In-silico Studies: Pioneering The Future Of Drug Discovery

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Abstract- **The process of drug discovery has been a time-consuming and costly one for a long time. To cut down on time and cost, *in-silico* or CADD approaches came into existence. It greatly helped to reduce the time taken by wet lab experiments. It gives assurance to the researcher that the compound that is being synthesised will be effective. We can easily find the binding affinity of lead with macromolecules. Computer-aided drug design helps to study the interactions between drugs and receptors; it also clarifies ADME and the physiological properties of drugs. *In-silico* studies have now become a very important part of the drug discovery process by making a key contribution to the whole process.**

Key words: **CADD, SBDD, LBDD, QSAR and *De novo* drug design.**

INTRODUCTION:

Drug discovery is a time taking and lengthy process this takes 13 to 15 years to complete the process. It takes approx. 2.558 billion USD to finally reach market. It is a multi-step process that starts with choosing an appropriate drug target, followed by validating the drug target, finding hits that led to lead optimization and conducting preclinical and clinical research. The success rate during clinical trials is only 13%, with a very high drug attrition rate, despite the significant financial outlays and time required for discovery of new treatments[1].

Lack of optimal pharmacokinetic feature on absorption, distribution, metabolism, excretion, and toxicity has led to medication failure in majority of cases (40-60%). Leading pharmaceutical corporations and research organizations have accelerated the drug discovery and development process by using computer aided drug discovery tool in preliminary investigation to reduce cost and failure in the final stage[2].

Pharmacophore modelling, quantitative structure-activity relationship (QSAR), molecular docking, quantum mechanics, statical learning methods are few of the techniques used to find new inhibitors in chemical database. Both approaches have been heavily utilized in the drug discovery process to find suitable lead molecules. CADD can be broadly divided into two categories: structure based, and ligand based drug design approaches[1].

Candidate drugs with favourable bioactivity and side-effect profiles can be chosen with the help of CADD. This can be used when creating new drugs or when changing out old ones. CADD research has so far produced positive results for drugs that treat pain and inflammation brought on by musculoskeletal conditions. In the process of drug discovery and development CADD is now a vital tool. Additionally, it offers alternatives for comprehending chemical systems in various ways, yielding data that is difficult to obtain in laboratory analysis and requiring significantly less time and money than experiments[3].

CADD is still a field that is developing quickly. Unfortunately, CADD is plagued by cognitive dissonance (bias to seek consonance) and shoddy research due to inadequate training. Before predicting any property or a complex system, each step should be verified[4].

There are two distinct types of research that can be divided.

1.Crystallography, NMR or homology modelling. With the help of X ray a detailed molecular structure of target molecule and drug receptor is identified.

2. The inconsistent activity of otherwise comparable molecules.

Only by understanding both of these approaches can one infer the characteristics of the target receptor binding site[5].Molecular docking is one of the powerful tools for designing and preparing any drug or protein molecule. It allows you to optimize the required drug and protein and helps to find best suited site for the binding and interaction of drug and molecule[6]. Docking have solved problems caused due to serendipity which helped in saving time and money. The drug molecule also called ligand is allowed to interact with protein molecule also called macromolecule. Their binding generates certain conformations which helps to know the energy of binding site. Minimum energy denotes highest stability. These conformations are called binding modes.

Molecular docking is a part of rational drug design. It has made the process of drug discovery quite easy and convenient than conventional drug design. Earlier serendipity was the only way for drug design[7]. Over thousands of molecules were selected and then each molecule was assessed this caused a wastage of time and sometimes we even do not have any drug at ending step. Enhanced sampling methods, such as free energy calculations, which can determine the binding affinity between a ligand and its macromolecular target, can be used to complete this task in the later phases of lead optimization[8].

Overcome this problem CADD came into existence. CADD is a powerful tool around research which combines various theory and aspects about research to give a fruitful result. Theoretically CADD involves the quantum mechanics and molecular modelling studies such as ligand-based drug design, structure-based drug design, binding affinity, and energy. These studies collectively gives CADD result [5].

