

A Novel Perspective In Drug Design And Drug Discovery (4d) With Computer-Aided Drug Design (Cadd): A Review

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ABSTRACT

Nowadays there are so many types of diseases that are causing to human and animal health. This disease or disorder makes human health very severe, lethal, and life-threatening to survive. Several troubling diseases make the body's condition abnormal or cause a disturbance in the function and structure of the body or organ systems. It states that the person is ill or sick which is characterized by the manifestation or symptoms which may be seen internally or externally. To overcome these manifestations there are some specific substances or molecules are used. These substances are called drugs and can cure various diseases or disorders. A drug compound may be natural or synthetic obtained from a plant, animal sources, or any chemical compound which can treat and prevent diseases. There are some modern methods to produce a drug. To discover a new drug is called a drug discovery which saves time and trial discovery takes a lot of time for selecting, researching, optimization, of a drug. These drugs are beneficial and lifesavers. Several days or years pass or are required to discover a new molecule or to design a single molecule. Drug discovery is the research of new compounds and new moiety. Drug design is a very convenient and time-saving method for drug discovery. Drug design is a type of invention and it is a computational method and it is an important part of drug discovery. There are two techniques of drug design ligand-based and receptor-based drug design. Computer- aided drug design is a computational method in which there is a prediction of the structure and molecules by a mathematical equation. In LBDD QSAR & Pharmacophore model is there and in RBDD Molecular Docking & De Novo Design is present. In QSAR there are of the efficacy of a biologically active compound. It is a mathematical relationship that identifies and quantifies the molecule. These methods can be applied and then virtual screening. Then the identification of the molecule binds to the binding site or receptor and gives its action..

Keywords: Drug Design; Pharmacophore modeling; QSAR; Molecular Docking; Virtual Screening..

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INTRODUCTION

Drug: A molecule or a substance intended for use in the diagnosis, mitigation, cure, prevention, or treatment of disease or disorder or abnormal condition in man and animal and alter or modify a person's mental and physical condition. Those substances are used to treat various diseases and used to cure the symptoms and reduce the severity. Drugs may be synthesized naturally or synthetically and used to treat various types of diseases. It gives a therapeutic effect by inhibiting or inducing the function of biomolecules. The drug's effect on the living

system. A drug design is a modern technique in which drugs are designed by computational methods and also save time and money [1].

Drug Design: Drug design is a part of drug discovery there is a need to research a new drug for certain diseases. Drug design is a software-based method. In this technique various tools are assisted, thereby minimizing the cost of research and time for the development of new drugs. This technique of drug design is called computer-aided drug design (CADD). It has prominent approaches that are extensively used in pharmaceuticals. For inventing new drugs there are so many stages or phases which finally

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produce the single moiety which gives a therapeutic effect. These time and saving methods are invested by the pharmacological laboratories and have various phases of drug discovery. Lead moiety is a compound that gives therapeutic and pharmacological effects that treat abnormalities or symptoms [2-3].

Drug design is a type of invention in which there is a searching of new medications based on the biological target or receptor in which the drug binds to the receptor making the complex and giving the pharmacological activity. Drug design is a systematic approach to finding, researching, inventing, and selecting drug molecules based

on their interactions between drugs and target proteins. Drug discovery is to separate a large number of compounds into small ones for predicting the active compounds and the predicting compounds for the optimization of biological properties like affinity, effect, and ADMET. Computational techniques are widely used in CADD which are used to create and analyze new medications and other therapeutically active compounds (Figure 1) [4-5].

Drug Development:

