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**Review Article**

# A REVIEW ON COMPUTER AIDED DRUG DESIGN (CAAD) AND IT'S IMPLICATIONS IN DRUG DISCOVERY AND DEVELOPMENT PROCESS

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## Abstract

Discovery and development of new drug is generally known as a very complex process which is a time consuming process. So, computer aidded drug design approaches are used very widely to increase the efficency of the drug. Many approach of CADD are evaluated a promising techniques in all the structure based drug design and ligand based are known efficient and powerful techniques in drug development and discovery. So, both methods can be applied with molecular docking to virtual screen for identification and optimisation. Computational tools are widely used in pharmaceutical industries and research with many facets. The theoretical basis of CADD uses quantum mechanics and molecular modelling studies. It's also based on the database searching and binding affinity on the basis of biological target. Computational techniques reduces the cost upto 50% in the drug design process. In review we give an view of computational approaches, CADD tools and current advancement in the field of chemistry.

***Keywords:*** Computer aided drug design (CADD) , Structure Based Drug Design, Ligand Based Drug Design, Docking, Virtual Screening.

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## INTRODUCTION

Innovative process of finding a new medicine based on the knowledge of a biological target is the drug design also known as rational drug design or rational design. The drug is an organic small molecules that inhibits the function of a biomolecule such as protein. In basic, drug design involves the design of small molecules that are complementary in shape and charge to the bimolecular target which interact and bind to it [1].

It's really meant by drug design is ligand design, although modeling techniques for prediction of binding affinity are reasonably successful, there are many other property such as bioavailability, metabolic half life, lack of side effects, etcthat first must be optimized before a ligand can become a safe and effective [3-6].

CADD techniques helps in different stages of drug design thus reducing the cost of research and development time. Developing a new drug is a long, complex, costly and highly risky process that has many problems in commercial world. So, CADD are widely used in industry to accelerate processes. The cost of using computational tools in the lead optimization is less. The invested time by the pharmacological research lab are heavy during various phases of drug discovery[9,10].

## DRUG DISCOVERY AND DEVELOPMENT PROCESS

Various aspects are therapeutic identification drug optimization through pre clinical and extensive clinical experiment for the effectiveness of newly developed drugs. It's stated that drug discovery process from lead identification to clinical trails, takes about 10-15 years and 500-800 million dollars to introduce into market. From the past few years, CADD has grown up rapidly, by perceptive of multifaceted and difficult biological process, with help of these it's possible to find out new pharmacological active agents in short duration [5,6,7,11,12].

In the past few years, CADD has grown up rapidly, enhancing the perceptive of multifaceted and difficult biological process. With the help of these computational tools, it is now possible to find out new pharmacological active agents in a short duration of time [13].

**Table 01: Showing the examples of few drugs by CADD process [10]**

| YEAR | DRUG NAME | USED AS |
|---|---|---|
| 1989 | Zanamivir | Anti HIV |
| 1997 | Nelfinavir | Anti HIV |
| 1998 | Raltitrexed | Anti cancer |
| 1999 | Amprenavir | Anti HIV |
| 2007 | Raltegravir | Anti HIV |

## DRUG DISCOVERY PROCESS

Is a series of process in which identify the drug compounds for the effective treatment or control of disease targets. It starts by screening of large number of chemical compounds to optimize the disease. It wants in vitro information about the structure of drug receptor so that the drug molecules can be adjusted for binding site [14,15].
Drug discovery process starts by understanding the disease for the drug to be designed. It consist of the following steps [16].

1. **Drug discovery**
   Selection of therapeutic target Lead discover
   Lead optimization
2. Pre clinical and clinical trials to evalute the safety, efficacy and adverse effects of the drug.
   Animal study
   Clinical trails
3. FDA approval process for the newly discovered drug and bring the drug to market for public use.
   Additional post marketing testing
   Further improvement of the drug .

**Various stages of drug design**

- Choose a disease
- Choose a drug target
- Identify a bioassay
- Find a lead compound
- Isolate and purify the lead compound if necessary
- Determine the structure of the lead compound
- Identify structure Activity relationship
- Identify the pharmacophore
- Improve target interaction.