CADD approaches are particularly useful for drug designing and in interpretation or guidance of any experiment. Structure Based Drug Design (SBBD) and Ligand Based Drug Design (LBDD) are two of the main approaches used in CADD. Identification of interacting and key sites which are important for biological activity is important. SBDD is the approaches which deals with analysis of molecular target and 3D information of structure (protein or RNA) [9].

LBDD is proved to be extremely useful tool in the absence of 3D structure of drug target. It is one of the powerful tools for in drug discovery and lead optimization. Pharmacophore modelling and 3D QSAR are the 2 most important part of ligand based drug design approach [10].

CADD plays a key role in drug discovery process specially in the initial phase of discovery. It is such a powerful tool through which we can screen out and select compounds reducing load on wet lab experiments. It is also possible to find multiple use of single drug by the help of CADD by allowing it to interact it with various receptors. And this process is called drug repurposing. CADD have given its contribution in treatment of glaucoma, influenza virus infections, acquired immunodeficiency syndrome and many more[11].

COMPUTER-AIDED DRUG DESIGN

The interaction of drug with target molecule or protein to obtain the information about active site and a pharmacologically active compound can be easily done with the help of computational methods. *In-silico* studies helps us to cut down the time and capital investment in drug discovery process[12].The first step of target identification is carried out by the help of bioinformatics and data mining. Once target is identified they are validated whether they are potential target or not. The linkage between disease and target strengthens the hypothesis and rate of success. After target is identified novel hit compounds are screened. These compounds undergo property check such as ADME, absorption, distribution and toxicity testing[13].

STRUCTURE BASED DRUG DESIGN

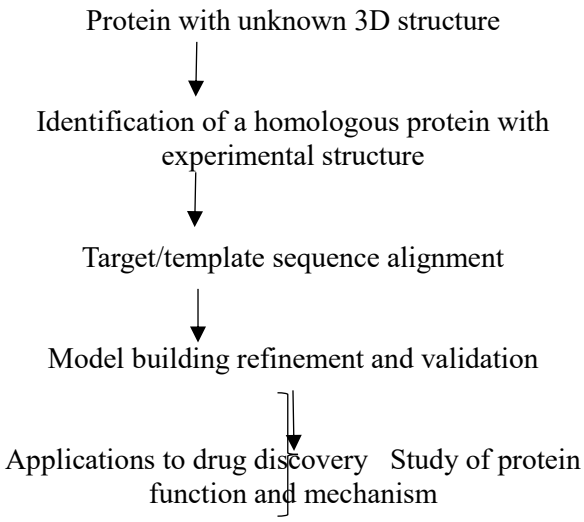
SBDD is a cyclical process that involves the collection of information in steps. In silico investigations are carried out to find possible ligands starting with a known target structure. Following these molecular modelling approaches, the most promising molecules are synthesized[14].

In addition to predicting the essential binding pocket locations and ligand affinity to the target macromolecular, which are critical for the ligands' individual biological activities, SBDD can visualize the binding process of ligands to the target. Using this knowledge, high affinity ligands with the required characteristics for the intended pharmacological and therapeutic effects may subsequently be designed. However, there are still several drawbacks to SBDD, including the high incidence of false positives in virtual screening, the challenge of taking target flexibility into account in docking, and the imprecision of scoring systems for target-Free energy bound by ligands[15].As mentioned above SBDD is a cyclic process steps involved are protein structure preparation, binding site identification, ligand library preparation, docking and scoring functions.

STRUCTURE PREDICTION

Homology Modelling

One of the computational structure prediction techniques used to ascertain a protein's three-dimensional structure from its amino acid sequence using a template is homology modelling, also known as comparative modelling. Two key discoveries serve as the foundation for homology modelling. The amino acid sequence of a protein plays a major role in determining its 3D structure. Second, compared to the sequence throughout evolution, the structure of proteins is more conserved and changes considerably more slowly. Among the techniques for predicting computational structures, homology modelling is thought to be the most precise. It is a step-by-step, low-cost approach for predicting the 3D structure of proteins that requires less time. As a result, homology modelling is frequently employed to produce high-quality 3D protein structures. This has altered the drug development process's docking and virtual screening techniques, which rely on structure[16].



