Advances in Computational Methods for Drug Design: A Revolution in Pharmaceutical Development

Oluwafemi Shittu Bakare [1*], Okoye Oluwabukola [1], Olajuyigbe Olakunle Julius [1]

Abstract

Computational methods of drug design involve the use of various software and algorithms to predict the properties of drug molecules, screen for potential targets, and optimize drug candidates for therapeutic efficacy, it lowering the cost of drug research and development time. The discovery and development of a novel medicine is a lengthy, complex, expensive, and high-risk process that has no commercial counterpart. CADD has previously been used to uncover drugs that have gone through clinical trials and become innovative medicines for many ailments. CADD approaches are widely divided into two categories: structure-based drug design (SBDD) and ligand-based drug design (LBDD). SBDD is used when the three-dimensional structures of target proteins are available, while LBDD design is used in the absence of receptor 3D information and relies on knowledge of molecules that bind to the biological target of interest. Some applications in CADD are Lead Optimization, Virtual screening (VS), ADMET prediction, and toxicity prediction. Medicinal chemists use a variety of computational approaches to modify the chemical structure of a compound to maximize its in vitro activity, drug discovery is driven by the idea that a ligand with higher binding affinity to a target should be more efficacious than that with lower binding affinity to the same target. Target flexibility is one of the key issues that still need to be resolved in drug discovery. The majority of molecular docking tools give the ligand high flexibility, but they fix or give the protein's residues close to or inside the active site only limited flexibility. It is very difficult to provide complete molecular flexibility to the protein as this increases the space and time complexity of the computation. In conclusion, computational methods have revolutionized the field of drug design by enabling faster, more cost-effective, and more efficient drug discovery

Keywords: Computer-Aided Drug Design (CADD), Structure-Based Drug Design (SBDD), Ligand-Based Drug Design (LBDD), Virtual Screening, Molecular Docking

Significance | Computational methods accelerate drug development, reduce costs, and enhance efficiency, leading to faster discovery of therapeutic candidates and novel medicines.

*Correspondence. Oluwafemi Shittu ,Department of Biochemistry, Faculty of Science, Adekunle Ajasin University, Akungba Akoko, Ondo State, Nigeria
E-mail: bakfemsonline@gmail.com; oluwafemi.bakare@aaua.edu.ng.
Telephone: +2348068902669

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Introduction

Computational methods of drug design (CMDD), sometimes known as computer-aided drug design (CADD), involve the use of various software and algorithms to predict the properties of drug molecules, screen for potential targets, and optimize drug candidates for therapeutic efficacy. It also lowers the cost of drug research and development time. The discovery and development of a novel medicine is a lengthy, complex, expensive, and high-risk process that has no commercial counterpart. To speed up the process, computer-aided drug design (CADD) technologies are commonly utilized in the pharmaceutical sector. Using computational methods in the lead optimization phase of drug

Author Affiliation.
[1] Department of Biochemistry, Faculty of Science, Adekunle Ajasin University, Akungba Akoko, Ondo State, Nigeria

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development has a significant economic advantage. Pharmacological research facilities invest a lot of money and time in various stages of drug discovery, beginning with therapeutic target identification setting the stage for candidate drug discovery, assessing the efficacy and safety of newly created medications, and optimizing drugs through preclinical and comprehensive clinical studies. Major pharmaceutical corporations have made significant investments in routine Ultra-High Throughput Screening (uHTS) of vast numbers of drug-like compounds. Simultaneously, computers are increasingly being used for virtual screening in medication design and optimization. Recent improvements in DNA microarray research have revealed that thousands of genes linked to a disease can be exploited to learn more about disease targets, metabolic pathways, and medication toxicity. Empirical molecular mechanics, quantum mechanics, and, more recently, statistical mechanics are examples of theoretical techniques. The most recent development made it possible to include overt solvent effects. All of this is largely due to the availability of workstations that handle high-quality computer graphics (Ms.Priti *et al.*, 2022).

