Computer Aided Drug Design an Approach in Modern Drug Discovery

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ABSTRACT

Drug discovery and development is an extremely time consuming, lengthy, and interdisciplinary process. In-silico chemistry and molecular modelling have been increasingly popular in recent years as tools for computer-aided drug design. The fields of molecular biology, nanotechnology, and microbiology all use in-silico drug design techniques. However, structure-based drug design and ligand-based drug design approaches are extremely efficient and effective strategies in drug discovery and development. A variety of CADD approaches are considered as potential methodologies depending on their needs. These approaches could be combined with molecular docking to do virtual lead development and identification screening. To increase the effectiveness and efficiency of drug discovery and development, computational techniques have recently gained popularity in the pharmaceutical business and academic disciplines.

Keywords

Quantum mechanics, virtual screening, Ligplot analysis, molecular docking, and molecular dynamics.

1. INTRODUCTION

Drug discovery and development is extremely complex, prolonged and there are many factors responsible for the failure of different drugs such as lack of efficiency, side effects, poor pharmacokinetics, and marketability. The expenditure of this method has amplified ominously throughout the past thirty-four years. The Pharmaceutical Manufacturer's Association undergo the industry average information which has shown that the expenditure on drug development has enlarged from $4 million in 1962 to over $350 million in 1996. The improvement time of a drug from the first synthesis to its foreword in the market

has almost multiplied between 1960 and 1980. It has remained comparatively unaffected since 1980 with a period of 9-13 years [1].

Computer-aided drug design discovered and designed highly effective therapeutic medications that have application in the biomedical sector. It transfers two -dimensional or three-dimensional diagrams of product material, process tolerances, and dimensions with detail for the manufacturing process. The basic steps in drug designing are such as selection of disease, target selection, lead compound identification, lead optimization, pre-clinical trials, and pharmacogenetic optimization [2]. The testing is based on the products obtained from a natural source or by synthesis of compounds. Compounds exhibiting carcinogenicity, complex synthesis, insufficient efficacy, high toxicity, and low activity cannot be used as a drug. Because of this, only one of the 1000 examined compounds is accessible in the market. The cost of the products and time-consuming processes are also minimized. Drug development is a series of procedure employed to identify the drug compounds for the effective treatment or control of disease targets. To begin, a large number of chemical compounds are screened in order to optimize the most suitable disease targets [3].

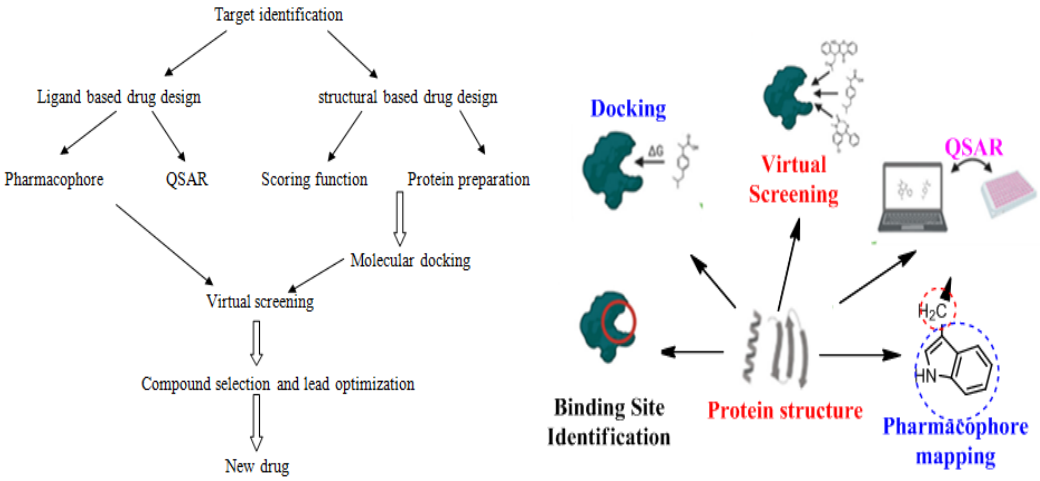

Figure 1.1: (A) Representative workflow for computer-aided drug design (B) Schematic representation of CADD process.