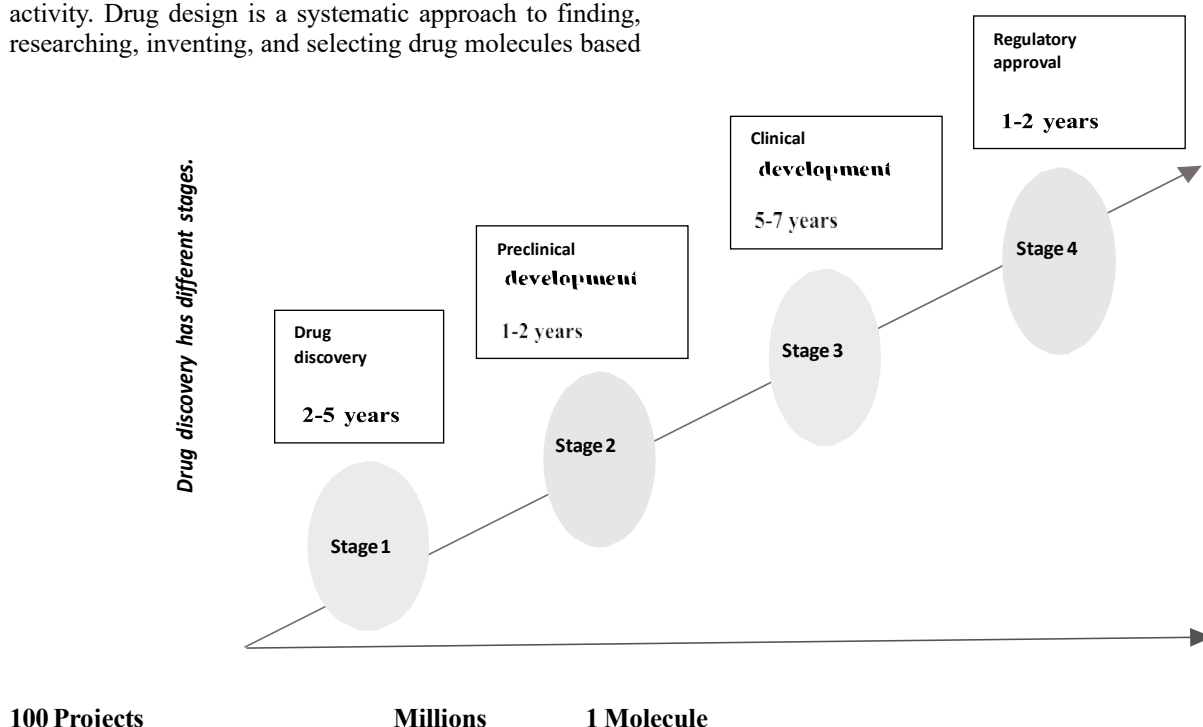


Figure 1. Stages of Drug Discovery

Drug development is a methodology in which a new pharmaceutical drug is brought into the market when a lead moiety has been recognized then the process of drug discovery begins and brings the new drug into the market. It includes drug discovery, chemistry, pharmacology, pre-clinical testing, manufacturing, clinical trials, and regulatory submissions (Figure 2).

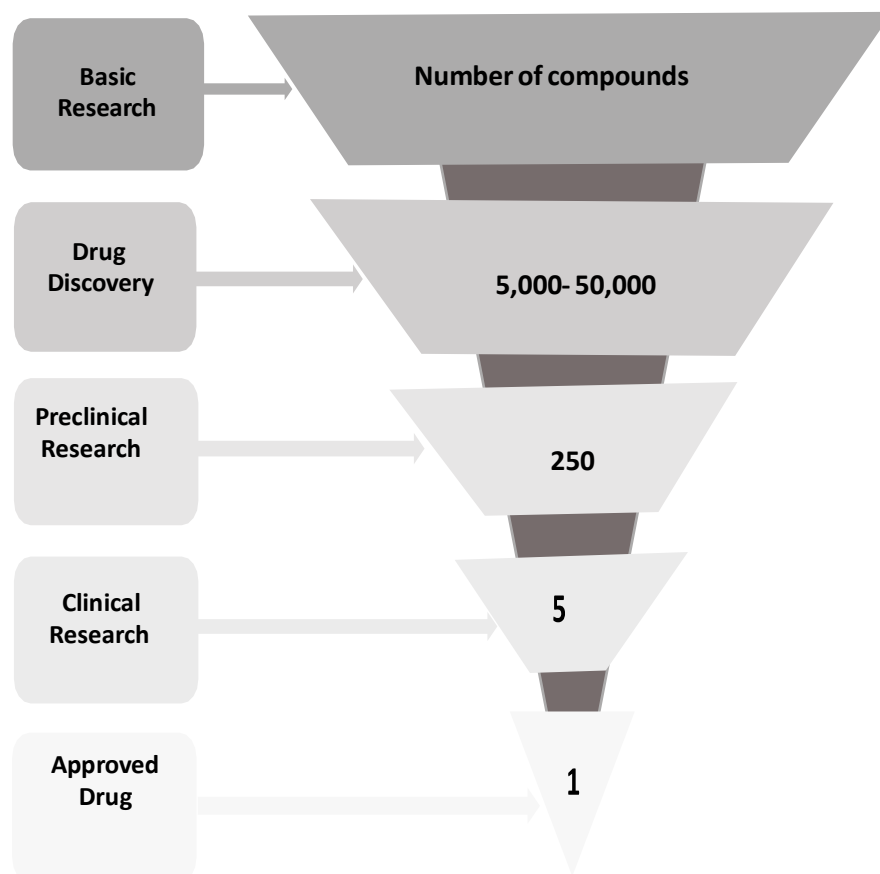


Figure 2. Process of Drug Discovery

Drug discovery includes first the research of a drug or lead compound that gives therapeutic activity and can treat or reduce the severity by binding to the target site. Research takes several years to find new moiety to give the effect. Drug discovery takes several years to discover one compound there are some procedures like pre-clinical and clinical trials after the testing of the drug the drug gets approved by regulatory approval. The drug has to be passed through some phases and developed into a single drug. Drug design is a computational method in which a drug is discovered by computers and there is a virtual screening is a computational method used to search libraries of small molecules to identify the structure where a drug bind such as proteins (Figure 2) [6-7].

Drug Discovery Process: It is the process of the identification of chemical entities or lead compounds which treat diseases or abnormalities. Research of drugs is an integral part of drug discovery from research to the launch of a finished product, developing a new drug. A goal idea can come from a variety of sources, including-clinical, clinical research, and the commercial sector. It may take many years to generate a single molecule. Once a target has been selected, then make the suitable molecules. Product Characterization.

Formulation, Delivery, and Packaging Development.

Pharmacokinetics and Drug Disposal.

Preclinical Toxicology Test and IND Application.

Bioanalytical Test.
Clinical trials [8-9].