Computer-aided drug design (CADD) has resurfaced as a method of drastically reducing the number of compounds required to screen while maintaining the same degree of lead compound discovery. Many molecules that are projected to be inactive can be avoided, while those that are predicted to be active can be prioritized. This lowers the cost and workload of a comprehensive high-throughput screening (HTS) screen while maintaining lead discovery. Furthermore, typical HTS assays frequently necessitate significant development and validation before they may be employed. Because CADD takes much less time to produce, experimenters can conduct CADD investigations while the typical HTS test is being prepared. The fact that both of these tools can be utilized concurrently adds another advantage for CADD in a drug discovery effort. To find inhibitors of the enzyme tyrosine phosphatase-1B, which is linked to diabetes, researchers at Pharmacia (now a division of Pfizer) used CADD technologies. A hit rate of over 35% was achieved out of the 365 compounds that came from their virtual screen. This team also conducted a conventional HTS simultaneously on the same target. Only 81 of the 400,000 tested compounds demonstrated inhibition, yielding a success rate of 0.021%. This comparative case demonstrates the power of CADD in a powerful way (Doman *et al.*, 2002).

CADD has previously been used to uncover drugs that have gone through clinical trials and become innovative medicines for several ailments. The following are some of the earliest examples of authorized pharmaceuticals that attribute their development in major part to CADD tools: Dorzolamide, a carbonic anhydrase inhibitor that was approved in 1995 (Vijayakrishnan 2009). Drug design aims to create a chemical element that can physically and chemically fit into a specific cavity on a protein target. It is generally known that developing new medications requires a lot of time and resources. To hasten drug discovery, design, development, and optimization, there is an increasing push to use computer capacity in the combined chemical and biological domain. Computer-aided or in-silico design is used in the biomedical industry to optimize the absorption, distribution, metabolism, excretion, and toxicity profile, as well as to speed up and simplify hit identification, hit-to-lead selection, and hit-to-hit selection. Years of scientific investigation are needed to understand the biochemistry of a disease to develop a potential treatment. Consequently, particular receptors (targets) are discovered. In the post-genomic era, the range of applications for computer-aided drug design (CADD) has considerably increased, encompassing nearly all phases of the drug development pipeline, from target identification to lead discovery, lead optimization, and preclinical or clinical trials. HTS and combinatorial chemistry were two techniques that the industry quickly adopted. To find lead compounds that can regulate a specific result, large libraries of compounds are screened against therapeutic targets in HTS. However, setting up a program for combinatorial chemistry and HTS is expensive and does not meet the special requirements of many biological (drug target) systems. Due to poor ADME (absorption, distribution, metabolism, and elimination) characteristics, compounds discovered in such screenings may not be appropriate for future medicinal chemistry research. Even though these technologies have accelerated the identification of lead compounds, new chemical entities (NCEs) have not been introduced into the global pharmaceutical market at a rate that has kept pace with that (Md. Mofizur *et al.*, 2012). CADD approaches are widely divided into two categories: structure-based (SB) and ligand-based (LB) drug design. The CADD approach utilized is determined by the availability of target structural data. SBDD tools require knowledge of target structures to be used. X-ray crystallography or nuclear magnetic resonance (NMR) is commonly used to get target information experimentally. When neither is available, computational methods such as homology modeling can be employed to predict desired three-dimensional structures. Knowing the structure allows you to employ structure-based tools on targets and potential therapeutic compounds, such as virtual high-throughput screening and direct docking procedures. The affinity of molecules to targets can be assessed by calculating various binding free energy estimations. Following that, prospective medication compounds are further filtered and optimized. The activity of the final lead compounds is evaluated in vitro. When the target structure cannot be identified experimentally or predicted using computational methods, ligand-based approaches are frequently utilized as an alternative. These techniques, however, rely on information about the target's known active binders.

CADD has played an important part in the discovery of several accessible pharmaceutical medications that have received FDA approval and have reached the consumer market [Talele *et al.*, 2010; Kitchen D *et al.*, 2004].

2. Classification Of Computational Methods For Drug Design

CADD can be classified into two general categories: structure-based drug design and ligand-based drug design.