2. CADD Strategies in the Drug Discovery and development

The process of finding new therapeutic molecules for the treatment or control of disease targets is known as drug discovery. To begin, many chemical compounds are screened in order to find the best disease targets. In order for the drug molecules to be adjusted to the binding site, it is necessary to have insight knowledge about the structure of the drug receptor.

CADD relies on the binding of the receptor (protein) and the ligand. It consists of the following steps:

I. Candidate drug discovery

- ❖ Selection of Therapeutic Target
- ❖ Lead Discovery
- ❖ Lead Optimization

II. Preclinical and clinical trials to assess the drug's efficacy, safety, and side effects

- ❖ Clinical trials
- ❖ Animal studies

III. The FDA's approval process for the newly discovered medicine is made available for usage by the general public.

- ❖ Further post marketing testing
- ❖ Advance development of the drug

Ehlirch introduced the concept of pharmacophore in 1909. The pharmacophore is a framework of molecules carrying the necessary features for the pharmacological response. The pharmacophore is an addition of stearic and electronic properties which is necessary to assure the flawless interaction of supramolecules with a specific biological target and to block its activity. A pharmacophore can either be structure-based or ligand-based. The Pharmacophore

approach is employed in virtual screening, denovo design, and other applications such as lead optimization and multitarget drug design [4].

Most important pharmacophoric features representing stereoelectronic properties

Steric features- L (Substituent length), B5 (Substituent width), MR (Molar refractivity), Volume, Surface area

Electronic features- Hammet constant, FR (field and resonance parameters), Ionization constant, Atomic charges

Lipophilic features - Π (Hansch constant), F (hydrophilic fragmental constant), logP (partition coefficient), logkw (capacity factor values from RP-HPLC), MLP (Molecular lipophilic potential)

H-bonding features - HBA (number of H-bond acceptors), HBD (number of H-bond donors) [5].

2.1.Structure based pharmacophore modelling

Structure-based drug design (SBDD) approach includes the 3D structure of a macromolecular target required to obtain a structure-based pharmacophore model. Protein 3D structure provides fundamental details at the atomic level that can be very functional for the design and development of novel medications. This concept is specific and efficient in discovering the lead molecules and their optimization to recognize the disease at a molecular level. SBDD employed general processes consisting of structure-based virtual screening (SBVS), molecular docking, and molecular dynamics (MD) simulations. These methods find numerous applications to estimate binding energies, protein-ligand interactions, and conformational changes in receptors upon binding with a ligand. It is employed in abundance by pharmaceutical industries and researchers responsible for discovery of several drugs available in the market [6].

