Review Paper:

Drug designing: Lifeline for the drug discovery and development process

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Abstract

Drug discovery and development field has entered into a revolutionary phase with the introduction of Computer Aided Drug Designing (CADD) tools in the designing and development of new drugs. Traditional drug discovery and designing is a tedious, expensive and time-consuming process. Pharmaceutical industries spend billions of dollars to launch a potential drug candidate into the drug market. It takes 15-20 years of research to discover a new drug candidate. The advancements in the Computer Aided Drug Designing techniques have significantly contributed towards lowering the cost and time involved in new drug discovery. Different types of approaches are used to find out the potential drug candidates. Numerous compounds have been successfully discovered and launched into the market using computational tools.

Various novel software-based methods like Structure-Based Drug Designing (SBDD), Ligand-Based Drug Designing (LBDD), Pharmacophore Mapping and Fragment-Based Drug Designing (FBDD) are considered as powerful tools for determining the pharmacokinetics, pharmacodynamics and structure activity relationship between target protein and its ligand. These tools provide valuable information about experimental findings and the mechanism of action of drug molecules. This has greatly expedited the discovery of promising drug candidates by sidestepping the lengthy steps involved in the synthesis of unnecessary compounds.

Keywords: Computer Aided Drug Designing (CADD), Ligand Based Drug Designing (LBDD), Structure Based Drug Designing (SBDD), Virtual High Throughput Screening (VHTS).

Introduction

Development of novel pharmaceuticals is a tedious and expensive task. A drug has to pass through many phases before entering into market [Fig. 1]. New drug molecules getting approval per billion US dollar spent on research and development has halved every nine years since 1950[12]. Though pharmaceutical industry has increased allocation towards new drug development from the year 1993 to 2007, but the new medicinal entities coming in the market are not in proportion to the investment mainly led by increased failure rates towards new drug development[25]. Emergence of Computer Aided Drug Designing (CADD) has facilitated the drug discovery, designing and optimization of potential therapeutic drug molecules. It leverages technology and related platforms for facilitating drug designing process[1].

CADD involves utilization of computational softwares, algorithms and 3D visualization techniques to help building models about creating or modifying molecules and implementing decisions in the drug designing process[4]. It involves the designing of molecule complementary in shape and charge to the target protein with which they interact and bind[13]. The advantages associated with CADD technique are:

1. It reduces the numbers of animals sacrificed in preclinical stages of drug discovery.
2. Handling of huge compound libraries with ease.

Computational methods provide insightful information about the ligand and its target protein by envisioning the 3D structures of protein and ligand and their interaction thereafter. The aim of all the research work in a drug discovery process is obtaining an active lead compound. Screening of bioactive compounds with the help of CADD is the most important step in drug discovery. CADD has wider applications in the designing and discovery of new pharmacological agents due to its higher hit rate as it uses more targeted search as compared to traditional drug discovery process. CADD involves three major steps:

(1) Identification of smaller set of predicted active compounds through filtration of libraries related to large number of compounds leading to reduction in experiment related workload;
(2) Increasedefficacy in lead compounds such as increasing its affinity or optimizing Drug Metabolism and Pharmacokinetics (DMPK) properties;
(3) Newer compounds are designed by developing functional groups of starting molecules or by combining the fragments[27]. CADD adds value to the drug designing projects if it leads to faster decisions taken by a project team member.[10]

Databases used in CADD

Success can be achieved in drug designing and development by utilizing the data of organic molecules, biological

sequences and related information stored in data bases (Table 1). Combinatorial libraries have been designed by using computational algorithms[14].

Many open access resources and public platforms like GitHub are available for research purposes which help in generation of libraries for drug designing. Web based search tool Click 2 Drug has comprehensive list of open resources[19]. ezSMDock is a small-molecule docking web application in which structure of receptor is imported by entering a PDB ID. It offers numerous options for computational chemists for importing the ligand structure: (1) PDB, MOL2, SDF/MOL format is used for 3D ligand file (2) SDF/MOL format is used for 2D ligand file (3) SMILE and (4) InChI. These formats are easily available in databases such as Wikipedia or Google searches Drugbank, ChEMBL, PubChem, RSCB/PDB.

