(REVIEW ARTICLE)

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A review of approaches in computer-aided drug design in drug discovery

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Abstract

The process of discovering and developing a new medication is often seen as a lengthy and expensive endeavors. As a result, computer-aided drug design methods are now frequently utilized to improve the efficiency of the drug discovery and development process. Various CADD approaches are regarded as potential techniques based on their needs; nevertheless, structure-based drug design and ligand-based drug design approaches are well-known as highly efficient and powerful strategies in drug discovery and development. Both of these approaches may be used in conjunction with molecular docking to conduct virtual screening for the purpose of identifying and optimizing leads. In recent years, computational tools have become increasingly popular in the pharmaceutical industry and academic fields as a means of improving the efficiency and effectiveness of the drug discovery and development pipeline. In this post, we'll go over computational methods, which are a creative way of discovering new leads and assisting in drug discovery and development research.

Keywords: Computer Aided Drug Design (CADD); Structure-Based Drug Design; Ligand-Based Drug Design; Virtual Screening and Molecular Docking

1. Introduction

Computational methods to drug design, discovery, and development are being explored, implemented, and admired at a rapid pace. In terms of time, money, and people, introducing a new medication to the market is an extremely difficult, hazardous, and expensive procedure. In general, it is estimated that the medication research and development process takes 10-14 years and costs more than $1 billion in total. As a result, computer assisted drug design (CADD) is extensively employed as a novel drug design methodology to reduce time, cost, and risk borne elements. It has been demonstrated that using CADD methods can cut drug research and development costs by up to 50%. Any software program-based approach for developing a standard to link activity to structure is referred to as CADD.