2.1 Structure-Based Drug Design (SBDD)

Structure-based drug design (SBDD) is the process that includes virtual screening and de novo drug design. These methods are a highly efficient and alternative approach to the discovery and development of the drug design course. In virtual screening, drug chemical compounds are computationally screened against known target structures. In classical or advanced pharmacology or legacy drug design and development, rational drug design is very costly and efficient. The first step in a rational drug design method or reverse pharmacology is to identify promising target proteins used for screening small molecule libraries. Structure-based virtual screening (SBVS), molecular docking and molecular dynamics (MD) are methods used in SBDD, a more specific, efficient, and rapid process for lead discovery and optimization because they are approximately related to the 3D structure of a Target protein. analysis of disease and binding energies at the molecular level, ligand-protein interaction induction insertion process (Lionta *et al.*,2014; Kalyaanamoorthy *et al.*,2011). The three-dimensional (3D) structure of proteins (more than 100,000) is provided in SBDD.

2.1.1 Identification of Target Protein and Binding Site:

Target protein identification is the key step in the SBDD process. It provided clear information on the binding site of the target macromolecule, protein-ligand interaction, post-docking dynamics, as well as hydrogen bond formation, which helped to calculate the best pharmacophores of the 'new' ligand. The binding sites are determined experimentally by integrative structural biology techniques in the 3D structure of the target macromolecule such as NMR, and X-ray crystallography. The next step is to identify the binding pocket after the target protein is resolved. It is a very small space where the ligand binds and also exerts its therapeutic or desired effect. These methods provide information on energy interaction and Van der Waals (vdW) forces for binding site mapping. There are many methods developed by energy interaction calculations for binding site mapping specifically for SBDD, and these methods identify specific regions of the target protein that interact with appropriate functional groups on drugs. These identify with the protein Q-site Finder (Laurie *et al.,* 2005; Zhang *et al.,* 2016; Grant 2009; Pau *et al.,* 2017).

2.1.2 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). The theoretical basis is that the process of ligand and receptor recognition relies on spatial shape matching and energy matching, which is the theory of "inducing fit". Determining the correct binding conformation of small molecule ligands and protein receptors in the formation of complex structures is the basis for drug design and studying its action mechanism. Molecular docking can be roughly divided into rigid docking, semi-flexible docking, and flexible docking. In rigid docking, the structure of molecules does not change. The calculation method is relatively simple and mainly studies the degree of conformation matching, so it is more suitable for studying macromolecular systems, such as protein-protein, and protein-nucleic acid systems. In semi-flexible docking, the conformation of molecules can be varied within a certain range, so it is more suitable to deal with the interaction between proteins and small molecules (de Ruyck *et al.*, 2016).

2.1.3 Scoring Function

The scoring function assists an insertion program into the ligand binding site. The scoring function also helps calculate the binding affinity between protein and ligand functions. Scoring functions are divided into force field, empirical, knowledge-based, and machine learning.

An early general-purpose empirical scoring function was developed by Bohm to describe the binding energy of ligands to receptors (Ms.Priti *et al.,* 2022).

2.2 Ligand-Based Drug Design (LBDD)

Ligand-based drug design is an approach used in the absence of receptor 3D information and relies on knowledge of molecules that bind to the biological target of interest. 3D quantitative structure-activity relationships (3D QSAR) and pharmacophore modeling are the most important and widely used tools in ligand-based drug design. They can provide appropriate predictive models for lead identification and optimization.

Ligand-based drug design is an approach used in the absence of receptor 3D information and relies on knowledge of molecules that bind to the biological target of interest.

a) Ligand-Based Drug Design consists of the information of molecules that bind to the desired target site.

b) These molecules can be used to derive a Pharmacophore model.

c) A pharmacophore model is defined as a molecule with the necessary structural abilities to bind to a desired target site.

d) Once the Pharmacophore is identified, it is determined whether it is suitable for the receptor, otherwise the Pharmacophore is further modified to make a potential drug (Crasto AM 2023).