Stages of drug design:

Choose a disease

Selection of drug target

Define a bioassay

Search for precursor compound

Describe structure Activity relationship

Identification and detection of pharmacophore

Improve Targeting [10-11]

Drugs discovered by drug design: (Table 1)

Table 1. Drugs discovery by CADD

Drug	Disease	Target
<i>Saquinavir</i>	AIDS	Inhibits proteases of HIV1 & HIV2
<i>Zanamivir</i>	Influenza A & Influenza B	Inhibits neuraminidase
<i>Captopril</i>	Hypertension	Inhibits angiotensin-converting enzyme
<i>Dorzolamide</i>	Glaucoma	Inhibits carbonic anhydrase

Drug Discovery Process: (Figure 3)

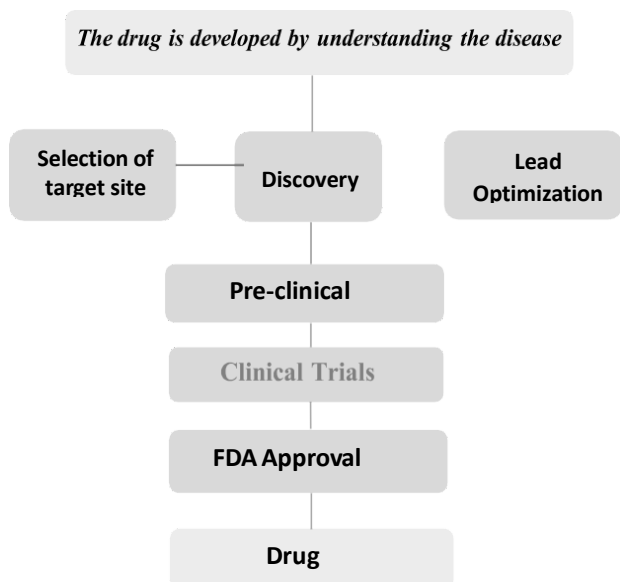


Figure 3. Drug Discovery Process

Methods in Drug Design: There is main two types of drug design Ligand-based drug design (LBDD) and Structure-based drug design (SBDD): (Figure 4)
 Ligand-based drug design also known as indirect drug design
 Structure-based drug design also known as direct drug design
 Rational drug design
 Computer-aided drug design [12-13]

TYPES OF DRUG DESIGN: (Figure 4)

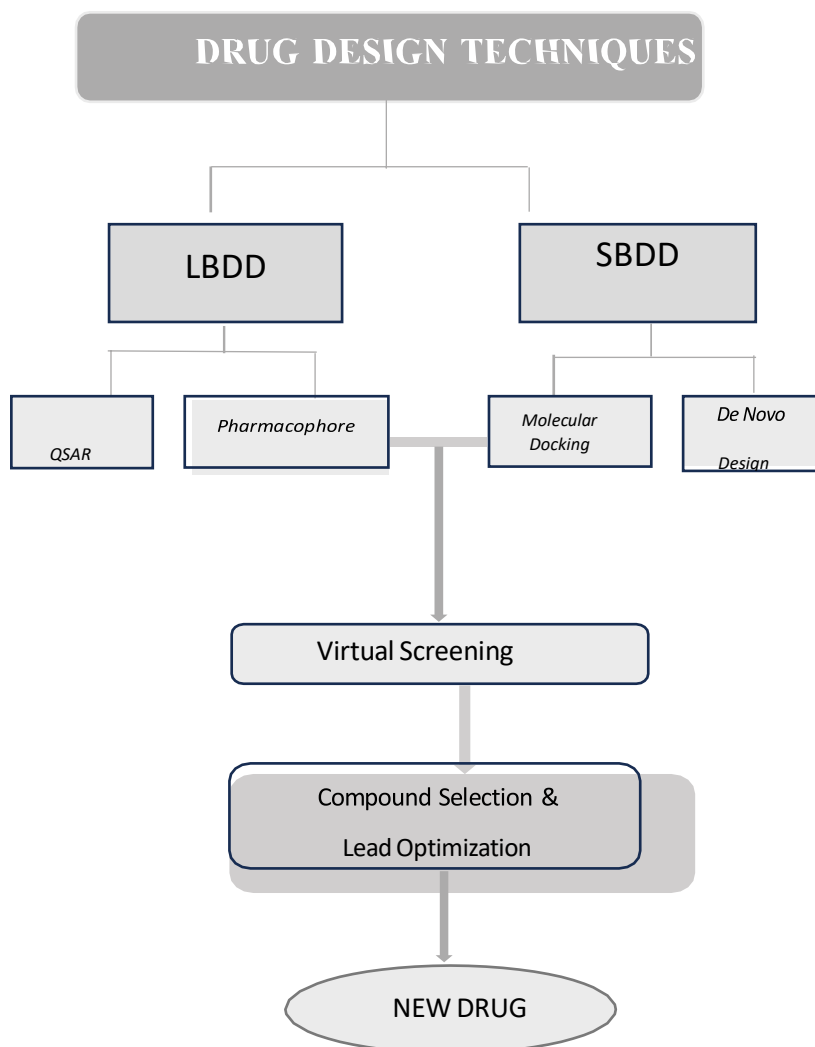


Figure 4. Types of Drug Design

Ligand-Based Drug Design:

LIGAND

A ligand is a molecule or a compound or a substance which donates a pair of electrons or binds to a central atom to form a complex. Ligands may be cations, anions and neutral molecules or compounds.

Ligand-based drug design is an approach used when there is no receptor present in 3D information. and betrothed biological target. 3D quantitative structure- activity relationships (3D QSAR) and pharmacophore modeling the mostly used tools in ligand-based drug design. These tools provide appropriate predictive models for lead compound identification and optimization of lead compound. Ligand based drug design is depend on drug or ligand which used to bind particular receptor and that specific drug or ligand binds and gives its particular therapeutic effect. Ligand based drug design is a type of drug design which is used to find new ligand which binds and show effect. Ligands maybe positive or negative charged ions which attract to particular site and make a complex [14-15].