Combination of PDB ID, InChI and SMILES allows users to perform a docking experiment without downloading and uploading files. De novo designing using ezSMDock utilizes PubChem Sketcher to draw and modify molecular structures of interest. It helps in generating the new combination structures as ligand input and advancing them into receptor binding site.

Fig. 1: Drug discovery and development process

Table 1
Small molecule and biological databases used in CADD[3,9,28]

S.N.	Database	Website/URL
1.	Zinc	http://zinc.docking.org
2.	SPECS	http://www.specs.net
3.	NCI	https://cactus.nci-nih.gov/
4.	CoCoCo	http://cococo.isof.cnr.it
5.	Enamine	http://www.enamine.net
6.	ChEMBL	http://www.ebi.ac.uk/chembidb/index.php
7.	ChemDiv	http://www.chemdiv.com
8.	ASINEX	www.asinex.com/libraries_synergy.html
9.	INTERBIOSCREEN	https://www.ibscreen.com
10.	emolecules	https://www.emolecules.com
11.	Life chemicals	http://www.lifechemicals.com
12.	Drug bank	http://www.drugbank.ca
13.	GDB-17	http://gdb.unibe.ch
14.	Chem Mine	http://chemminedb.ucr.edu
15.	Chem Bank	http://chembank.broadinstitute.org
16.	Binding DB	http://bindingdb.org
17.	Protein Data bank	http://rcsb.org
18.	Drug bank	http://drug bank.ca
19.	KEGG Ligand	http://genome.jp/kegg/drug
20.	Super DRUG2	cheminfo.charite.de/superdrug 2
21.	Drug 3D	chemoinfo.ipmc.cnrs.fr/MOLDB/index.php
22.	Super target	http://insilico.charite.de/supertarget/index.php?site=home

These advantages make ezSMDock an effective tool to quickly enumerate varied structural probabilities and foresee binding affinity changes for exploring structure activity relationships (SARs) and related formulating hypothesis[20].

UCSF Chimera, VMD and PyMOL are most widely used macromolecular visualization software packages. Optimization of different set of tasks has been done in each software. Python based PyMOL helps in creating detailed images and Python related scripts from PyMOL WiKi community are highly scriptable.

To read, analyze and visualize various kind of simulation trajectories Molecular Dynamics VMD is used. It utilizes tcl scripts as addons for doing analysis and functional improvements. UCSF Chimera is used for the interaction-based visualization and scrutiny of molecular structures including density maps, supramolecular assemblies, sequence alignments, docking results, trajectories and conformational ensembles. But these packages are not adaptable for online communications or real-time participation between computational chemists and medicinal chemists. Different images of macromolecular structures can be obtained by using powerful offline visualization techniques, but they have some disadvantages too.

For example, the visualization scene on real-time basis cannot be shared directly between users at different places. Various codes are provided by developers for installation on different operating platforms and these tools are platform dependent. WebGL andHTML5 technology can be used for visualization of macromolecules. No plugins are needed to be installed for a web browser and data can be seamlessly shared among users at different locations.[26]

Structure based drug designing

SBDD technique is preferred in case the three-dimensional structure of target protein is known. Drug molecules are designed with the help of the knowledge of the structure of the target protein. Two most commonly used methods in SBDD are molecular docking and de novo ligand designing. Molecular dynamics (MD) simulations give information about ligand binding with target proteins and knowledge about target flexibility and pathways of interaction. Molecular dynamics is useful in case when membrane permeability is important for drugs and when drug targets are membrane proteins[8].

MD simulations offers many advantages:1. Provide information about protein dynamics beyond crystallographically available structure 2. Exposing new cryptic binding sites 3. Expansion of draggability of the targets. Application of MD to drug discovery is expanding as there is need for in depth details about binding and conformational changes at the spatial and temporal resolution[16]. SBDD computational techniques have also been advanced in biophysics, medicinal chemistry, statistics and other fields. Many scientific advancements have resulted in development of techniques that are used in predicting protein structures. Technologies such as Nuclear Magnetic Resonance (NMR), X-ray crystallography and computational methods like Molecular Dynamic (MD) simulation and homology modeling are used in the determination of large number of proteins[2].