***Ab initio* Structure Prediction**

Despite decades of research, predicting the structure of a protein from its amino acid sequence remains a challenge. If the query protein has a known homolog, the procedure is rather simple, and high-resolution models may frequently be produced by replicating and improving the framework of the solved structure. A template-based modelling technique, on the other hand, does not help to address the problems of how and why a protein adopts its unique shape. Models must be built from start if structural homologs do not exist, or if they do exist but cannot be recognized. This approach, known as ab initio modelling, it is required for a comprehensive solution to the protein structure prediction issue; it can also assist us in understanding the physicochemical principles that govern how proteins fold in nature [17].

Approaches for predicting protein structure may be divided into three groups comparative modeling, fold identification, and ab initio approaches. Comparative modeling and fold identification approaches use previously solved protein structures to predict protein structures. These template-based techniques rely heavily on finding homologous/analogous templates in the Protein Data Bank. Abs initio approaches, on the other hand, are template-free and may, in theory, predict protein structures without the need to discover a structurally comparable, solved protein structure [18].

Protein Model Validation

Because of the massive and ever-increasing quantity of data generated by genome sequencing, developing trustworthy computer algorithms capable of inferring protein structures from sequences is a critical step in protein functional annotation. In reality, functional annotation is sometimes completely reliant on the availability of structural data, which is currently challenging to get experimentally. As a result, efforts and advancements in high throughput X-ray and NMR approaches must be complemented with computational tools capable of predicting three-dimensional structure [19].

Docking Based Virtual Screening

The development of novel leads for particular biomolecular targets is critical in the early phases of drug research. Among the different strategies used to aid in hit detection, experimental high throughput screening has likely received the most attention. The virtual screening approach comprises the quick evaluation of huge libraries of chemical compounds in order to assist the selection of lead candidates using computer-based approaches. In comparison to high throughput screening, the virtual screening technique is faster and less costly, and it may be used to select compounds for a specific binding site [20].

Computational virtual screening functions essentially as a filter that consists of the virtual selection of molecules based on a certain predetermined criterion of potentially active compounds against a chosen pharmacological target. This technology may be used in two ways: ligand-based virtual screening and structure-based virtual screening. The first entails comparing the similarities and physicochemical properties of active ligands in order to predict the activity of additional molecules with comparable properties. The second method is used when the three-dimensional structure of the target receptor has previously been determined [21].

Binding Site Detection

In structure based drug design it is essential to validate receptor. Once the receptor is validated ligands are designed to in a way that they can bind to receptors binding site and can give desired pharmacological results. Hence it becomes very important to know about the binding site of receptor. To detect the binding site on 3D structure of receptor an accurate in-silico algorithm is required. F-pocket is widely used geometry based tool. Geometry tools help in

identification of hollow spaces and then ranking them in accordance with binding ability. Another metho is probe based method in this method small molecule is placed on surface of receptor hence helping in finding best binding site [22].

Docking

Molecular docking is a computer process that explores a search space specified by the molecular representation and ranks possible solutions to find the optimal binding mode. Docking therefore necessitates the use of both a search method and a scoring system[23].

Molecular docking is a structure-based drug design process that simulates receptor-ligand interactions and predicts binding modes and affinities. The real docking mechanism is so adaptable that receptors and ligands must alter shape to match each other well[24].

Proteins with unknown structures can be docked against homology-modelled targets. Docking Techniques can determine a compound's drug ability and specificity against a target, enabling further lead optimization [25].

It was initially intended for small molecules to interact with large macromolecules. But in recent years there has been an increase in interest in protein-protein, nucleic acid ligand, and nucleic acid protein ligand docking [26].

Docking Algorithms

Docking simulations rely heavily on speed and precision. The goal of developing a docking algorithm is to provide a rapid and accurate approach for discovering novel lead compounds in virtual screening or reproducing experimental conformations for confirmation against experimental data. There are several docking programs, including Dock, Autodock, Gold, Flexx, Zdock, M-Zdock, Msdock, Surflex, Mcdock [27].

