computer aided drug design)

- Through it we can reduce the synthetic and biological testing efforts.
- It gives the most promising drug candidate by eliminate the compounds with undesirable properties (poor efficacy, poor ADMET etc.) through *in silico* filters.
- It is a Cost-effective, time saving, Rapid and automatic process.
- Through it we can know about the drug-receptor interaction pattern.
- It gives compounds with high hit rates through searching huge libraries of compounds *in silico* in comparison to traditional high throughput screening.
- These approaches minimize chances of failures in the final phase.

CONCLUSION AND FUTURE ASPECTS

Computer aided drug design is an efficient tool in the area of drug discovery and development, through it we can find the most promising drug candidate in a very cost-effective way. It always provides a hope for betterment in drug discovery area. In the past years through Computer aided drug design many impressive researches are achieved so it will play a very much important role in the near future. With the current achievement's, there is a promising future of computer aided drug design to aid drug discovery of many more curatives in future.

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