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In silico methods and tools for drug discovery

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ABSTRACT

In the past, conventional drug discovery strategies have been successfully employed to develop new drugs, but the process from lead identification to clinical trials takes more than 12 years and costs approximately $1.8 billion USD on average. Recently, *in silico* approaches have been attracting considerable interest because of their potential to accelerate drug discovery in terms of time, labor, and costs. Many new drug compounds have been successfully developed using computational methods. In this review, we briefly introduce computational drug discovery strategies and outline up-to-date tools to perform the strategies as well as available knowledge bases for those who develop their own computational models. Finally, we introduce successful examples of anti-bacterial, anti-viral, and anti-cancer drug discoveries that were made using computational methods.

1. Introduction

Conventional drug discovery and development are risky, time-consuming processes that include target identification and validation, lead compound discovery and optimization, and preclinical and clinical trials [1]. In recent years, the estimated cost of bringing a new drug to market has reached about $1.8 billion USD [2], and the attrition rate of drug candidates is as high as 96% [2]. The reasons underlying this high attrition rate are poor drug efficacy and deficient drug absorption, distribution, metabolism, and excretion, and toxicity (ADME-Tox) [3]. Typically, *in vivo* and *in vitro* techniques are employed to examine drug safety, including adverse effects and toxicity. Recent advancements in *in vitro* models, such as organ-on-chip technology, have accelerated ADME-Tox assessments [4]. However, these approaches remain time-consuming, labor-intensive, and costly. High-throughput screening (HTS) methods have been developed to accelerate the identification of pharmacologically active chemical compounds from large numbers of molecules using automated assays [5]. Although automatic HTS systems reduce the need for human intervention, the scale of HTS remains low compared to the diversity of chemical structures. In addition, automated instruments remain expensive.

Recently, computer-aided drug discovery (CADD) approaches are attracting increasing attention as they can help mitigate the scale, time, and cost issues faced by conventional experimental approaches. CADD includes computational identification of potential drug targets, virtual screening of large chemical libraries for effective drug candidates, further optimization of candidate compounds, and *in silico* assessment of their potential toxicity. After these processes are conducted computationally, candidate compounds are subjected to *in vitro/in vivo* experiments for confirmation. Thus, CADD approaches can reduce the number of chemical compounds that must be evaluated experimentally while increasing the success rate by removing inefficient and toxic chemical compounds from consideration [6]. To date, CADD has been successfully employed to bring new drug compounds to market for diverse diseases, including human immunodeficiency virus (HIV)-1-inhibiting drugs (atazanavir [7], saquinavir [8], indinavir [9], and ritonavir [10]), anti-cancer drugs (raltitrexed [11]), and antibiotics (norfloxacin [12]).

Several CADD approaches have been developed and integrated with machine learning techniques to improve the accuracy and efficiency of CADD methods [13]. Structure-based drug discovery (SBDD) [14] and ligand-based drug discovery (LBDD) [15] are two different approaches taken in CADD. The selection of a suitable CADD approach relies on the availability of target protein structural information. To use the SBDD approach, structural information on the target protein is required, which is usually obtained experimentally by nuclear magnetic resonance or X-ray crystallography [14]. When neither is available, *in silico* prediction methods such as homology modeling [16] or *ab initio* modeling [17] can be used to predict the 3D structure of the target protein. Once the structure is available, structure-based virtual screening and molecular docking are possible [18]. When the structure is not available and it is not possible to predict a high-quality structure using *in silico* methods, the LBDD approach is often taken as an alternative. Although this

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Table 1
Web servers for target prediction.

Name	Description	URL	Ref.
Harmonizome	- Harmonizome is a collection of comprehensive and processed knowledge gathered from over 70 major online resources on genes and proteins. - It enables the discovery of novel relationships and functional associations between biological entities (proteins/genes).	https://maayanlab.cloud/Harmonizome/	[40]
Open Targets Platform	- Open Targets Platform is a knowledge-based platform that provides evidence about the association between known drug targets with diseases and enables the identification and prioritization of drug targets.	https://www.targetvalidation.org	[41]
TargetHunter	- TargetHunter predicts targets using the TAMOSIC algorithm, which can efficiently predict the biological targets of queried compounds.	http://www.cbligand.org/TargetHunter	[47]
Similarity Ensemble Approach (SEA)	- SEA ranks target proteins based on the chemical similarity between ligands. - 65,000 ligands are assigned to groups of human protein targets. Ligand topology is used to calculate a similarity score.	http://sea.bkslab.org	[49]
SwissTargetPrediction	- SwissTargetPrediction performs a similarity search to predict the potential drug targets of queried molecules. - The updated version contains 376,342 experimentally active compounds and 3068 macromolecular targets.	http://www.swisstargetprediction.ch	[59]
SuperPred	- SuperPred is a linear regression model trained using ECFP4 fingerprints to predict the target proteins of compounds.	https://prediction.charite.de	[60]
Polypharmacology browser	- Polypharmacology browser uses ten different fingerprints, molecular shapes, and substructure information to predict the most probable drug targets of a given small molecule.	http://gdbtools.unibe.ch:8080/PPB	[61]
HitPick	- HitPick predicts possible drug targets of hit compounds by a B-score method, a one-nearest-neighbor similarity search, and a modified naïve Bayesian model.	http://mips.helmholtz-muenchen.de/proj/hitpick	[62]
MolTarPred	- MolTarPred provides a list of possible drug targets and potentially similar compounds.	http://moltarpred.marseille.inserm.fr	[63]
MuSSeL	- MuSSeL uses a multi-fingerprint similarity search algorithm to predict the potential drug targets of small molecules.	http://mussel.uniba.it:5000	[64]
DisGenNET	- DisGenNET provides information on genes and variants associated with human diseases.	https://www.disgenet.org	[65]