Ligand Based Drug Design

Instead of using costly and time-intensive conventional procedures, novel possibilities for substantial therapeutic approaches in current technology have been created by the development of computer-aided drug creation and high-throughput virtual screening. Thus, this continued to be a global issue of struggling. Due to this issue, the concept of ligand-based drug design has shed light on the similarity principle, which states that related compounds have comparable biological characteristics. The integration of these approaches resulted in an increase in the scope of the chemical and biological data as well as a rise in the complexity of the R&D operation [28].

QSAR

Chemometrics is a chemical discipline that analyses chemical data to produce the most chemical information possible. It does this by designing or choosing the best processes and experiments using statistical and mathematical techniques [29]. The quantitative structure–activity relationship, or QSAR, is a technique for developing computational or mathematical models that looks for a statistically significant association between structure and function. The QSAR approach expedites the process of developing new compounds for use as materials, additives, medications, and other applications while also conserving resources [30]. In QSAR, a molecule's structure has to include the characteristics and attributes that give rise to its physical, chemical, and biological activities [6].

QSAR objective

- To enhance the biological activity of the current leads by optimization
- Unknown or no available substances biological activity can be identified.
- In order to understand which chemical qualities are most likely to be determinants of their biological activities, it is necessary to quantitatively correlate and summarize the links between trends in alterations to chemical structures and corresponding changes in biological endpoints [31]

2D QSAR

Two-dimensional descriptors, or those that do not make use of data pertaining to the three-dimensional properties of model substances, can be used to extract significant information from a QSAR dataset [32]. Different electronic, hydrophobic, and steric properties are associated with the biological activity for a congeneric series of compounds using the classical QSAR method, also known as the Hansch-Fujita methodology [10]. Hansch analysis also known as 2D QSAR.

3D QSAR

Involve 3D descriptors to describe 3D features of molecule in developing QSAR model. The ability to meaningfully explore the third dimension, for example, by examining conformers, has resulted in the creation of 3D QSAR approaches [32]

CoMFA

In order to correlate various molecular traits, such as steric and electrostatic properties, with their biological activities, Comparative Molecular Field Analysis (CoMFA) uses interactive visuals and statistical approaches. It should be mentioned that in the last several decades, CoMFA has been incredibly common in areas of academic and industry study pertaining to QSAR investigations. Both conformational and alignment of molecyle are required in CoMFA procedure.[33]

The first QSAR technique to link a molecule's biological activity to its three-dimensional shape-dependent steric and electrostatic characteristics was CoMFA. This approach involves aligning molecules on a 3D grid according to their 3D structures, and then computing the steric and electrostatic potential energies at each grid point. Typically, CoMFA makes the assumption that the bioactive conformer is the minimum-energy conformer [10].

CoMSIA

Unlike CoMFA, CoMSIA's molecular field expression includes hydrophobic, hydrogen-bond donor, and acceptor components, as well as steric and coulombic contributions [34] .Comparative Molecular Similarity Indices (CoMSIA) is a 3D QSAR approach related to CoMFA. CoMSIA produces similarity indices rather than interaction energies by comparing each ligand molecule to a common probe with a radius of 1Å and charge, hydrophobicity, and hydrogen bond characteristics equal to 1 [10].

Pharmacophore

The most crucial first step in knowing the interaction between a receptor and a ligand is perceiving a pharmacophore [35]. QSAR method and pharmacophore modeling are the most widely used techniques for ligand-based drug design [10]. Creation of pharmacophore model by placing active molecules and extracting common chemical features that are essential for their bioactivity, or by investigating potential interactions between the macromolecular target and ligands. Pharmacophore techniques are commonly utilized in virtual screening, de novo design [36].

***De novo* Drug Design**

The process of creating new lead molecules with desirable pharmacological and physiological features is called *De novo* drug design[37]. *De novo* design helps to construct desired ligand molecule for required pharmacological properties. As a result, de novo design could potentially be thought of as an addition to other virtual approaches, such as database searching, as well as non-virtual procedures, like high-throughput screening [38]. The capacity of de novo design techniques to produce structures like those of recognized inhibitors has been evaluated, and they also propose new scaffolds that are then synthesized and examined for activity [39].