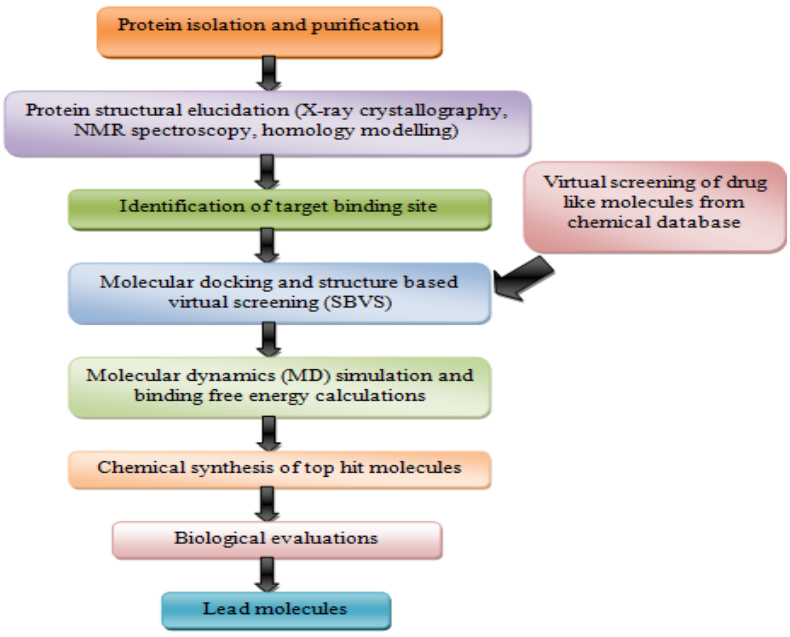

Figure 1.3: Essential steps involved in structure based drug design

2.1.1. Preparation of the Target Structure

Over the last several decades, advancement in structural elucidation techniques such as X-ray and NMR, the structures deposited and available in protein data bank (PDB) have increased. Many target protein structures have not been figured out yet due to the limits of experimental methods. A computational method such as comparative homology modeling and ab initio modeling has been rather successful in analyzing the structures of the proteins from their sequences [7].

2.1.2. Identification of the Ligand Binding Site

The information about the ligand-binding site is imperative for carrying out specific docking. Site-directed mutagenesis research or X-ray crystallographic structures of proteins co-crystallized with ligands or inhibitors can both offer information on the binding sites. Although there is a lack of experimental data about the binding sites of many proteins, we can estimate the potential binding

sites of the target proteins using a variety of programs and web servers, including CASTp, DoGSite Scorer, NSiteMatch, DEPTH, MSPocket, MetaPocket, and Q-SiteFinder. During the lead identification process, the bulky compounds that do not fit well into the binding site pocket are discarded [8].

Molecular docking tools for protein-ligand interaction studies-

- **AutoDock:** Lamarckian genetic algorithms simulated annealing searches, an traditional genetic algorithm searches are all options for conformational searching methods in AutoDock. A semiemprical free energy force field is used to estimate the binding free energies of small compounds to protein targets.
- **AutoDockVina:** When compared to AutoDock, AutoDock Vina computations are faster and more accurate in predicting binding modes because they use a sophisticated gradient optimization approach [9].
- **GOLD:**GOLD (genetic optimization for ligand docking) is an automated liga nd docking tool that permits complete ligand conformational flexibility with p artial protein flexibility and investigates the binding conformations using a ge netic algorithm.
- **CDOCKER:** CDOCKER (CHARMm-based DOCKER) is a computerized docking program that applies the CHARMm19 family of force fields and provides full flexibility of ligand and CHARMm engine with lower computation time [10].
- **DOCK6:** It is a docking tool that assesses small molecule conformational sampling using the anchor-and-grow search algorithm.
- **FlexX:** FLEXX is a fully automated docking tool for flexible ligands that generates accurate and dependable results.

- **Glide:** Glide (Grid-based ligand docking with energetic) executes an extensive search of the positional, orientational, and conformational space of a ligand binding to a receptor with the required computational speed.
- **SwissDock:** A web server that enables the docking of small molecules to specific target proteins [11].

2.1.3. Compound library preparation

Lipinski's Rule of Five, ADMET (absorption, distribution, metabolism, an d toxicity) parameters, and other toxicity parameters like acute rat toxicity, serum glutamic oxaloacetic transaminase elevation, carcinogenicity and hepatotoxicity are employed to sort drug-like compounds prior to molecular docking.Lipinski's rule of five states that a substance is considered orally bioactiv e if its physiochemical characteristics fall within the acceptable ranges, such as molecular weight (MW)≤ 500, partition coefficient between n-octanol and water logP ≤ 5, number of hydrogen bond donors (HBD), ≤ 5, and number of hydrogen bond acceptors (HBA) and ≤ 10. Human gastrointestinal absorption (HIA), blood-brain barrier (BBB) permeability, plasma protein binding, P-glycoprotein (P-gp), and cytochrome P450 (CYP) inhibition, and are a few of the ADMET features that are often employed. The synthetic accessibility of these molecules should be considered in addition to the pharmacokinetic characteristics, drug, and safety [12].