Drug design can be achieved by exploration of the lead compound which has search for a new lead exploration of the existing leads to produce more

active compound with less toxicity than the original lead compound[17,18,19].

**Their are four methods commonly used in drug designing [20]**

- Ligand based drug design or indirect drug design
- Structure based drug design or direct drug design
- Rational drug design
- Computer assisted drug design

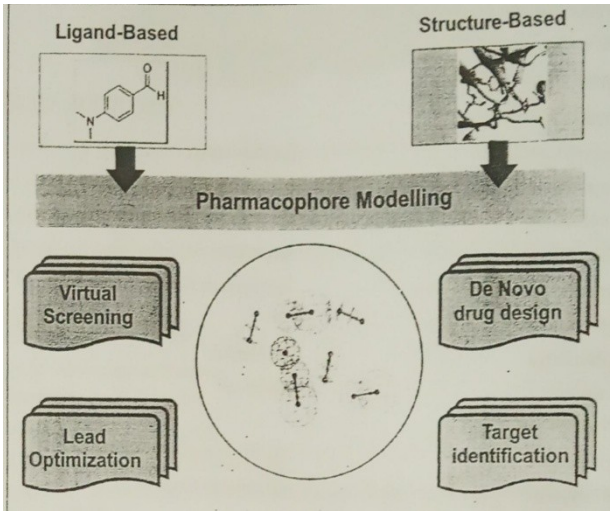


**Figure 01 : Representing the Pharmacophore Modelling [8]**

## LIGAND BASED DRUG DESIGN : (LBDD)

It's the 3D structure of the targeted protein which is not known but the knowledge of ligands which bind to the desired site is known. Which can be used to develop a pharmacophore model or molecules which possesses all required structural features for binding to a target site [20].

Generally these technique are pharmacophore based approach and quantitative structure activity relationship (QSARs) . So, it's assumed that compounds which have similarities in their structure also have same biological action and interaction with target protein [20].

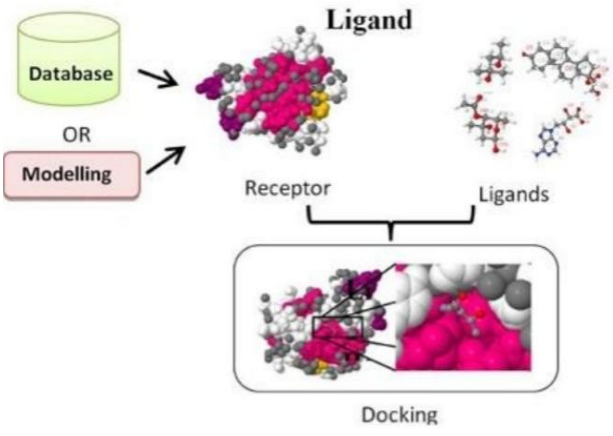


**Figure 02 : Representing the process involved in LBDD [7]**

Ligand based drug design is an indirect drug design which gives the knowledge of other molecules that bind to the biological target of interest. These may be used to derive a pharmacophore model that defines the minimum necessary structural characters. A molecules must posses in order to bind to the target drug. A model a biological target may be built based on the knowledge of what binds to it and these model in turn may be used to design new molecular entities that interact with the target. QSAR in which a correlation between calculated property of molecules and their biological activity (experimentally determined) may be derived. These QSAR relationship in turn may be used to predict the activity of new analogue [20,21].

## STRUCTURE BASED DRUG DESIGN : (SBDD)

Structure of the target protein is also known and interaction or bio affinity for all tested compounds is calculated after the process of designing a new drug molecule, which shows a better interaction with the target protein [22].

SBDD is also known as direct drug design gives knowledge of the 3D structure of the biological target obtained by methods such as X- ray, spectroscopy, crystallography or NMR if an experimental structure is not available, it may be possible to create the homology model of the target and target based on the experimental structure of a related protein [22].