2.2.1 Quantitative Structure-Activity Relationships (QSAR)

QSAR is a quantitative study of the interactions between small organic molecules and biological macromolecules. It contains a correlation between calculated properties of molecules (e.g., absorption, distribution, metabolism of small organic molecules in living organisms) and their experimentally determined biological activity (Vucicevic *et al.,* 2019). In the case of unknown receptor structure, the QSAR method is the most accurate and effective method for drug design. Drug discovery often involves the use of QSAR to identify chemical structures that could have good inhibitory effects on specific targets and have low toxicity (non-specific activity). With the further development of structure-activity relationship theory and statistical methods, in the 1980s, 3D structural information was introduced into the QSAR method, namely 3D-QSAR. Since the 1990s, with the improvement of computing power and the accurate determination of the 3D structure of many biomacromolecules, structure-based drug design has gradually replaced the dominant position of quantitative structure-activity relationship in the field of drug design, but QSAR with the advantages of a small amount of calculation and good predictive ability (Kumar *et al.,* 2019) still plays an important role in pharmaceutical researches. Based on 3D structural characteristics of ligands and targets, 3D-QSAR explores the 3D conception of bioactive molecules, accurately reflects the energy changes and patterns of interactions between bioactive molecules and receptors, and reveals the drug-receiving mechanism of body interactions. The physicochemical parameters and 3D structural parameters of a series of drugs are fitted to the quantitative relationship. Then, the structures of new compounds are predicted and optimized. In short, 3D-QSAR is a research method combining QSAR with computational chemistry and molecular graphics. It is a powerful tool for studying the interactions between drugs and target macromolecules, speculating the image of simulated targets, establishing the relationship between drug structure, and designing drugs (Lin *et al.,* 2020).

2.2.2 Pharmacophore

A pharmacophore is a molecular frame that describes the vital features responsible for the biological activity of a molecule (Guner *et a*l., 2005). Pharmacophore models are generated to increase the understanding of the ligand-protein interactions. They can be employed in identifying new molecules that satisfy the pharmacophore requirements and are thus expected to be active (Sanders *et al*., 2012). Pharmacophore models can be built by using the structural information about the active ligands that bind to the target if the target structure is not available. This is known as the ligand-based pharmacophore modeling approach (Lin *et al*., 2000). In conditions where the structure of the target is available, pharmacophore models can be built by using the structural properties of the target. This is known as the structure-based pharmacophore modeling approach (Sanders *et a*l., 2012). There are several pharmacophore modeling tools in use. HipHop, HypoGen, Pharmer, PHASE, GASP, PharmaGist, PharmMapper, MOE, LigandScout, and GALAHAD are examples of software used for pharmacophore model generation (Prachayasittikul *et al*., 2015). With the use of such software, pharmacophore modeling has been employed at the various stages of the drug discovery process (Gao *et al*., 2010). Virtual screening, drug target fishing, ligand profiling, docking, and ADMET (absorption, distribution, metabolism, excretion, toxicity) prediction are among its popular application areas (Langer *et al.,* 2006; Vel *et al*., 2012; Schuster *et al.,* 2010).

A pharmacophore model includes several patterns arranged in a particular 3D (three-dimensional) pattern. Each pattern is depicted by a typical sphere containing a radius that determines the deviation tolerance from the exact position. There are also various other displaying ways. These patterns can be displayed as a single pattern or their combinations (Sheridan *et al.,* 1989). In the ligand-based pharmacophore modeling, the first active ligands are identified by using the literature available or database search. The data set is split into a training set and a test set. Then, a feature analysis of the training set ligands is done. The common features are detected through the alignment of the active ligands. The next step is pharmacophore model generation and ranking of the generated models. Finally, pharmacophore model validation is performed and the best pharmacophore model is selected depending on the results obtained (Noha *et al.,* 2013; Leelananda *et al.,* 2016). In structure-based pharmacophore modeling, the selection and preparation of target protein structure is the first step. The second step is binding site prediction. Then, complemental chemical features of the binding site amino acids and their layouts are identified by analyzing them carefully. After this, the pharmacophore features, which should be optimized by the adjusted tools in the programs employed, are generated. Finally, crucial pharmacophore features responsible for the activity are selected (Sanders *et al.,* 2012).