PHARMACOPHORE MODELLING:

Pharmacophore modeling is a technique in which a new molecule or compound can be identified. Pharmacophore is identified by LDBB. It can be featured as:

- 1D (Physical or biological properties)
- 2D (Substituents)
- 3D (Hydrophobicity, Ionization)

It is a schematic representation along with bioactive functions and their interatomic structure and its distance. A

pharmacophore modeling is the common steric and electronic parameter. When it interacts, it makes complex with specific biological targets and gives pharmacological response. They are made by utilizing structural information. It is used to identify the interaction between the ligand and binding sites. It is very important to design a new drug for treatment and prevention of intended use. It is a geometrical arrangement of functional groups which is responsible for pharmacological activity. Pharmacophore modeling is used to identify small molecules. Molecular description can be described by the molecular values and from physicochemical properties for example molecular weight, surface area, particle size, electro- negativities, solubility, aromaticity, and others. Molecular description can be derived from experiments, mathematical representation of molecules, graph theory, functional groups, and quantum mechanical theory. 2D identification is derived from molecular structure and 2D fingerprint and 3D identification is derived from the conformation of molecules and 3D fingerprints. The software can predict molecular annotation. Pharmacophore Modelling is most often applied to virtual screening in which the identification of molecules provides the pharmacological response. It is a computational method applied to various biological applications using drug design i.e. approaches in ligand-based drug design by using pharmacophore modelling technique (Figure 5) [16-18].

Pharmacophore Modelling-Based Drug Design

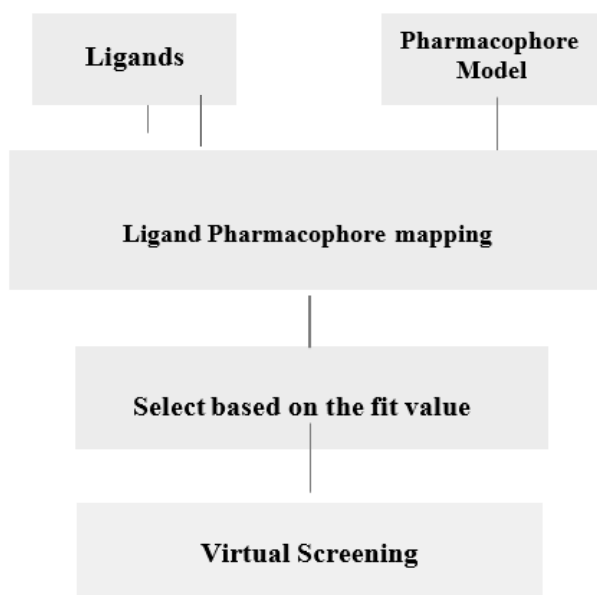


Figure 5. Pharmacophore Modelling

Common software used to predict molecules

Table 2. Software for prediction

Software	Types of prediction
ADAPT	>260 (physicochemical)
ADMET Predictor	>290 (hydrogen bonding)
CODESSA	>1500 (geometrical)
DRAGON	>5200 (RDF, functional groups)
MOE	>300 (physical properties)
MARVIN Beans	>500 (finger prints)
Pre-ADMET	>955 (topological, physico-chemical)

Structure-Based Drug Design:

STRUCTURE

The structure is an arrangement of a molecule or a compound of its atom and its bond. Specifying the molecule and geometrical electronic structure of the target molecule. Atoms are arranged within molecules. Structure-based drug design includes molecular docking and de novo drug design. These methods are highly efficient and have an approach to drug discovery and development of drug design. After the development of the drug, there is virtual screening in which computational methods are used in which compounds are screened against known target structures. Structure-Based Drug Design is a type of drug design that depends on the structure of a molecule which is directly targeted to the molecular structure and makes a complex then gives its action on a particular disease. Structure Based Drug Design is a study on molecules or lead compound find the structure of the compound. It is based on the electronic structure of the molecules these molecules or atoms are attached to the target molecule which is based on structure and gives the action or desired pharmacological activity [19-22].

LBDD refers to drug discovery efforts in the absence of any target structures and in the presence of chemical structures. The approaches for ligand-based drug design are the QSAR method and pharmacophore modeling. SAR is a computational method to quantify the correlation between the chemical structures of a compound and a chemical or biological process. Also known direct as direct drug design. The most popular approaches for ligand-based drug design are the QASR method and Pharmacophore modeling. Recently methodologies are developing in ligand-based optimization with an emphasis on the conformational sample pharmacophore (CSP) SAR Method (CSP-SAR) in the laboratories [2-6].

TOOLS USED IN LBDD:

VEGA platform
 DEMETRA
 T.E.S.T
 OCHEM
 E-DRAGON
 See SAR
 Dragon

LBDD is a computational method in which there is no presence of 3D receptor and its information gives knowledge about molecules that binds to the biological target. In ligand-based drug design, there is the presence of chemical structure that is known to the target. The popular approaches of LBDD in CADD is QSAR and Pharmacophore modelling. It is a direct method of drug design in which the quantification and correlation between the chemical structures and to a specific biological target [7-8]. LBDD includes QSAR and pharmacophore modelling which is widely used techniques used in ligand-based drug design. QSAR is a mathematical method which we can measure the activity of the drug on basis of their structure. A pharmacophore model is defined as a molecule with the necessary structure that binds to a desired target site. Once the Pharmacophore is identified, then there is determined whether it is suitable for the receptor, otherwise, the Pharmacophore is further modified to make a potential drug that gives therapeutic activity [9-10].