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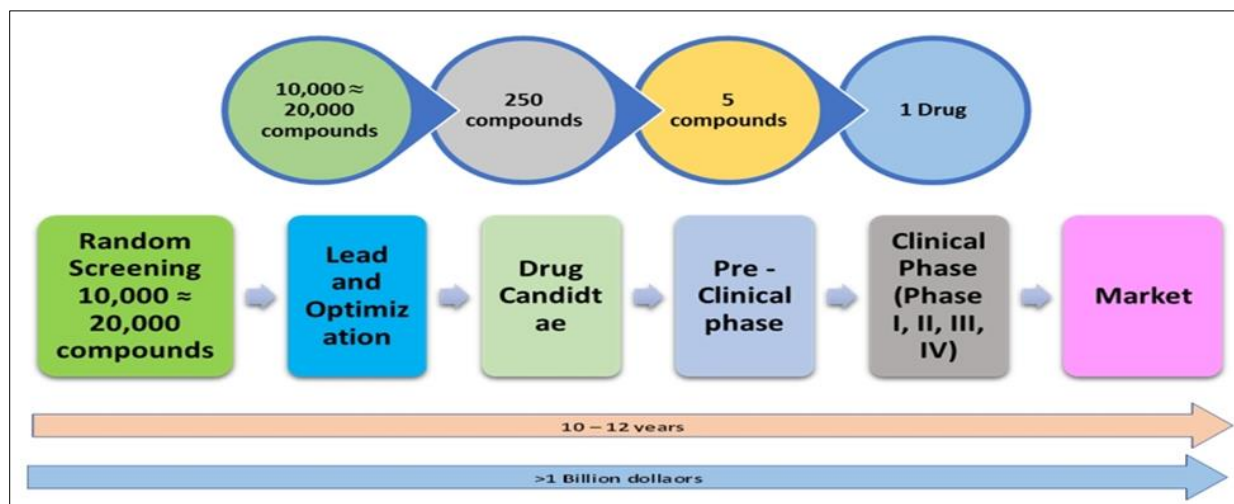
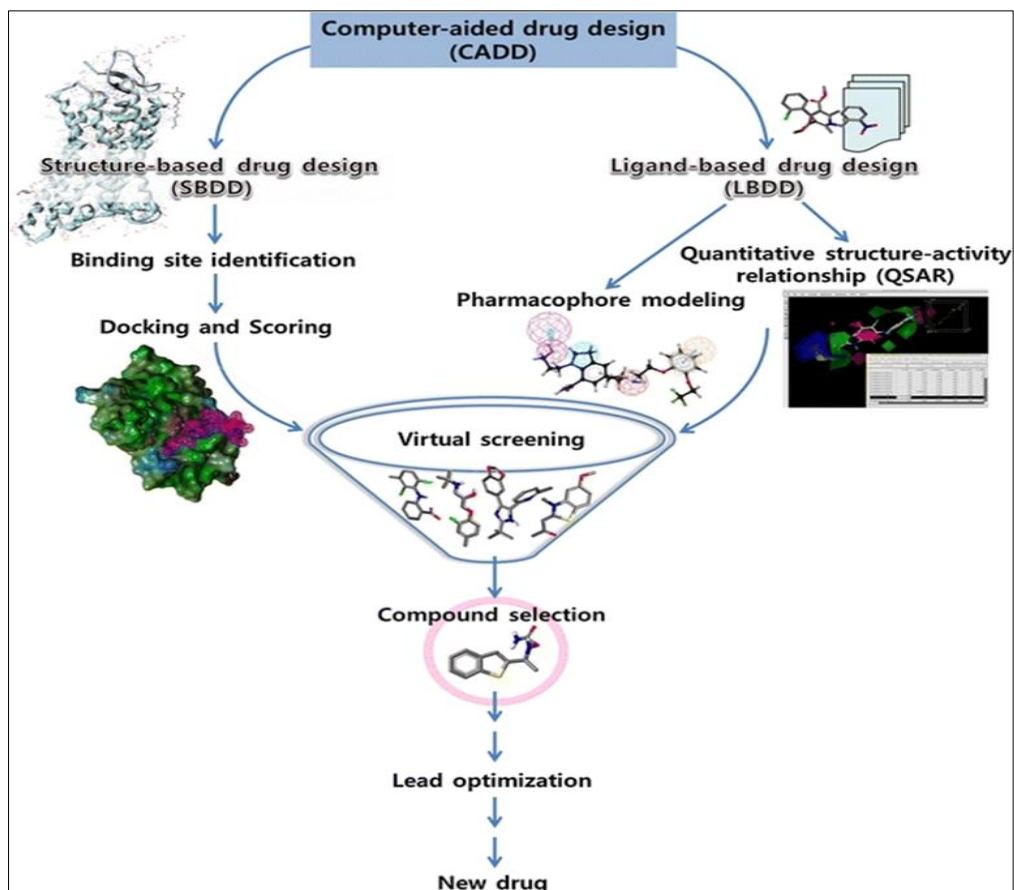**Figure 1** Traditional drug research and development procedure
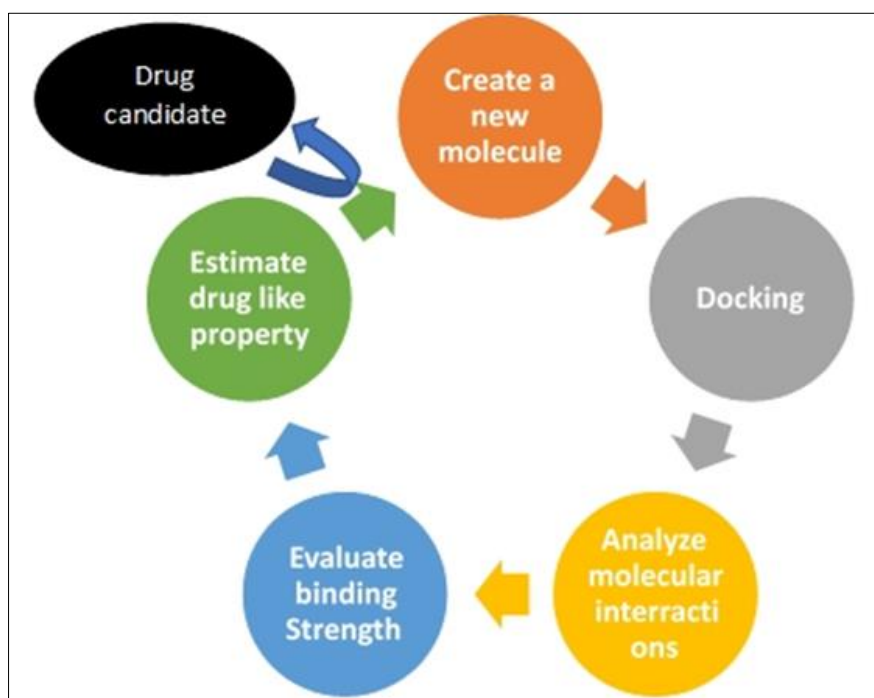
Figure 2 General Principle for Drug design through CADD

2. CADD methods are divided into several categories

There are mainly two types of approaches for drug design through CADD is the following:

- Structure based drug design / direct approach
- Ligand based drug design / indirect approach