3.1 Applications Of Computational Methods For Drug Design

3.1.1 Lead optimization

Lead optimization compares the properties of various lead compounds and provides information to select the compound or compounds with the greatest potential to be developed into safe and effective medicines. The candidate drugs with better therapeutic profiles are accessed for quality, taking into account factors such as the ease of synthesis and formulation. After this, they are registered as an investigational new drug and submitted for clinical drug (Maria *et al.,* 2012).

3.1.2 Visual screening

Virtual screening (VS) is a computational technique used to identify from a large library of compounds those that bind to a specific target, usually an enzyme or receptor. Virtual screening is usually approached hierarchically in the form of a workflow, sequentially incorporating different methods, which act as filters that discard undesirable compounds. This makes it possible to take advantage of strengths and avoid limitations of the individual methods (Scior *et al.,* 2012; Kumar *et al.,* 2015). Compounds that survive all the filters of the VS are usually referred to as hit compounds and they need to be tested experimentally in the laboratory to confirm their biological activity. Virtual screening methods can be classified into two major groups: Ligand-based methods, which rely on the similarity of the compounds of interest with active compounds.

Receptor-based methods, which focus on the complementarity of the compounds of interest with the binding site of the target protein. Like high-throughput screenings (HTS), VS protocols are normally used as an early step in the drug discovery process to enrich the initial library with active compounds (Scior *et al*., 2012).

3.1.3 ADMET Prediction

ADMET (absorption, distribution, metabolism, excretion, and toxicity) data is considered an essential part of discovering and developing new drugs. Both in vitro as well as in vivo models provide parameters regarding drugs' ADMET properties, which in turn can be used to predict drugs' behavior after administration. ADMET parameters determine whether drug candidates are to be advanced, held, or terminated (Zhang *et al.,* 2012). Preclinical data of drugs' ADMET properties play a role in the assessment of drug targeting after administration since pharmacokinetic profiles can be estimated based on drugs' ADMET data. Parameters including the absorption rate, the deposition, and the metabolism of the drug within the targeted organ are being taken into consideration when assessing drugs' exposure in the targeted site of action (Zhuang and Lu, 2016). To develop drugs with desired properties and optimal dosing regimens, it is very essential to determine the pharmacokinetic properties of these drugs, including their ADMET (Hop, 2012b). Due to various risk factors associated with the development and discovery of drugs along with the time-consuming processes involved, in vivo models were conducted to reduce the expected undesired properties of drugs in the preclinical stages before introducing them to the market (Bohnert and Prakash., 2012). Properties that are taken into account when predicting the behaviors of newly developed drugs are related to the size of doses and their frequencies as well. These properties include drugs' bioavailability, oral absorption, clearance, volume of distribution, as well as penetration through the blood-brain barrier (BBB) (van de Waterbeemd and Gifford, 2000).

3.1.4 Toxicity Prediction

Toxicity evaluation is of fundamental importance in drug development and approval. It is well known that drugs must undergo clinical trials to become legal (Ting *et al.,* 2006; Janodia *et al.,* 2007). Unfortunately, clinical trials are always associated with a certain degree of risk. It was reported that about half of the new drugs were found to be unsafe or ineffective in late human clinical trials (Hwang *et al.,* 2016). For example, the drug Sitaxentan was urgently withdrawn from global markets due to specific and irreversible hepatotoxicity in humans (Galiè *et al.,* 2011; Erve *et al.,* 2013). The safety of clinical trials highlights the importance of preclinical evaluations, which are necessary to prevent toxic drugs from entering into clinical trials.

3.2 Challenges in Computational Methods for Drug Design

Computational drug design faces several significant challenges that impact its effectiveness. One of the primary challenges is ensuring the accuracy of the results, which heavily depends on the quality of input data, such as protein structures and ligand conformations. Additionally, the precision of the computational methods, including the scoring functions used to evaluate ligand-protein interactions, is crucial to achieving accurate outcomes. Another challenge is the inherent complexity of drug design, as it involves numerous factors like ligand-protein interactions, solubility, and toxicity. Developing computational methods that can accurately model these multifaceted elements is a significant hurdle. Furthermore, the time required for computational drug design is often substantial due to time-consuming calculations, such as molecular dynamics simulations or large-scale virtual screening, which can create bottlenecks in the drug discovery process. Finally, reproducibility presents another critical challenge, as variations in software tools or input parameters can lead to inconsistent results, complicating the ability to compare and reproduce findings across different studies (Feher et al., 2003; Kitchen et al., 2004).