SBDD predicts the binding as well as the strength of binding of target protein with the ligand. By optimizing the interactions between ligand and target protein, docking programs predict the geometry and position of ligand molecule on the target. Examples of docking programs are Autodock Vina and Autodock[4]. The steps involved in SBDD are (Fig. 2):

- The first step in the docking is to determine the 3D-structure of target protein using techniques such as NMR or X-ray crystallography.
- The second step is docking simulations of ligand molecules and target protein to determine the binding sites.
- The third step involves protein ligand docking sampling algorithms.
- In the fourth step, protein-ligandcomplexes are given scoring functions.
- In the fifth step, structure-based virtualhigh-throughput screening is performed.
- Last step involves a high-resolution docking.[17]

Homology modelling

With the advent of genomicsequencing, it becomes easier nowadays to determine the sequence of proteins rather than its three- dimensional structure. These sequences of proteins are used to determine the active sites on the target protein. For a broad-spectrum drug, highly conserved amino acids are conserved. Unique amino acids within active site are considered for organism specificity. Online server SWISSMODEL.20 can be used to study template-based homology modelling.[21]

Ligand-Based drug design

LBDD technique is used when 3D structure of target protein is unknown and it uses the structural properties of ligands that bind with the target protein. LBDD is based on the principle that compounds having identical structures have similar biological properties and interactions with target protein[24]. A pharmacophore model is developed having all the essential structural features that are required for binding with the target protein. Two most commonly and widely approaches under LBDD are:

1. Pharmacophore modelling
2. Quantitative structure-activity relationships. The basic steps involved in LBDD are:

Using some similarity measure chemically similar compounds to known actives are selected.
Prediction of biological activity from chemical structure by building QSAR model.

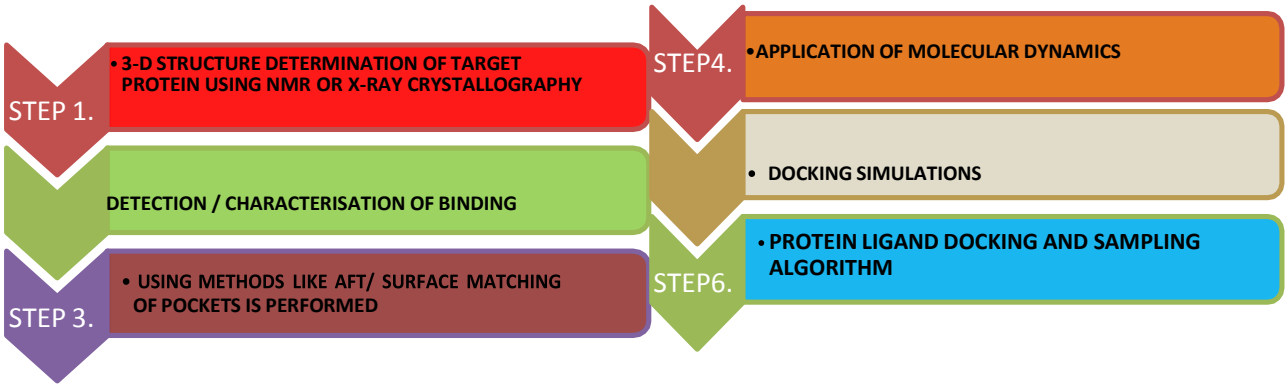

Fig. 2: Steps involved in Structure based drug designing

Table 2
Softwares used in SBDD[6,24]

S.N.	Software	Description
1.	GOLD	It is a quantum mechanics and molecular docking tool which deals with protein ligand interactions indrug design. It is a paid software.
2.	Gaussian (ONIOM)	It is a combined mechanistic tool. It is a paidsoftware.
3.	AUTODOCK	It studies ligand-protein interactions. It is a freesoftware.
4.	GLIDE	It deals with ligand-protein interactions. It is a paid software.
5.	Rosetta Dock	It deals with biological complexes and quaternary structures. It is an open software.
6.	pyDOCK	It deals with biological complexes and quaternary structure. It is an open software.
7.	Aquasol	It deals with biological complexes and quaternary structure. It is an open software.
8.	FlexX version2.1.3	It predicts binding mode using virtual highthroughput screening.
9.	Autodock	It is used for flexible ligands
10.	FREDversion2013	It performs a systematic examination and scoring analysis of all possible ligand-protein complexes.It is a fast virtual screening program.
11.	Hex	It is mainly used for protein –DNA docking.
12.	HAD-dock	It is used for ligand-protein docking.
13.	Affinity	It predicts the binding model of target protein andligand.