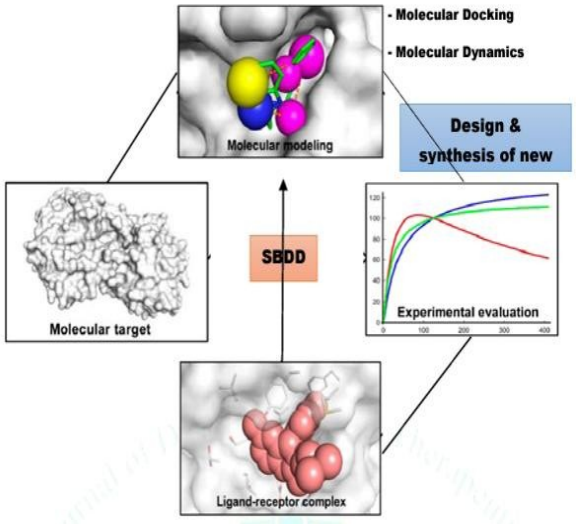


**Figure 03: Representing the model of SBDD [12]**

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 by

interactive graphics and medicinal chemistry. Various automated computational procedures may be used to suggest new drug candidate. The 3D structure of the bio molecular targets are obtained by x-ray, crystallography and NME techniques, however the information about the structural dynamics and electronic properties about ligands are obtained from calculations. The rapid development if SBDD had encouraged by the current methods. SBDD can be divided into two categories. Firstly about finding the ligand fir given receptor, which is reffered as database searching. In this case large no of potential ligand molecules are screened to find those fit binding pockets to receptor. The advantage of database searching is it saves synthetic effort to obtain new lead compound. Another category is about building ligands, also known as receptor based drug design [23].

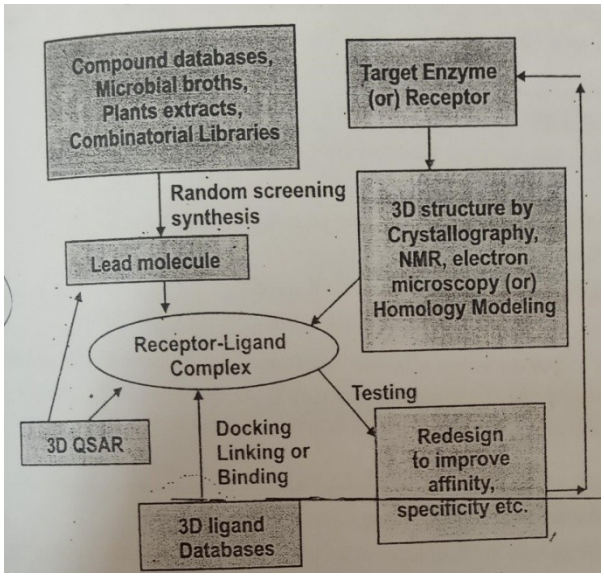


**Figure 04: Representing the SBDD processes [22]**

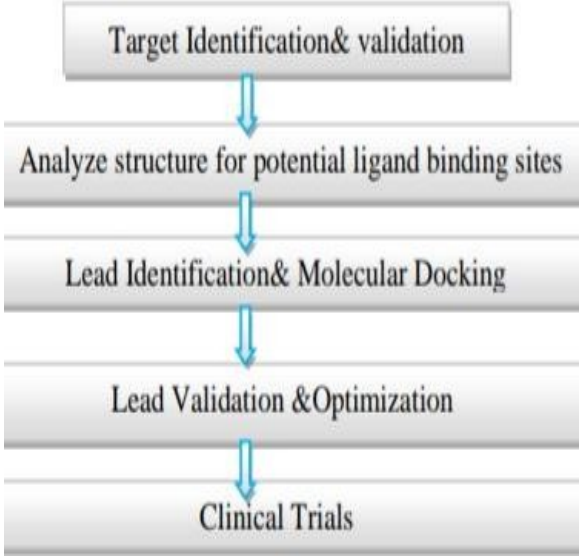


**Figure 05: Representing the steps involved in SBDD [18]**

So, the ligand molecules are built up within the constraints of the binding pocket by assembling small pieces in stepwise manner as shown in fig-6. The pieces can either be individual atoms or molecular fragments. Advantage of these method is novel structures not contained in any database [23,24].