QSAR Technique:

The QSAR technique is an essential part of the drug optimization process. To quantify the correlation between the chemical structure and biological process of a series of compounds the QSAR method is used. The developed QSAR models used as a guiding tool for the identification of compounds to modify and optimize the active compound to maximize relevant biological activity. The methods are used in QSAR:

Experimentally measure the value of desired biological activity and then, identify the ideal ligand

Determine molecular descriptors with physico-chemical properties of molecules.

The molecular description and biological activity correlation discover.

The workflow of the Sareth First, identify or select the series of molecules or compounds with experimentally measured values of the desired biological activity. When the molecules are selected then, they are studied in the silico-model by using molecular mechanisms or quantum mechanical methods. After identifying active ligands, the molecular descriptors are generated for describing the chemical features of molecules. They determine suitable molecular descriptors with the physico-chemical properties of molecules. Molecular descriptors are used to create a molecular 'Fingerprint' for each molecule. The

knowledge- based, molecular mechanical, or quantum chemical tools are used to generate molecular descriptors. Molecular descriptors are used to develop a mathematical relation, which explains the variability of the biological activity of molecules. The final step is to develop models that are subjected to validation procedures (internal and external) to test their statistical robustness and predictive power. It is a mathematical method that detects the identity and quantity of biologically active compounds. It is the relation between chemical and structural properties of compounds [23-24].

TYPES OF QSAR Technique:

1D QSAR: Correlation of molecular activity with its properties for e.g., pika, log P.

2D QSAR: Correlation with structural 2D patterns for egg, pharmacophore.

3D QSAR: Correlation with non-covalent interaction.

SBDD proceeds through cycles lead to optimized drug for clinical trials. Generally, drug discovery consists of some steps: the discovery phase, the development phase, the clinical trials and the approved phase. SBDD usually used the computational tools in which the structure of a proteinosis used to design or predict a new compound or molecule which binds to specific target and gives the action. Subdues the 3D structure of the proteins. It is rapid process of drug discovery and optimization because of 3D structure of target protein. Analysis of disease and binding site. Most of the drugs are identified by SBDD by using some techniques. Three-dimensional structure provides in SBDD. Structures determined by NMR spectroscopy, homology modelling, etc. SBDD is also known as reverse pharmacology (Figure 6) [3-5].

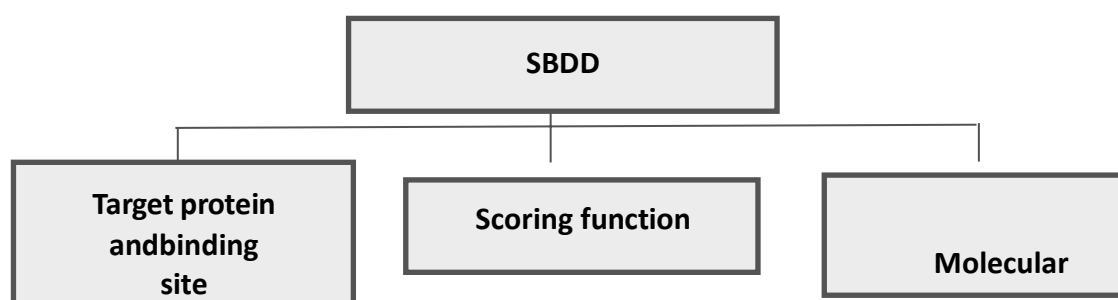


Figure 6. SBDD

Determination of target protein and binding site

Target protein identification is the process of SBDD. It provides information about binding site. The binding sites determined by structural biological techniques in the 3D structure such as NMR, X-ray crystallography. Next step is the identification of the binding site of the target protein. The ligand binds and gives its therapeutic effect. There are some methods for binding site mapping specifically for SBDD, and these methods identify particular regions of the target protein that interact with appropriate functional groups on drugs.

TOOLS USED IN LBDD:

- SWISS MODEL
- MODELER
- CASTp
- Autodocking
- Active site prediction tool [17-18].

Scoring function:

The determination of binding site and ligand. Prediction of protein target and identification of leads. The scoring function helps to calculate the binding affinity between protein and ligand. Scoring functions are divided into force field, empirical, knowledge-based. It is the computational methods widely applicable to structure-based drug design for determining protein -ligand interaction [19].

Molecular Docking:

Molecular docking is a virtual simulation technique used to model the interaction between a small molecule and a protein at the atomic level. This technique is also used to characterize the behavior of small molecules at the binding site of the target protein. The insertion process involves two basic steps - the estimation of ligand conformation and the second is the binding of the ligand within the target active site with accuracy, so this technique is widely used in structure-based drug design (SBDD) (Table 3) [14].

Table 3. Software with its release year

Software	Release Year
Sees AR	2019
Auto dock	1990
Auto dock Vina Extended	2018
Swiss Dock	2011
Infini see	2019

Dock	2010
GOLD	1995
Glide	2004
Flex AID	2015
GEMDOCK	2004
Sees AR	2019
MS-Dock	2008
Ligand fit	2003
UCSF Dock	1982
GalaxyPepDock	2018
Stardrop	2016
rDock	1998
Way2Drug	2016
Blaster	2009
Haddock	2003

Molecular Docking approach is used to model the interaction between molecule and protein.

Application:

Association between proteins and macromolecules.
Establishment between drug molecular structure and cytotoxicity.