Novel compounds having biological activity of interest are screened using thesemethods.

These can also be utilized for optimization of DMPK/ ADMET (Drug Metabolism and Pharmacokinetics/ Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of potential drug candidates.

In comparison to structure based virtual screening, ligand based virtual screening gives more potent compounds[5]. A relationship is derived between the structural properties and its biological activity in QSAR which is used to predict the biological activity of novel compounds. QSAR methods are used to identify potential ligands using 2D or 3D descriptors. Relationship between the activity and structure of the compound is predicted using regression analysis. These methods result in designing of drug molecules that fit best into the target protein binding sites. Regression models are also used to calculate or predict biological activity and for prediction of favorable and unfavorable interactions.

Changes in functional groups of ligand molecules will result in deviation in biological activity. In QSAR method, data set is splitted into training and test set with available activity values. Training set is used to predict QSAR model and test set is used to predict the performance of QSAR model[23].

Structural and physicochemical properties of molecules are represented using numerical values which are known as molecular descriptors[7] (Table 3). Molecular descriptor field is interdisciplinary and it involves a number of theories.

0D-4D	Molecular descriptors
0D	Constitutional and count descriptors
1D	Chemical fingerprints
2D	Graph invariants (bonds are designated as edges and atoms as nodes)
3D	Geometrical, WHIM etc.
4D	COMFA, DRID methods

Table 4
Software(s) used in LBDD[15]

S.N.	Softwares for LBDD	Description.
1.	SYBYL	Prepared by Tripos
2.	Discovery Studio	Prepared by BIOVIA
3.	MOE	Prepared by Chemical computing Group
4.	Boomer	Pharmacokinetic drug monitoring
5.	Cyber Patient	Pharmacokinetic simulations
6.	Pkfit	Pharmacokinetic modelling
7.	JPKD	Therapeutic drug monitoring
8.	Tdm	Therapeutic drug monitoring
9.	Pharma gist	Ligand based pharmacophore search
10.	Zinc Pharma	Both PDB and pharmacophore based ligand search

Fig. 3: Drugs successfully designed using CADD

Modern QSAR started way back in 1962 with the publication by Hansch group. The five shape descriptors for substituents were successfully used to describe the steric effects of substituents. 3D-QSAR and COMFA (Comparative Molecular Field Analysis) methods include numerous 3D- conformations of analogues and their electrostatic energies. Steric and electrostatic molecular fields of ligands are correlated with bioactivities using partial least square. Partial least square (PLS) is used to calculate and correlate steric and electrostatic molecular fields of ligands with bioactivities.

In CoMSIA (Comparative Molecular Similarity Index Analysis), hydrogen bonding, hydrophobic effects, steric and electrostatic effect are included. 3D QSAR methods, COMFA and COMSIA are applicable only to static structures of chemical analogues. It does not consider or neglect the dynamic nature of ligand[2]. Different types of softwares are available for designing and building of pharmacophore model and for evaluating its ability to correlate biological activity of compound with its structure (Table 4). Examples of the softwares used for pharmacophore modelling are Discovery studio, MOE and SYBYL.[22]

Successful cases of drugs designed using CADD

Numerous compounds have been successfully developed using CADD techniques such as Saquinavir, Captopril, Indinavir, Ritonavir, Dorzolamide, Triofiban, Raltegravir, Zanamivir, Aliskiren, Boceprevir etc. [Fig. 3]. Some of these drugs are active against HIV virus, some of them are

carbonic anhydrase inhibitor, hepatitis C virus inhibitor, influenza A and B virus inhibitors.[2,7,24]

Conclusion

Computational tools are used efficiently these days by medicinal chemists for finding the potential therapeutic compounds used in treatment of various diseases. With the help of docking programs and QSAR models, active binding sites on the target proteins can be determined and the strength of binding molecules can also be determined. These computational tools have really expedited the new drug development and designing process.

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(Received 25th December 2021, accepted 20th February 2022)