Figure 3 A general representation of the CADD process

2.1. Structure based drug design

The structure of the target protein is known in structure based drug design (SBDD), and following docking, the interaction or bio-affinity for all tested compounds is calculated, allowing a new therapeutic molecule to be designed that has a better interaction with the target protein. These methods are very efficient and alternative approach to the discovery and development of drug design course. The three-dimensional (3D) structure of proteins (more than 100,000) are provided in SBDD
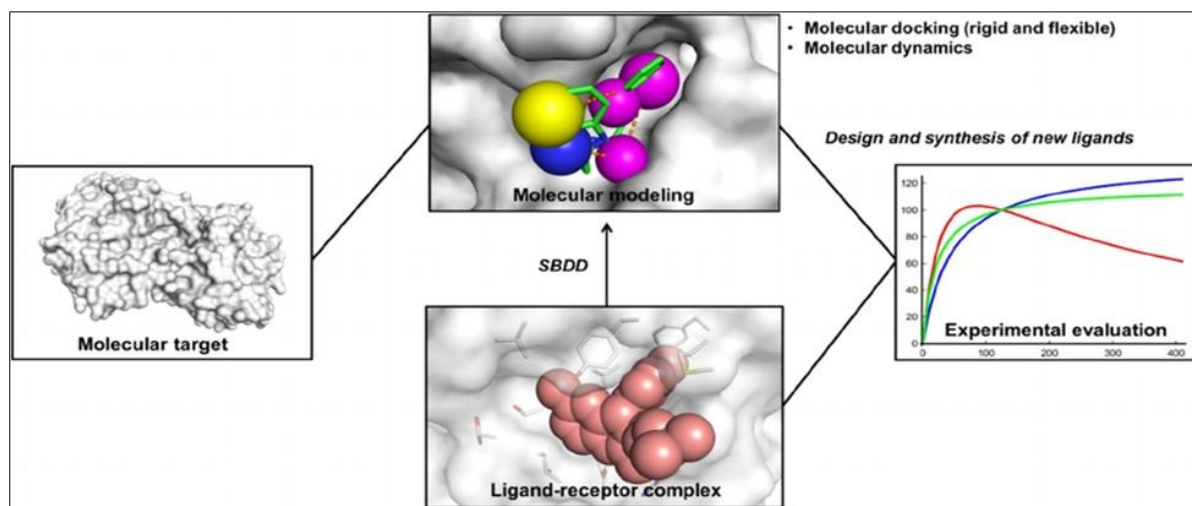

Figure 4 Layout of SBDD

2.1.1. A description of the steps involved in SBDD

SBDD goes through several cycles before reaching clinical trials with the best lead. The first cycle involves isolating, purifying, and determining the structure of the target protein using one of three key methods: X-ray crystallography, homology modelling, or nuclear magnetic resonance (NMR). Compounds are identified via virtual screening of several databases and then put in a specific area (active site) of the protein. These compounds are graded and rated based on their steric, hydrophobic, and electrostatic interactions with the target protein's active site. Biochemical tests are used to test the top-ranked substances.

The second cycle involves determining the structure of the protein in combination with the most promising lead from the first cycle, the one with the lowest micro molar inhibition in vitro, and identifying locations of the drug that may be improved for further potency enhancement. Following numerous more cycles, such as lead synthesis and further optimization of lead via a complex structure of protein with lead molecule, the optimized compounds often exhibit a significant increase in target selectivity and binding affinity.

2.2. Ligand based drug design

The 3D structure of the target protein is unknown in ligand based drug design (LBDD), but the ligands that bind to the intended target location are. These ligands can be utilized to create a pharmacophore model or molecule that has all of the structural characteristics needed to bind to a target active site
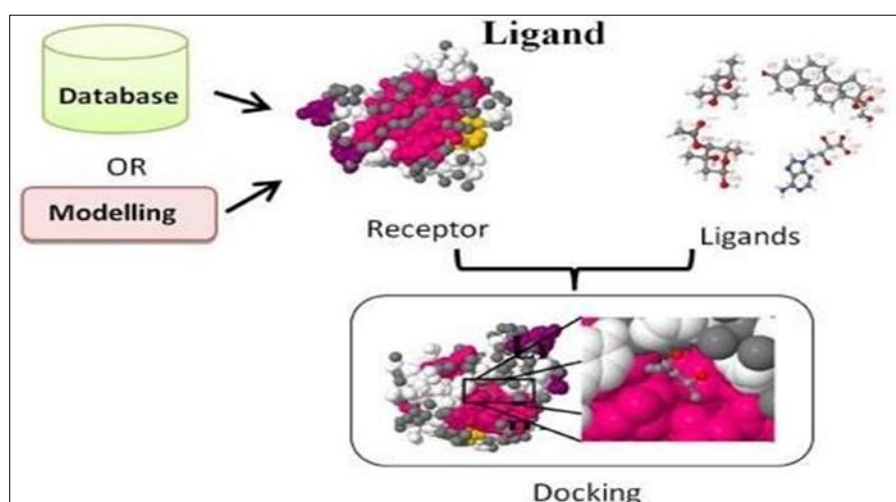