2.1.4. Molecular Docking and Scoring Functions

A computational technique called molecular docking; studies the interaction between ligands and target receptors at the molecular levels and permit the ranking of the compounds by determining their binding affinity against the receptor using a variety of scoring functions. It studies the interaction between a target receptor and ligand at the molecular level. A large conformational space that takes into account many binding poses and explicit reduction of the binding

affinity of the ligands corresponding to each binding pose is two elements that contribute to the favourable binding poses of the ligands with a target active site. Flexible-ligand search docking and flexible-protein docking are two diverse forms of molecular docking [13].

2.1.5. Fragment-based design

High molecular weight lead compounds have poor solubility, which leads to unfavorable pharmacokinetic features, which is a challenge for researchers. An FBDD strategy was proposed by scientists as a solution to this problem. The basis of FBDD is the discovery of soluble, low-molecular-weight, and chemically complex ligands (150 Da) which target subpockets within a huge binding site. Because they are easier and simpler to handle, these fragments serve as the foundation for "hit-to-lead optimization." Through successive steps, adding functional groups, or connecting various fragments, the selected fragments are optimized. A chemical compound must follow the Rule of Three to be classified as a fragment. This criterion states that fragments must have a molecular weight of less than 300 Da, cLogP of three, three hydrogen bond donors, and three hydrogen bond acceptors. The three stages of the FBDD technique are fragment library design, fragment screening, and fragment elaboration [14].

2.1.6. Molecular Dynamic (MD) Simulation

In the late 1970s, a protein was simulated using MD simulation for the first time. This powerful physical method, is based on Newton's laws of motion governing interatomic interactions, is used to predict the positions of each atom in a molecular system concerning time. A suitable force field is utilized to estimate the forces between interacting atoms, and this estimate is then used to calculate the system's overall energy. A suitable force field is utilized to estimate the forces between interacting atoms, and this estimate is then used to calculate the system's overall energy. Numerous factors have resulted in the widespread use of MD

simulations [15]. It is extremely challenging to record the position and velocity of every particle in a system at every instant using any experimental approach. The simulation conditions can be precisely controlled and are known in advance. As this technique helps to uncover many atomistic features, such as binding, unbinding, and conformational changes in the receptor at a fine resolution that generally cannot be achieved through experimental research, MD simulations have been widely used in the structure-based drug development process [16].

Table 1.3: Commonly used molecular dynamic simulation software [17]

Software	Features	Simulation system
GROMACS	GROMACS (Groningen machine for chemical simulation) is a well-organized and versatile MD program with source code suited for simulation of biological macromolecules in aqueous and membrane environments.	Proteins, lipids, carbohydrates and nucleic acids
NAMD	NAMD is a high-performance bimolecular simulation tool that employs the prioritized message-driven implementation capabilities of the charm+/converse parallel runtime system compatible with parallel supercomputers and workstation clusters.	Proteins, lipids, carbohydrates and nucleic acids
AMBER	Amber is a widely used bimolecular simulation method with a compilation of codes that work together.	Proteins, carbohydrates and nucleic acids
CHARMM	CHARMM (Chemistry at Harvard molecular mechanics) is extensively used molecular simulation program that examine biological molecules such as proteins, lipids, nucleic acids, peptides, carbohydrates, and lipids.	Proteins, lipids, carbohydrates and nucleic acids
Desmond	Desmond is a prevailing molecular dynamics simulation program developed by D.E. Shaw with significant speed, accuracy, and scalability.	Proteins and lipids

2.2.Ligand based pharmacophore modelling

The preliminary step of ligand based pharmacophore modelling is information of compounds which interact to the similar target protein having an orientation similar to compounds showing chemical features and hence finally head to construction of pharmacophore. Ligand-based drug design is broadly used method in computer-aided drug design and is applied when the three-dimensional structure of the target receptor is not accessible. Based on the fact that structural similarity corresponds to similar biological functions, the information obtained from a set of active compounds against a particular target receptor can be used in the identification of physicochemical and structural properties responsible for the given biological activity. Some of the widespread techniques used in the ligand-based virtual screening approach consist of pharmacophore modeling, quantitative structure-activity relationships (QSARs), and artificial intelligence (AI) [18].