**CADD in the drug discovery process**

It vary depending on the extent of the structural and information regarding the target and ligands. Direct and indirect design is the two major modeling strategies currently used in the drug design process. Indirect approach the design is based on comparative analysis of the structural Features of the known active and inactive compounds. In direct design the three dimensional features of the target are directly considered [25].

**Working of CADD : ( process)**

- Preparation of a target structure
- Homology modelling
- Molecular dynamics based detection
- Genetic algorithm
- Scoring function for evalution of protein ligand complexes Force field
- Empirical scoring function
- Knowledge based scoring function
- Consensus scoring function
- Structure based virtual high screening
- Ligand based computer aided drug design
- Molecular

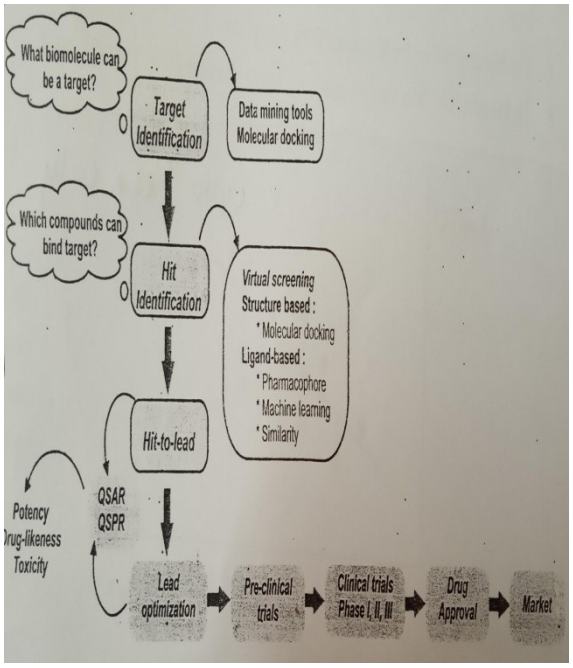


**Figure 06: Representing the CADD drug design process ( work flow)[20]**

CADD uses computational chemistry to discover, enhance or study drugs and related biological active molecules. Molecules dynamic is most often used to predict the confirmation of the small molecules and to model changes in the biological target that may occur when the small molecules vinds to it. Molecular mechanic method may be used to provide semi- quantitative prediction of the binding affinity and knowledge based scoring function mat be used to provide binding affinity estimates [25].

**Drug design with computers may be used at any stages during drug discovery**

- Hit identification using virtual screening
- Hit -to- lead optimization of affinity and Selectivity
- Lead optimization :
  of the other pharmokinetic property while maintaining affinity.

To over come the insufficient prediction of binding affinity is calculated by recent scoring functions, the protein ligand interaction and computer 3D structure information are used for analysis

**Quantitative structure activity relationship**

QSAR approach attempts to identify and quantify the physicochemical properties of a drug and to see whether any of these properties has an effect on the drugs biological activity by using a mathematical equation. A range of compound is synthesized in order to vary one physicochemical property and to test it affects the bioactivity. A graph is then drawn to plot the biological activity on you axis versus the physicochemical feature on the x axis. It is necessary to draw the best possible line through the data points on the graph. This is done by using the procedure known as linear regression analysis using the least square method. If we draw a line through a set of data points will be scattered on either side of the line. The best line will be the one closest to the data points. To measure how close the data points are, vertical lines are drawn from each point [23,24,25].