Methods of Docking

Rigid ligand and rigid receptor
Flexible ligand and rigid receptor
Flexible ligand and flexible receptor [11-12].

VIRTUAL SCREENING:

High-throughput screening (HTS) has been important in identifying novel lead compounds in early-stage drug discovery by testing huge chemical libraries against biological targets. High-throughput screening (HTS) needs costly equipment and facilities, and success is dependent on the chemical library size. The computer technique of searching small chemical libraries for therapeutic targets is costly and has a low hit rate. Early-stage drug discovery relies heavily on this step due to its advantages over experimental HTS, including relevance to the drug target, competitive pricing, and efficiency. Med Chem Express (MCE) offers superior virtual screening. Screening involves detecting a certain substructure, matching estimated molecular characteristics, and fitting potential ligands to the target receptor site. This approach can create and optimize libraries using available substances.

Advantages:

Virtual screening for ligands and structures
High-performance computing
Building 3D pharmacophore models
Considering water and solvation effects.

The screening process includes target research, model development, molecular docking/pharmacophore mapping, and scoring/rank.

Advantages:

Ligand-based and structure-based virtual screening
High-performance compute
3D pharmacophore model building
Consideration of water and solvation effect.

Screening Process:

Target research
Model building
Molecular docking/pharmacophore mapping
Scoring/ranking
Compound selection [12-13].

COMPOUND SELECTION:

Compound selection is the process of selecting or choosing a particular molecule or atom for a specific activity in which that molecule or substances bind to the target site and shows the activity. In this process there is need to identify the moiety or a lead compound which shows the pharmacological effect. That particular compound may bind to receptor by Ligand Based Drug Design or by Structure Based Drug Design according to their design or modification. Compound should be select on the basis of the result. A compound should be active pharmacologically and must show the effect on low dose with less toxic effect. Lead compound must treat the abnormalities and must lower the symptoms of various diseases or disorder. Compound selection is based on the result of test or studies which is held on the particular moiety, if the results are showing normal or getting the desired result then the compound should be selected for new drug or new pharmaceutical compound in the market. It shows the desired therapeutic effect with least side effect or toxic effect and has ability to treat or prevent the manor animal

from various diseases or disorders. The compound should be chemically and physically inert in nature and may compatible with other ingredients. The compound should not show any lethal effect. It should be stable in nature and safe and effective in nature. Once the compound or molecule get identified it convert into newpharmaceutical product and get to the market after regulatory approval.

Compound Selection is done on the Basis of:

Design of compound

Structure of compound

On the basis of molecule

Active binding site

Mechanism

Effect of compound

According to Pharmacological & Toxicological study

Biostatics

Sensitivity

Bioequivalence study

Dose frequency

Physical & Chemical Parameters

According to 3D structures

Environmental Factors & other physicochemical and biological factors [14-15].

LEAD OPTIMIZATION:

Lead optimization is the method to detect lead compound or lead molecule. These is the process of identifying the lead compound for the therapeutic effect. Lead optimization is the process for discovering the molecules or compounds which gives the pharmacological activity with least side effect and treat the particular disease. Lead compound are those molecules which gives actual therapeutic effect on body. It converts body from abnormal situation to normal situation or reduces the symptoms of particular disease or disorder. Once the lead compound gets intensified or detected then the pre-clinical drug discovery process, after the preclinical process then the formulation process or produce a new product according to the strength, purity and efficacy of drug.

Stages of lead optimization:

Drug Discovery

Research

Testing

Implementation

Analysis

Pre- Clinical Phase

Clinical Phase

Regulatory Approval

Market [16- 17].

The objective of these stages to make the procedure reliable and form ease in the process. Lead optimization improves the process and profile and DMPK properties of the molecule or lead compound. Also improve the pharmacological properties like safety, efficacy, purity and pharmacokinetic & pharmacodynamic properties and make this process suitable and compatible for drug development process. The aim of the process is to enhance the compounds by evaluating the effect, in-vitro studies, biological properties, to identify the closely related

compound, to transfer effective potent drug and safe drug to evaluation and clinical trials important step in drug development.

It improves the biological effect, target specification, potential for toxicity, Study and evaluation on absorption, distribution, metabolism and elimination.

Lead optimization is a critical process that identifies the efficacy of molecule that how much potent and must be optimized and specific. The process refers to designing of the identified drug. These changes are made to optimize the properties of compound. The compounds are need to be novel and ADMET properties [18].

In computer-aided drug design (CADD), lead optimization refers to the application of computational techniques to refine and improve the properties of initial hit compounds identified through virtual screening or experimental assays. Here's a detailed breakdown of lead optimization in CADD, Hit Identification is the process that begins with the identification of initial hit compounds through virtual screening of chemical databases or high-throughput screening of compound libraries. Hits are compounds that show promising activity against the target of interest. Hit Validation once hits are identified, they undergo experimental validation to confirm their activity and assess their potency, selectivity, and other relevant properties. Experimental assays help prioritize hits for further optimization. Virtual Screening and Docking are Virtual screening techniques are used to explore chemical space and identify new compounds that are likely to interact favorably with the target. Molecular docking simulations are employed to predict the binding mode and affinity of ligands within the target binding site, aiding in the design of optimized compounds. ADME-Tox Prediction about Absorption, distribution, metabolism, excretion, and toxicity (ADME- Tox) properties of lead compounds are predicted computationally to assess their pharmacokinetic and safety profiles. This helps identify potential liabilities early in the lead optimization process and prioritize compounds with favorable ADME-Tox properties. Iterative Optimization is Lead optimization is an iterative process where computational predictions are validated experimentally, and new data are used to refine computational models.