Fragment Based Drug Design

Over the past few decades, fragment-based drug discovery (FBDD) has gained significance and attention. The first step in FBDD is usually to screen a limited library of low molecular weight compounds to see if any of them bind to a certain target [40]. High affinity and receptor ligand interactions can be found by fragment binding. Fragment can help to find certain sites for ligand binding. When pockets are detected fragments can be grown and linked to make required ligand [41].

Fragment Growing:

Once binding pocket is identified one can identify suitable fragment with required interactions in sub region inside binding pocket. After conformation single fragment can be substituted with another fragment to grow it. The compounds generated are thought to have better binding interactions between ligand and receptor once binding pocket is identified one can identify suitable fragment with required interactions in sub region inside binding pocket. After conformation single fragment can be substituted with another fragment to grow it. The compounds generated are thought to have better binding interactions between ligand and receptor [41].

Fragment linking:

Depending on the sub-region, the configuration of several residues might provide hydrophobic or hydrophilic environments. Preferred pieces from these different physical-chemical characteristics can be found in sub-regions. With each fragment occupying a specific subregion, it is possible to identify many fragments that interact with the particular binding pocket. To boost the druglikeness, fragment linkers might be used to join disparate fragments [42].

Molecular Dynamics Stimulation

A computational technique Molecular Dynamic simulation makes use of Newton's equations to assess the movements of ions, liquids, tiny and macromolecules, and more complicated systems. In particular, structural movements such as those influenced by temperature and solute/solvent ratios are crucial for understanding how ligand proteins or protein-protein complexes are recognized [43]. It helps to reduce computational problems by using Newtonian physics which

helps to stimulate motion of atoms [44]. Some of the best software for molecular dynamic stimulation are GROMACS, NAMD, LAMMPS, AMBER.

CONCLUSION

The drug design and discovery process are now simpler than it was in the past thanks to numerous CADD techniques. The use of docking to understand drug receptor interactions has proven to be very beneficial. Locating the binding pocket for interaction greatly facilitated the procedure. In addition, certain novel techniques like fragment-based and de novo drug design have made significant contributions to the field of drug discovery. There are still certain flaws and gaps in the process that can be fixed with careful research. As a whole, the application of in-silico research in drug design has proved advantageous and revolutionary in the field of drug discovery.

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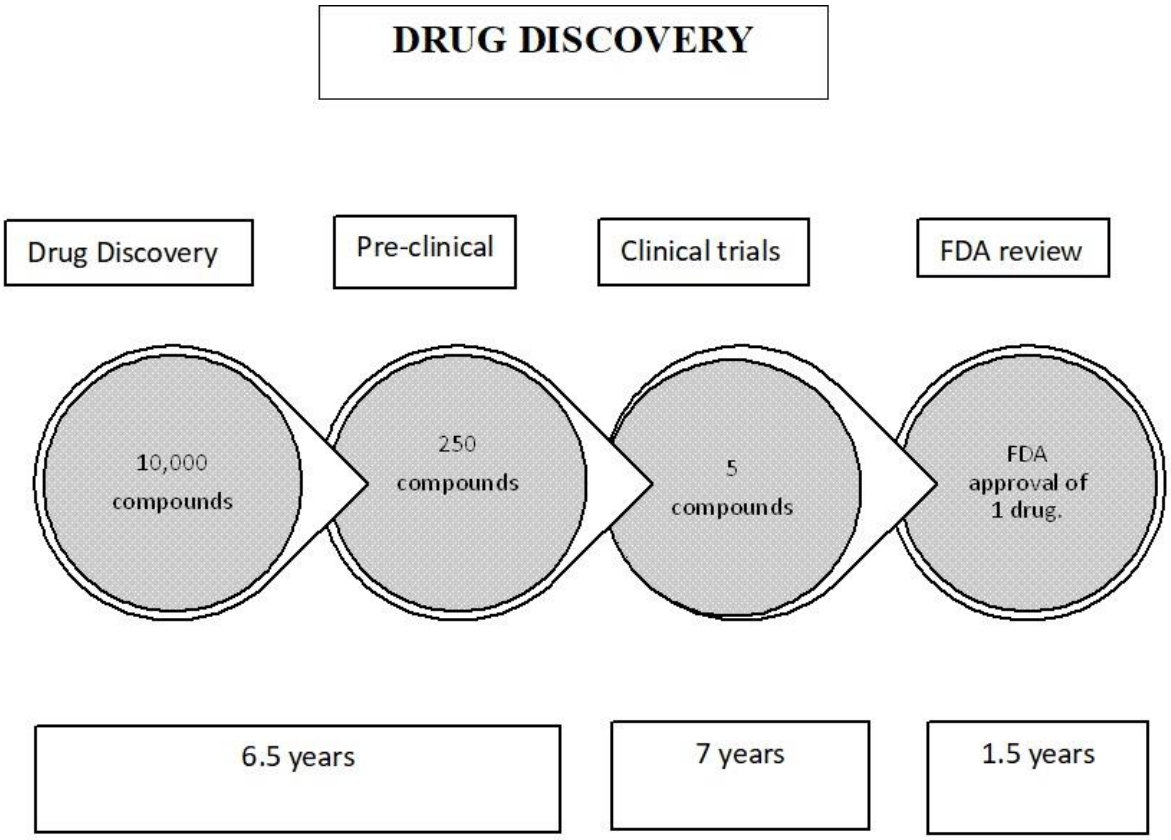