2.2.1. Pharmacophore based de novo design

The ligand binding site of a macromolecular target is depicted schematically above in terms of its chemical characteristics. Schematically in the middle represents several pharmacophore models created using a ligand-based pharmacophore modeling method. The conceptually low depicts many possibilities that could arise during virtual screening based on pharmacophore.

A symbol H depicts the form of the ligand-binding site [19]. Every atom or group in a molecule that exhibits certain characteristics related to molecular recognition can be reduced to a pharmacophoric feature. These molecular patterns are classified as hydrogen bond donors, acceptors, cationic, anionic, aromatic, or hydrophobic. Pharmacophore fingerprints are the term for comparing several compounds at the pharmacophoric level. It helps for counting topological fingerprints, the distance between feature points in bonds.

Fingerprints tool is applied to identify the biological function revealing important contributing features, to determine the similarity between molecules or among the molecules library, and to identify the same elements of the ligand [20]. The idea of a pharmacophore is utilized in virtual screening techniques to find compounds that have particular biological effects. The right 3D organization of the required interaction method is represented by query pharmacophore.

There are numerous different tools and techniques for pharmacophore modelling, including;

- **Catalyst-** it is based on an algorithm that analyze 3D configurations of chemical description common to a set of ligands, in which each configuration is scored based equally on estimated rarity and the intensity to which it is general to the input set [21].
- **Ligand Scout-** to create pharmacophore models for high throughput virtual screening, Ligand Scout is a fully automated program that identifies and classifies protein-ligand interactions (hydrogen bond interactions, charge transfers, and lipophilic areas).
- **DISCO-** In contrast to 3D QSAR, DISCO is an automated pharmacophore approach that analyzes the data for all pharmacophore hypotheses that fit.
- **Pharmer-** it is a pharmacophore search tool that uses the Pharmer KDB-tree and bloom fingerprints to organize molecular data. This enables the rapid screening of millions of compounds in a reasonable amount of time.
- **GASP-** it is a fully automated tool for generating pharmacophore models which detect and classifies protein-ligand interactions (hydrogen bond interactions, charge transfers, and lipophilic regions) which form the basis of the pharmacophore model used for high throughput virtual screening.

- **Pocket v.2-** it is an automated tool to generate a pharmacophore model from a given protein−ligand complex structure and has been intended using the pocket module of LigBuilder [22].

2.2.2. Virtual screening

Virtual screening is the *in silico* techniques used to investigate large compound databases to choose a smaller number of compounds for testing of biological activity. It is also used to choose compounds from internal databases for screening, from external suppliers to choose compounds for purchasing, and to choose compounds for synthesis. The first step in virtual screening is finding compounds that are similar to drugs but don't depend on the same drug target. The virtual screening process of estimating and analyzing collections of compounds in order to determine which compounds should be prioritized for synthesis or investigation [23].

The primary part of virtual screening is to assess drug likeness of small molecules, and drug like molecules represent favorable absorption, distribution, metabolism, excretion and toxicological parameters [ADMET].

In silico screening, also known as virtual screening uses methods for analyzing and estimating huge datasets of compounds to find potential novel medication candidates. Creative BIOLABS offers services of virtual screening for any targets with solved 3D structure in terms of our library, which is of excellent quality and contains over 10 million compounds. Virtual screening can evaluate enormous libraries of chemicals by employing computer tools [24-25].

2.2.3. Quantitative structure effect relationship (QSAR)

It is a mathematical expression showing biological activity according to structural framework of a series of homologous molecules. Based on the similarity between biological activity and the molecular descriptors prediction of activity of wide range of chemical compounds is done by QSAR. With the help of

statistical calculations results with calculative values such as chemical, physical, topological and molecular properties development of new molecules with desired properties by QSAR occurs. The final outputs of the QSAR estimations set of mathematical expressions relating chemical structure to biological activity QSAR analysis employs all the molecular descriptors from various representations of a molecule [1D,2D AND 3D representation] to compute a model [26-27].