**Virtual screening**

Has been worked as a most convenient tool now to find out the most favourable bioactive compounds with help of information about protein target or active ligands. In past virtual screening is known as mind blowing alternative of high screening mainly in terms of cost effectiveness and probability of finding most appropriate novel through filter of large libraries of compounds . There are two types of virtual screening approaches like structure based virtual screening (SBVS) and ligand based virtual screening ( LBVS) . SBVS method is related on the structure of target protein active site and LBVS is based on estimation of similarity between known active and from database[24]

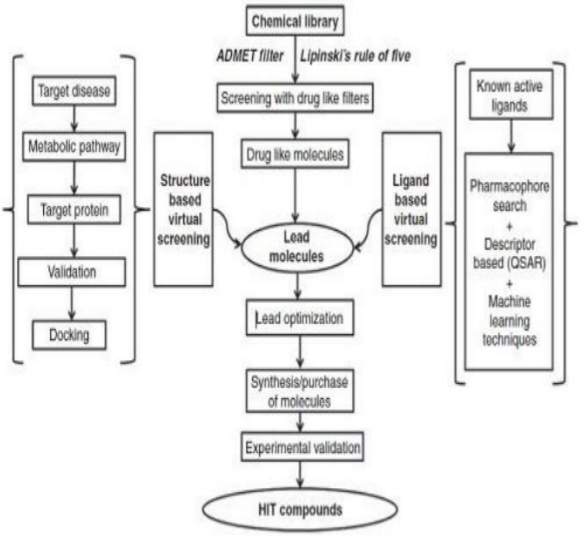


**Figure 07 : Representing the schematic diagram of virtual screening process for SBDD and LBDD [24]**

**Molecular docking**

Its an in-silico method predicts the placement of small molecules or ligands in the active site of target protein. Mainly used in accurate estimation of favourable binding modes and bio affinities of ligands with their receptor, so it has been broadly applied to virtual screening for optimization of lead components. These methodology comprises three goals which are interconnected to each other by : prediction of binding pose, bio affinity and virtual screening. In these method the basis of tools are search algorithm and scoring function for creating and analysing the ligand [23,24].

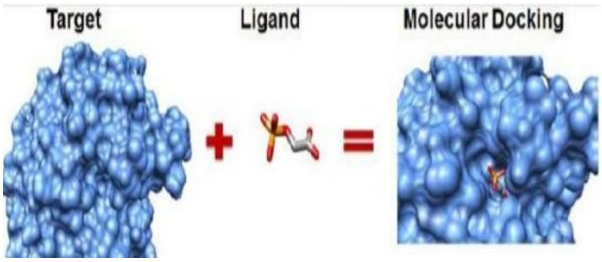


**Figure 08: Representing the process of docking 14]**

**Docking techniques**

In molecular modelling, docking is a method in which it predicts the preferred orientation of one molecule to a second by bounding to each other to

form a stable complex. The prefered orientation may be used as predicting the strength of association or binding affinity between two molecules by scoring function [24,25].

**Table 02: Showing the information regarding Docking tools [15]**

| Docking software | Docking algorithm |
|---|---|
| Dock | Shape fitting |
| Auto dock | Lamarckian algorithm, genetic algorithm |
| Gold | Genetic algorithm |
| Glide | Monte Carlo sampling |
| Ligand fit | Monte Carlo sampling |

**Advantages of CADD**

- Synthetic and biological efforts can be reduced
- Can choose the promising drug candidate by eliminating the compounds with undesirable properties through in silico filters
- It's less cost, time saving rapid and automatic process
- Drug receptor interaction pattern can be found
- Compounds formed gives high hit rates through searching huge libraries of compounds in silico comparison to the traditional high output screening.
- Reduces the chances of failure in the final phase.

## CONCLUSION

CADD is an efficient tool in drug discovery and development process by these we can find the most promising drug candidate in a very cost effective way. It gives a hope in betterment of drug discovery area. In past few years it is an impressive researchers have achieved, so it plays an important role in future.. CADD approaches by identifying the new lead compounds through the number of methodology like structure based, ligand based with an availability of numerous types of databases. It's also useful in the role of chemo informatics and bioinformatics in modern era of drug discovery and development. These techniques proved to be effective in various stages of drug discovery process by reducing both cost and time for developing a drug.

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