Figure 5 Outline of process involved in LBDD

The pharmacophore-based method and quantitative-structure activity connections are two common ligand-based approaches (QSARs). In LBDD, substances with comparable structural similarities are considered to have similar biological actions and interactions with the target protein.

3. Virtual screening

Virtual screening has been worked as a most convenient tool now a day to find out the most favorable bioactive compounds with the help of information about the protein target or known active ligands. Virtual screening has recently emerged as a game-changing alternative to high-throughput screening, primarily in terms of cost effectiveness and the likelihood of discovering the most relevant new hit by filtering vast libraries of chemicals.

There are two types of virtual screening approaches: structure-based virtual screening (SBVS) and ligand-based virtual screening (LBVS). SBVS relies on the structure of the target protein active site, whereas LBVS relies on the calculation of similarity between known active and compound compounds from databases.
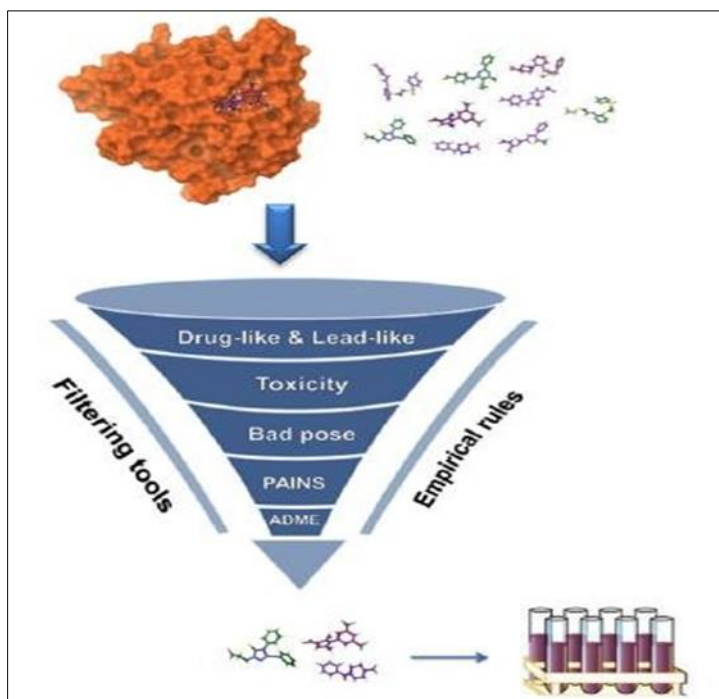
Figure 6 Overview of virtual screening process

4. Molecular docking

Molecular docking is an in-silico approach for predicting the location of tiny molecules or ligands within their target protein's active region (receptor). It is primarily utilized to accurately estimate the most favorable binding modes and bio-affinities of ligands with their receptors, and it is now widely employed in virtual screening for lead compound optimization.
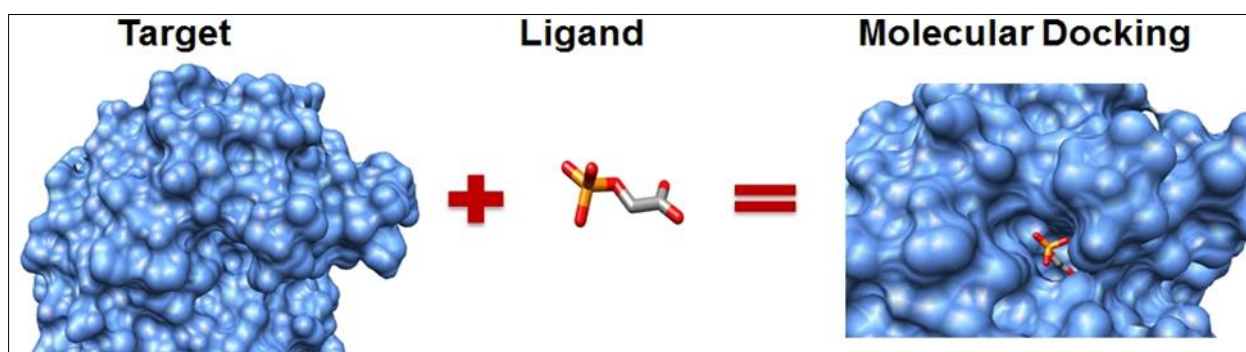
Figure 7 Molecular docking process