After the discovery of drug lead optimization takes place. Optimization is the promising method to identify the molecule for the therapeutic activity. Used to achieve molecular structure to optimize novelty, purity, safety and efficacy of the molecule. Prior to approval of drug to the market, it must go through pre-clinical and clinical stages to ensure the safety and efficacy. These studies include some stages of drug discovery and drug development process. The drug discovery process, the aim of finder identifies the compounds is called stages of lead, the process is called as lead optimization. Lead optimization is the combination of empirical, combinatorial, and rational approaches that optimize leads. This process is the complex, non-linear and depending on the chemical or molecular structure of compound.

Lead Optimization ADME

Pharmacokinetics and pharmacodynamics and absorption, distribution, metabolism, excretion, asses the general mechanism of action of drugs.

Lead Optimization Toxicity

Molecule may harm to human or animal while testing of drug. It may lead to toxicity which gives harmful or hazardous effect of drug on body. It may alter the mechanism of body. There are types of toxicity:

Acute toxicity

Sub-acute Toxicity Chronic toxicity

When there is a continuous exposure that can exposed to organism.

Lead Optimization Formulation and Delivery

The formulation and delivery of drug is a crucial part of drug discovery and development process. Formulation influences the design of lead compounds. Formulation and drug delivery are closely linked. E.g., intravenous injection gives rapid effect than the solid dosage form and enhance the solubility and absorption, bioavailability and effect of drug. Once the drug molecule gets identified then it converts into the product. After the drug get approved it commercialize to the market [9].

Table 4. Optimization of lead

Target ID Primary Target ID Secondary Target ID Toxicity Target ID	Hit to Lead Improving Specificity Prediction of Toxicity Identifying Target
Lead Optimization Target selectivity Avoiding Toxicity	Clinical Development Identifying Novel Target

This iterative cycle continues until lead compounds with the desired balance of potency, selectivity, pharmacokinetic properties, and safety are identified for further preclinical and clinical development. Overall, lead optimization in CADD integrates computational and experimental approaches to accelerate the discovery and development of new drug candidates with improved therapeutic potential. Lead Optimization Strategy is the Computational techniques are employed to guide the lead optimization process. This involves the use of molecular modeling, structure-based drug design, ligand-based drug design, and other methods to understand the interaction between the lead compound and its target, as well as to predict and optimize its pharmacokinetic properties. Structure-Activity Relationship (SAR) Analysis is a SAR analysis involves systematically modifying the chemical structure of the lead compound and evaluating the resulting changes in its biological activity. Computational methods play a crucial role in analyzing SAR data and guiding the design of

analogs with improved potency, selectivity, and other desired properties. Pharmacophore Modeling: Pharmacophore modeling is used to identify the essential features of the lead compound that are responsible for its interaction with the target. This information is used to design new compounds with similar pharmacophoric features, potentially leading to improved activity [25].

NEW DRUG:

A drug is a molecule or a substance intended for use in the diagnosis, mitigation, cure, prevention, or treatment of disease or disorder or abnormal condition in man and animal and alter or modify a person’s mental and physical condition and reduce the symptoms and abnormality in the body. Those substances are used to treat various diseases and used to cure the symptoms and reduce the severity. Drugs may be synthesized naturally or synthetically and used to treat various types of diseases. It gives a therapeutic effect by inhibiting or inducing the function of biomolecules. The drug treats various major and minor both types of symptoms and disease. A drug compound may be natural or synthetic obtained from a plant, animal sources, or any chemical compound which has the capability to treat and prevent diseases. There are some modern methods to produce a drug. To discover a new drug is called a drug discovery which saves time and trial discovery takes a lot of time for selecting, researching, optimization, of a drug. These drugs are beneficial and lifesavers. A number of days or years pass or are required to discover a new molecule or to design a single molecule. Drug discovery is the research of new compounds and new moiety. Drug design is a very convenient and time-saving method for drug discovery. Drug design is a type of invention and it is a computational method and it is an important part of drug discovery. Drug discovery is the First stage for new drug. After the research of new drug, it goes to lead optimization in which lead moiety is identified which gives pharmacological activity with its molecular and chemical structure. Then the drug gets approved by Regulatory Authority and commercialize to the market. The new drug is the original lead compound which brings in the market (Table 5) [11-12].

Process:

Table 5. New Drug approval process

Drug Discovery
Development
Approved
Marketed

APPROVAL OF DRUG:

After lead optimization, there is clinical and pre-clinical studies on particular drug then new drug application review. Once the drug or compound get identified for particular activity then it proceeds for regulatory approval. Application is submitted along with fees. After verification of drug review data of CMC then the conductance of Inspection if needed. Then the final approval and

specification in different form and fitted in criteria. Form 45- for import and marketing (product) Form 45- manufacturing and marketing (product) Form 45- import and marketing (substances). Form 45- manufacturing and marketing (substances) New drug Application. A new drug application (NDA) describes the full description of drug which is demonstrate that a drug is safe and effective for its intended use. The developer must add the data and information from discovery to clinical trial data in an IND.

Approval of New drug in India:

In India, if the company wants to manufacture or import new drug there is the need for application to seek the permission from the authority (DCGI) by filling the form and submit as given in schedule by Drug and Cosmetic Act 1940 (D&C Act) and Rules. The organization for drug approval in India is Central Drugs Standard Control Organization (CDSCO).