3.3 Future Direction

Artificial intelligence (AI) and machine learning are increasingly being utilized in drug design to predict the properties of new compounds and analyze vast datasets of molecular structures. These technologies offer the potential to accelerate the discovery of novel drug candidates while significantly reducing the cost and time associated with traditional drug discovery methods. Recent advancements, such as the application of deep learning to generate compounds with specific properties like efficacy and selectivity, highlight the transformative impact of AI in this field (Gómez-Bombarelli et al., 2018). Quantum computing, another emerging technology, promises to revolutionize drug design by enabling the simulation of molecular interactions with unprecedented detail, far surpassing the capabilities of classical computing methods. This could lead to the design of molecules with improved selectivity and binding affinity, although quantum computing is still in its infancy and rapidly evolving (McArdle et al., 2020). Additionally, multiscale

Figure 1. Schematic Representation of a Computational-Aided Drug Design (CADD)

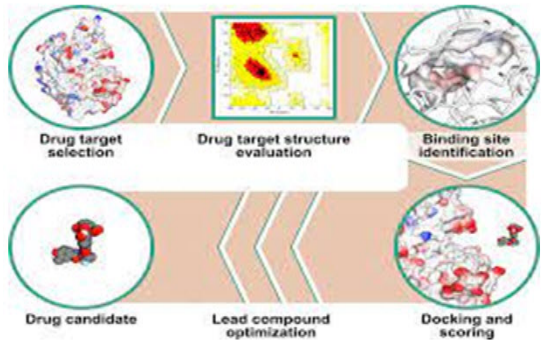

Figure 2. Workflow of Structure-Based Drug Design **(Ms.Priti *et al.*, 2022).**

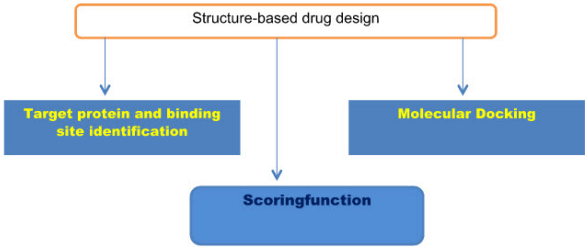

Figure 3. The Various Principles and Efficient Methods for SBDD Workflow

Table 1. Software for Structure-Based Drug Designing (SBDD)

Stages	Tools used	Brief Description	Links
1. Target modelling	SWISS-MODEL	Homology modelling	https://swissmodel.expasy.org/
	MODELER	Homology Modelling	https://salilab.org/modeller/
	Phyre and Phyre2	Template detection alignment as well as 3D modeling	http://www.sbg.bio.ic.ac.uk/phyre2/html/page.cgi?id=index
2. Binding site	CASTp	Binding site prediction	http://sts.bioe.uic.edu/castp/index.html?201l
	Active site prediction tool	Active site prediction	http://www.scfbio-iitd.res.in/dock/ActiveSite.jsp
3. Molecular Docking	AutoDockVina	Molecular docking and virtual screening	https://vina.scripps.edu/
	Schrodinger	Maestro	https://www.schrodinger.com/products/maestro