Prediction of binding posture, bio affinity, and virtual screening are the three major aims of molecular docking technique, which are all interrelated. The search algorithm and scoring algorithms used in the molecular docking technique are the foundation tools for producing and evaluating ligand conformations.

5. Pharmacophore

The term "pharmacophore" refers to a schematic depiction of bioactive functional groups and their interatomic distance. During the late 1800s, 'Paul Ehrlich' created the initial idea of the pharmacophore. At the time, it was thought that a biological impact was caused by certain chemical groups or functions of a molecule, and that compounds with comparable effects had similar functions.

Much later, in his book Chemo-biodynamics and drug design, 'Suhveler' developed the term 'pharmacophore,' which was described as a molecular framework that contains (phoros) the key characteristics responsible for a drug's pharmacon biological action. In computer-assisted drug design, the pharmacophore idea plays a critical role (CADD). The characteristics are pharmacophores that have been decreased by certain atoms and molecules. These compounds can be hydrogen bond donors or acceptors, cation, anionic, aromatic, hydrophobic, or any combination of these.
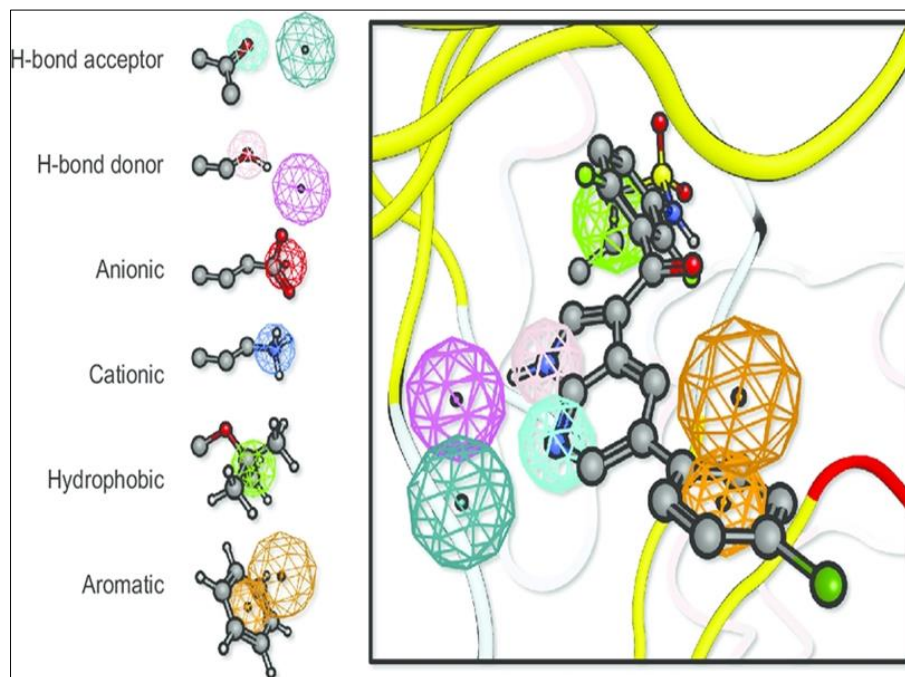
Figure 8 Overview of pharmacophore mapping

6. Quantitative structure–activity relationship (QSAR)

The QSAR technique is utilized in many instances when structural-based approaches are not relevant due to a lack of target macromolecule structure knowledge. In the form of a mathematical expression, QSAR provides information on the link between chemical structure and biological activity. The major benefit of the QSAR approach is that it may identify characteristics of new chemical compounds without requiring their production and testing. The structural descriptors of substances, physiological characteristics, and biological activities are all linked in studies.