Approval of New drug in US:

Drug approval process seeks FDA approval to sell the drug. NDA application which sponsors formally proposed the FDA approve a new pharmaceutical for sale and commercialization in US. The organization for drug approval in US is USFDA and then marketing [3].

LITERATURE & MARKET REVIEW

In market the CADD has the great scope. Nowadays it gets widely distributed because of time and money consuming method. The process of CADD is a virtual and modern method. Once the drug gets identified it convert into new pharmaceutical product. The product then marketed after the regulatory approval. There is a use of software in to draw and a physical designing.

The purpose of Literature:

Literature allows a man to learn about life

Gather better understanding

Learn the history

To entertain

To provide aesthetic pleasure

To focus on themselves

The arrangement giving pleasing effect

Experiencing worldview

Understanding about our topic

Identifying experts

Research in our area

Answerable to questions

Knowledge about current research [14-15].

The purpose of market review:

It can perceive the target consumer.

It can help how to make connections.

Inform and [plan for next step.

Making valuable business decisions.

Detecting new opportunities for business.

Avoiding loss in business.

Guard the investments.

Secure the funding of company.

Literature review and market research:

It provides the information and knowledge. Identify the gap in research. Literature review is made to prefer the overview and explore while searching a particular topic and demonstrate the research. A literature survey on a particular topic by the given source. Literature offers the overview knowledge and helps to detect various methods.

Market research of different types:

Primary research

Secondary research

Customer research

Product research

Qualitative research

Quantitative research [26].

Approval:

QA review verified all submitted data related to drug to make decision to approve or not depending on the process.

FDA drug review:

If a drug developer has proof from to present test for preclinical and clinical research that a drug is safe and effective for treating the disease and disorder. The FDA review team inspect the data which is submitted by researcher or developer. After the inspection the committee makes the decision and make sure that give the approval or not.

Accelerated Approval:

Probably, expiration to accelerate the method during approval of new drug. When identifying the new drug, it can take number of years whether the drug actually giving the therapeutic effect or not, in this how the patient is feeling and functioning. Positive effect has great impact on therapeutic index and has a meaningful methodology for disease and get the clinical benefits. In 1992 the institute the accelerated approval of regulation [8].

Software for General Purpose Molecular Modeling:

For workstations, minicomputers, and supercomputers, including SGI, Sun, and Cray.

AMBER research was conducted by Peter Kollman and colleagues at UCSF.

Computer-assisted model construction, energy minimization, molecular dynamics, and free energy perturbation calculations.

Midas Plus-UCSF's Computer Graphics Laboratory.

CHARMM-Martin Karplus and coworkers from Harvard.

Molecular Simulations Inc. (MSI) specializes in drug design, QSAR, and quantum chemistry.

Data analysis using X-rays and NMR Biopsy, Inc. provides insight and discoverability.

MSI and Biopsy have merged to form Ackerleys, Inc.

SYBYL - Tripos, Inc. ECEPP (Harold Schrage and al.,

Cornell) and MM3 (Norman Allinger et al., Georgia) were

responsible for personal computer systems such as Apple,

Compaq, and IBM.

Alchemy III: Tripos, Inc. Oxford Electronic Publishing's Desktop Molecular Modeler Molecular modeling using Pro-Window hem software.

Examples of energy-saving strategies include QSAR (surface area, volume, log), among others. PC MODEL - Serena Software [8].

DISCUSSION:

Computer-aided drug design (CADD) represents a paradigm shift in the pharmaceutical industry, offering a synergistic approach that combines computational techniques with traditional experimental methods to expedite the drug discovery process and accelerates the drug discovery process by rapidly screening large chemical databases to identify potential lead compounds. This significantly reduces the time and resources required for hit identification and optimization. Cost-Effectiveness by minimizing the need for synthesizing and testing numerous compounds in the lab, CADD reduces the overall costs associated with drug discovery. Pharmaceutical companies can allocate resources more efficiently, focusing on the most promising candidates. Additionally, experimental validation is essential to confirm the predicted activity and safety of identified compounds. Overall, CADD holds tremendous promise in revolutionizing the drug discovery process, leading to the development of safer, more efficacious, and targeted therapies for a wide range of diseases. However, ongoing research and collaboration between computational scientists, chemists, biologists, and clinicians are essential to fully harness the potential of CADD in advancing medicine [9].

CONCLUSION:

Computer-aided drug design (CADD) is a multidisciplinary field that attracts researchers from information technology, medicine, and pharmacology, among others, to develop new tools and techniques or improve existing ones to aid in the drug discovery process. These methodologies demonstrated to be beneficial at various phases of the drug discovery process, lowering the cost and time required to produce a medicine compared to conventional methods. There are no standardized virtual screenings for each technique. However, the data and information about the process should always be publicly available, and the technique should be improved. Various CADD tools that aid in the process of drug development are presented, along with a few instances of pharmaceuticals that are currently on the market and were successfully designed utilizing these tools. These tools can be used and improved to aid in the various stages of drug discovery. CADD uses computational methods such as molecular modelling, virtual screening, and quantitative structure-activity relationship (QSAR) analysis to anticipate a molecule's biological activity, pharmacokinetic features, and probable adverse effects. This method drastically decreases the time and money needed for medication development, resulting in the identification of safer and more effective medicines for a variety of ailments. However, it is crucial to note that CADD has limits and should be supplemented with experimental validation to

assure the dependability of anticipated outcomes. Overall, CADD has great promise for determining the future of pharmaceutical research and medical advancement [26].

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