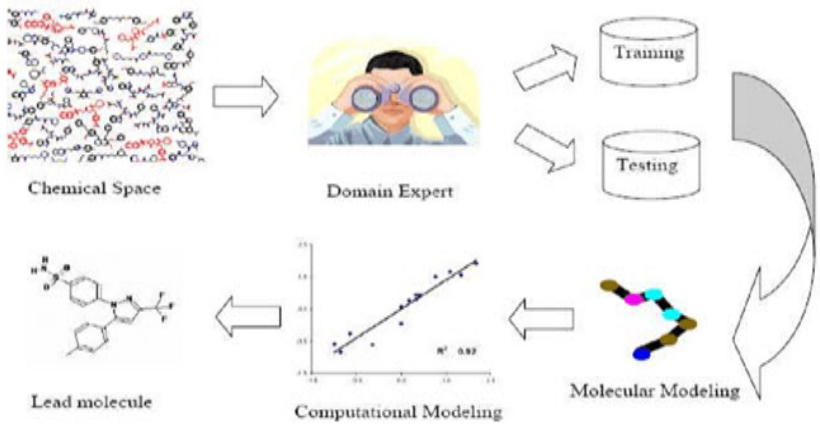

Figure 4. General Steps Involved in Ligand-Based Drug Design

Figure 5. Pharmacophore Modeling workflow

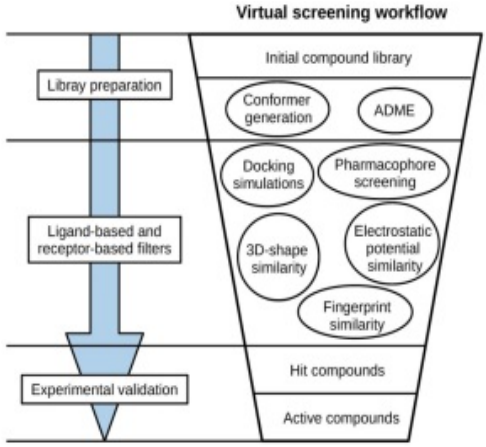

Figure 6. General Scheme of a Virtual Screening Workflow.

modeling approaches, which account for interactions occurring at different lengths and time scales, offer a more accurate representation of biological processes than traditional computational methods. By capturing these complex interactions, multiscale modeling can enhance drug design precision, identify potential off-target effects, and improve the safety of drug candidates (Klontz et al., 2018).

3.4 Successful Applications Of Cadd

3.4.1 *Design of Protease Inhibitors for HIV*:

The development of protease inhibitors for the treatment of HIV was a breakthrough in the field of drug design. The design of these inhibitors was facilitated by computational methods such as molecular docking and molecular dynamics simulations, which helped to identify compounds that could bind to the active site of the HIV protease enzyme. This led to the development of drugs such as saquinavir, ritonavir, and indinavir, which have been highly effective in treating HIV (De Clercq, 2009).

3.4.2 *Discovery of Tamiflu for Influenza*:

The antiviral drug Tamiflu was developed using a combination of computational and experimental methods. Molecular modeling was used to design analogs of the natural sialic acid molecule, which is a substrate for the influenza virus neuraminidase enzyme. These analogs were then synthesized and tested for their ability to inhibit the enzyme. Tamiflu, which was derived from one of these analogs, has been widely used to treat influenza (Hayden, 2009).

3.4.3 *Design of Kinase Inhibitors for Cancer*:

Kinases are enzymes that play a key role in cancer cell growth and proliferation. The design of kinase inhibitors for cancer treatment has been facilitated by computational methods such as virtual screening and molecular dynamics simulations. These methods have been used to identify compounds that can bind to the ATP-binding pocket of specific kinases and inhibit their activity. Drugs such as imatinib, dasatinib, and sunitinib, which target specific kinases, have been highly effective in treating certain types of cancer (Sharma and Almasi, 2019).

4. Conclusion

Computational methods have revolutionized the field of drug design by enabling faster, more cost-effective, and more efficient drug discovery. These methods include various techniques such as molecular docking, virtual screening, and machine learning algorithms, which can predict the activity, potency, and safety of potential drug candidates. The use of computational methods has led to the development of several successful drugs, such as HIV protease inhibitors, Tamiflu for influenza, and kinase inhibitors for cancer, which have significantly improved patient outcomes. Furthermore, computational methods have enabled the design of drugs that would have been impossible to discover using traditional methods, offering new hope for the treatment of complex and previously untreatable diseases.

Author contributions

O.S.B., O.O., and O.O.J. conceptualized the study. O.S.B. led data curation, formal analysis, and methodology development, with contributions from O.O. and O.O.J. O.S.B. and O.O. managed project administration, with O.O.J. supervising and validating. O.S.B. and O.O.J. drafted the manuscript, with O.O. assisting in review and editing. Data from this research can be accessed upon request.

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Competing financial interests

The authors have no conflict of interest.

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