Fig.1: Drug discovery timeline

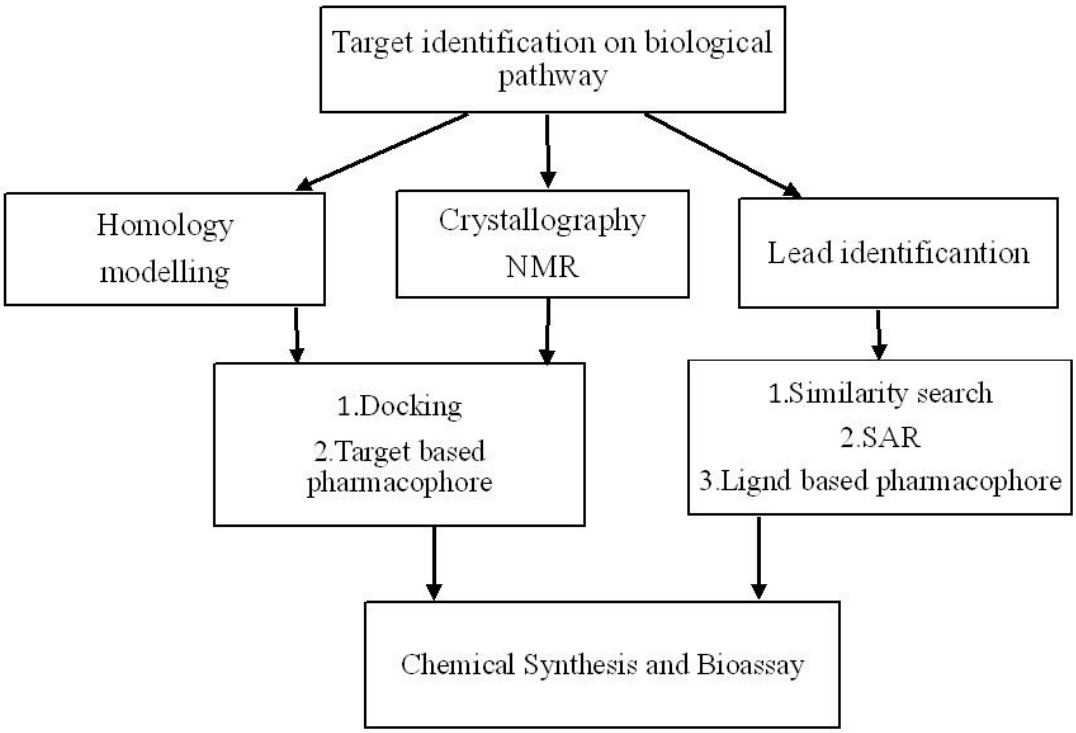

Fig.2: *In-silico* steps involved in drug discovery.