Quantitative structure activity relationship modelling leads to construction of predictive models of biological activity as a function of structural and molecular information of compound library, in the discovery of the drug. The concept of QSAR has been used and has been gained wide application for correlating molecular information with not only biological activities but also with physicochemical properties which has been termed as QSPR [quantitative structure property relationship] [28].

The QSAR study uses statistical techniques to determine the mathematical relationship between chemical structure and biological activity. It takes 10-12 years to identify a molecule as a medicine, and both the design and discovery of a drug are exceedingly challenging and time- consuming processes.

Drug candidate selection by QSAR research would lower the cost of production a nd failure at an early stage. Drugs frequently fail during preclinical and clinical tri als, and the cost of drug discovery is very high. QSAR methods assist in finding h its from a huge library of compounds; the found hits molecules may then be purch ased and their activity can be investigated through studies. OSAR studies save money and time [29].

Basic requirements in QSAR studies

- All homologous molecules belong to the congeneric series.
- All homologous molecules should exert the same mechanism of action.
- All homologous molecules should binds in a comparable manner.

- Isosteric replacement can be predicted.
- Binding affinity is correlated to interaction energies
- Biological activities are correlated to binding affinity [30].

Table 1.4: list of programs available for calculating molecular descriptors for building QSAR models [31, 32]

Programs	**Molecular descriptors**
ADMET Predictor	Predicts over 140 properties such as solubility, logP, pKa, sites of CYP metabolism and Ames mutagenicity
ChemAxon	Applied for chemical calculations such as molecular weight, elemental composition, LogP, pKa, LogD, LogS, hydrogen bond donor/acceptor (HBDA) count, and various 2D topological and 3D geometrical descriptors
PaDEL Descriptor	It is a standalone software for calculating molecular descriptors and fingerprints including 797 and 2D descriptors and 10 types of fingerprints.
E-DRAGON	It is the electronic remote version of the noted software DRAGON which is an application for evaluating molecular structure activity.
DRAGON 7.0	It calculates 5,270 molecular descriptors including the simplest atom types, functional groups and fragment counts, topological, geometrical, and 3D descriptors which are organized into 30 logical blocks.
Pre-ADMET	It is a web based program used for the calculation of drug like physicochemical descriptors such as lipophilicity (logP), molecular weight, polar surface area, and water solubility.
QikProp	This program allows the prediction of various pharmacologically important descriptors of chemical compounds such as octanol/water and water/gas logPs, log S, log BB, overall CNS activity, Caco-2 and MDCK cell permeability for human serum albumin binding etc.

2.2.4. Artificial Intelligence and Drug Discovery

Artificial intelligence (AI) is a subset of machine intelligence that depends on computer capacity to learn from data already in existence. To predict the biological activity and toxicity of pharmacological compounds, AI has been included into a number of computational modelling techniques. Additionally, AI has many uses in the drug discovery process, including de novo drug design, virtual screening, protein-protein interaction prediction, and protein-protein folding prediction [33]. Machine learning (ML) and deep learning are two potent techniques that are frequently employed in rational drug design (DL). Support vector machine (SVM), Random Forest (RF), and Naive Bayesian (NB) ML algorithms have been widely used in drug discovery (NB) [34].

CONCLUSION

Computer-aided drug design (CADD) is a multidisciplinary area that draws researchers from pharmacology, medicine, information technology, and other fields to develop new tools and techniques or improve those already in use to aid in the drug development process. These strategies have been beneficial at different phases of the drug discovery process, which has led to a decrease in the price and length of time needed to produce a medicine compared to traditional approaches. Several examples of medications that are currently on the market that were successfully designed utilizing these tools are given along with several CADD tools that aid in the drug development process. These technologies can be improved and utilized to help with the different stages of drug discovery.

Conflict of Interest

The authors declare no potential conflicts of interest with respect for publication of this article.

Source of Interest

No

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