7. Absorption, distribution, metabolism, excretion and toxicity (ADMET)

The requirement to evaluate the ADMET characteristics of leads in the early phases of drug screening was prompted by high attrition rates due to poor pharmacokinetic profiles. However, in terms of money and time, experimental examination of pharmacokinetic characteristics of millions of molecules is not a realistic alternative. Thus, virtual screening may be used to filter hits and remove compounds with unwanted properties prior to comprehensive experimental testing. In silico ADMET filters, like QSAR, are generated from chemical or molecular descriptors and are used to predict drug-like characteristics of compounds. Lipinski Rule of Five, Rule of Three for Fragments, and Veber rules are the most basic and well-known models. ChemBioServer and Free ADMET Filtering-Drugs2 (FAF-Drugs2) are two publicly available web servers that may be used to filter a huge chemical database or a list of possible leads. ChemBioServer can show and graph molecular characteristics, filter compounds based on chemical quality, steric conflicts, and toxicity, search for substructures, cluster compounds, and propose a representative for each group. Alternatively, FAF-Drugs2 has a number of pre-defined filters from which the user may pick, including the ones listed above as well as others like the central nervous system (CNS) Filter and the reactive group filter. Additionally, pharmacophore models derived from toxicity-causing inhibitors can be utilised to discover drugs with unfavorable moieties. Reactivity models, like as those used in SMARTCyp, are useful in addressing the issue of drug metabolism. SMARTCyp is a free web service and downloadable application that predicts locations in 2D compound structures that are likely to be metabolized by CYP450. It uses quantum chemical calculations to evaluate the reactivity of ligand fragments and the accessibility of atoms in the molecule to predict potential metabolic sites. MetaSite, on the other hand,

uses a similar algorithm to find possible metabolic reactivity sites, but the query input is a 3D configuration of the molecule. Table lists more ADMET filters and tools.

Table 1 Programs for prediction of ADMET properties

Function	Program/server	Free/commercial	Description	Institute/company	Website
ADMET properties	QikProp	Commercial	Rapid identification of ADME properties of drug candidates.	Schrodinger	http://www.schrodinger.com/
	ADMET predictor	Commercial	Estimates the number of ADMET properties from query molecular structure.	Simulations Plus, Inc.	http://www.simulations-plus.com/Products.aspx?grpID=1&cID=11&pID=13
	ADMET and predictive toxicology	Commercial	Predicts ADMET properties.	Biovia (formerly Accelrys)	http://accelrys.com/products/discovery-studio/ADMET.html
	FAF-Drugs2	Free	Subjects compounds to in silico ADMET filters.	University of Paris Diderot	http://www.mti.univ-paris-diderot.fr/recherche/plateformes/logiciels#

Most of the information about the listed programs can be found at http://www.click2drug.org/

When using these in silico ADMET models, it's important to remember that they're more useful for qualitative analysis of hits or compound sets than for precisely forecasting quantitative values. These approaches are useful for prioritising a defined class of drugs for in vitro or in vivo testing or evaluation of a certain descriptor and SAR.

Table 2 List of softwares used in various property determination in Computer Aided Drug Design (CADD)

Particulars	Software's
Virtual Screening	PyRx, DS Visualizer
Molecular Docking	AutoDock-vina,MOE-dock, GOLD
Pharmacophore Mapping	Pharmagist
QSAR	VEGA, ChemDraw ultra, Discovery Studio
ADMET	Swiss ADME, Swiss target predictor,ADMET predictor.

8. Advantages of CADD

- We can save time and money by reducing the amount of synthetic and biological testing we do.
- It identifies the most promising therapeutic candidate by excluding molecules with unfavorable characteristics (low effectiveness, low ADMET, etc.) using in silico filters.
- It is a low-cost, time-saving, rapid, and fully automated procedure.

- We can learn about the drug-receptor interaction pattern from it.
- In compared to traditional high throughput screening, it provides compounds with high success rates by exploring vast libraries of compounds in silico.
- These methods reduce the likelihood of failures in the last phase

9. Conclusion

Computer-aided drug design (CADD) is a useful tool in the field of drug discovery and development since it allows us to quickly identify the most promising therapeutic candidates at a low cost. It always gives me optimism for progress in the field of drug discovery. Many amazing investigations have been accomplished in recent years thanks to computer assisted drug design, and it will continue to play an essential role in the near future. With present achievements, computer aided drug design has a promising future in aiding drug discovery of many more curatives in the future.

Compliance with ethical standards

Acknowledgments

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Author's contribution

SSP and SGK conceived the concept of the study. SSP wrote the manuscript. SGK prepared figures and tables. SSP and SGK collected the literatures from various resources. AJA and KP corrected the manuscript.

Disclosure of conflict of interest

All the author approved the contents of the manuscript.

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