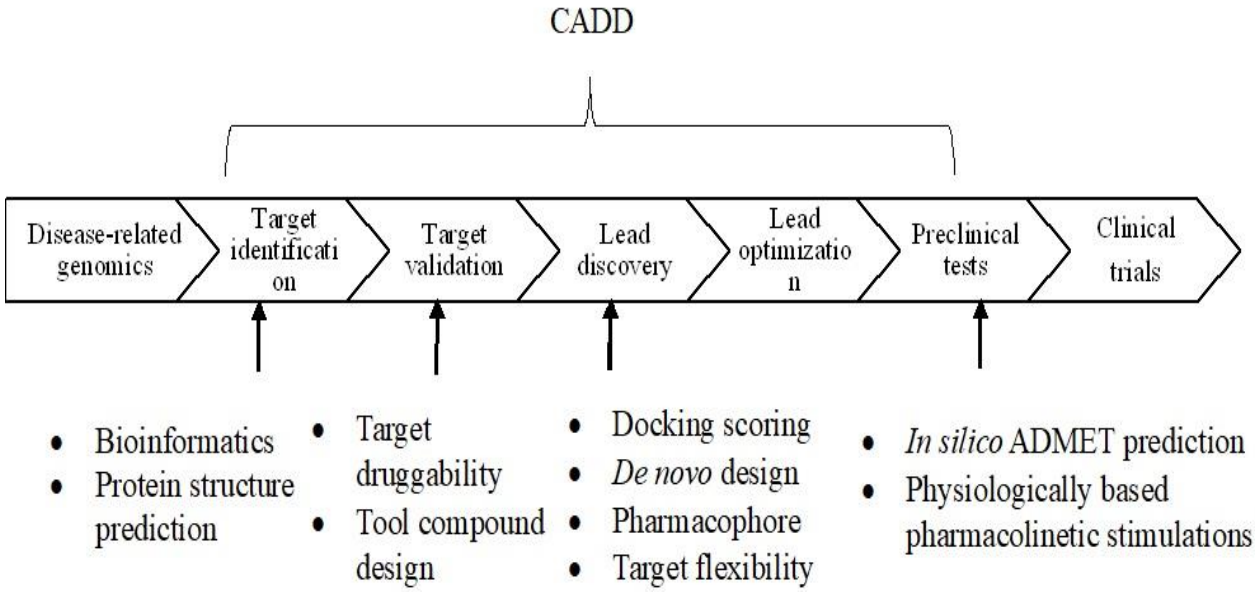

Fig.3: Involvement of CADD in drug discovery timeline

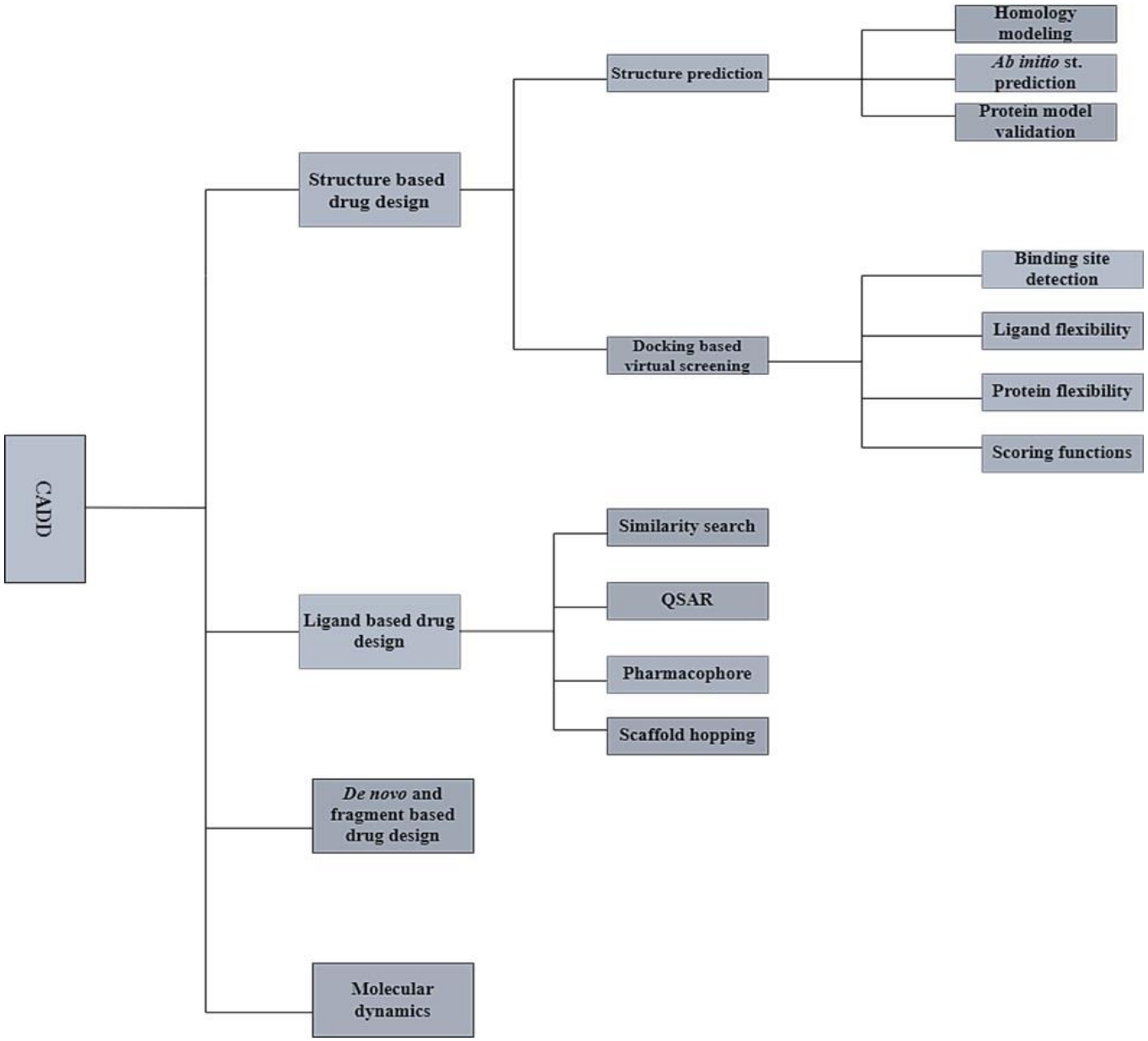

Fig. 4: CADD work flow

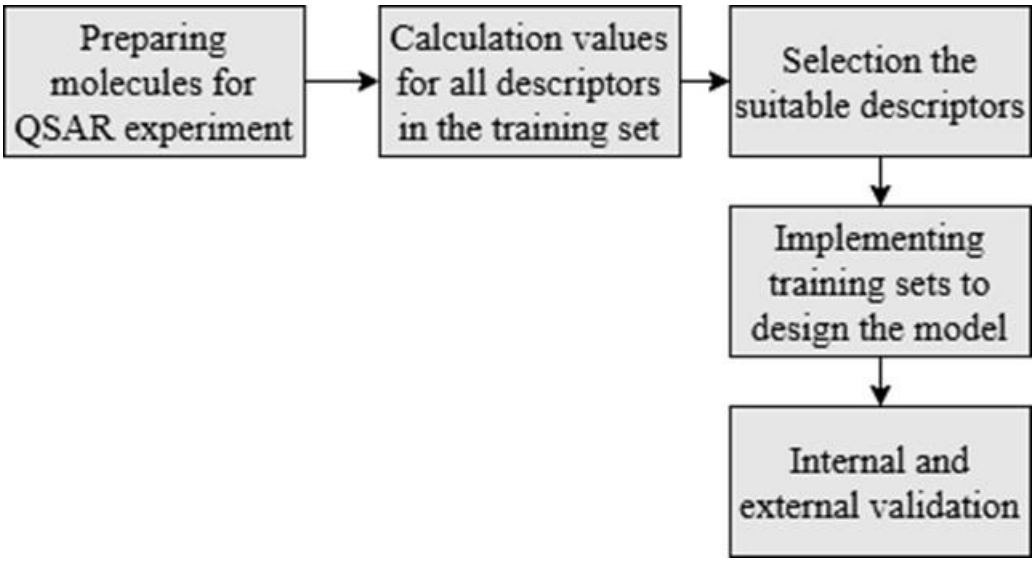

Fig.5: QSAR development process