Table 2
Protein target databases.

Database	Description	URL	Ref.
DrugBank	- A collection of 13,857 drug entities including 2661 approved drug molecules and 1425 approved biologics (peptides, proteins, and vaccines)	https://go.drugbank.com	[66]
ChEMBL	- A collection of 13,382 drug targets and 1.9 million drug molecules	https://www.ebi.ac.uk/chembl	[67]
ChemBank	- Information on hundreds of biomedical assays and millions of small drug compounds	https://data.broadinstitute.org/chembank/assay	[68]
Therapeutic Target Database (TTD)	- Experimental validation data on 37,316 drug compounds and 3419 drug targets	http://db.idrblab.net/ttd	[69]
Comparative Toxicogenomics Database	- Information on 45 million toxicogenomic relationships of 16,300 chemical compounds, 51,300 genes, 5500 phenotypes, and 7200 diseases	http://ctdbase.org	[70]
Traditional Chinese Medicines (TCM) Database	- Information on 37,170 unique compounds from 352 different herbs, minerals, and animal products	http://tcm.cmu.edu.tw/	[71]
SuperTarget	- Information on 195,770 small drug compounds and 6219 drug targets	http://insilico.charite.de/supertarget/	[72]
MATADOR	- Information on manually annotated drugs and targets from Drug Bank and SuperTarget	http://matador.embl.de/	[73]
ChemSpider	- Structural and text information on over 67 million chemical compounds	http://www.chemspider.com/	[74]
The Toxin and Toxin (T3DB)	- Information on 3678 toxins, 2073 toxin targets, and 42,374 toxin-target associations	http://www.t3db.ca/	[75]
Chem2BioRDF	- Information on chemical compounds, biological targets, and phenotypic data	http://chem2bio2rdf.org/	[76]
Promiscuous	- Information on 991,805 small molecules, 9430 drug targets, and 2,727,520 drug-target interactions	http://bioinformatics.charite.de/promiscuous2/index.php	[77]

approach requires prior information on the known active molecules of the target protein, many compounds have been discovered to treat diseases and are compiled in public databases unless the target is novel [19–21]. These approaches are introduced in section 4.

The field of CADD is rapidly advancing, and techniques and methods are under active development. Over the past few years, the integration of biological big data and machine learning approaches has opened new possibilities to increase the accuracy and efficiency of *in silico* drug discovery. This review introduces the overall procedures and methodologies behind *in silico* drug discovery, including target protein identification, chemical library screening, and toxicity assessment using machine learning approaches, summarizes available prediction tools and databases, and lists Federal Drug Administration (FDA)-approved and reported drug compounds developed using CADD techniques.

2. Increase in biological data on chemical molecules for drug discovery

Over the past few decades, large-scale data has been generated on hundreds of thousands of small molecules through biological screening, and this data is compiled in online repositories that are available for research. For example, due to advancements in HTS techniques, large-scale experiments of >1 million chemicals have been generated [22]. In addition, this biological assay data has been compiled in chemical library databases, and the amount of data is increasing rapidly due to advancements in chemical synthesis and HTS techniques. This accumulating data and its public availability have enabled the development of machine learning models and facilitated modern *in silico* drug discovery.

Traditional prediction methods, such as quantitative structure-activity relationship (QSAR) models, can be used in the early stages of drug discovery to prioritize drug candidates by their pharmacological properties and potential adverse effects [23]. Recently, due to increasing public resources, many machine learning-based prediction methods have been developed to predict drug-target interactions [24], the blood-brain-barrier permeability of compounds [25], and ADMET-Tox properties of drug candidates [26,27]. The integration of machine learning algorithms and accumulating data may pave the new way to CADD methods [13,28]. Available public databases are listed and summarized in Tables 1 and 2.

3. Target identification

A drug target is defined as a biological entity, usually a protein, that can modulate disease phenotypes [29]. Thus, the identification of prime drug targets is the first and most important step in drug discovery. Conventional drug target identification strategies are performed experimentally, such as identifying differentially expressed genes between normal and diseased cells or tissues and proteins that are highly interconnected with disease-related proteins.

3.1. Experimental approaches

Conventional experimental approaches for target identification require molecular and biochemical studies of disease pathophysiology. Although such studies expand our knowledge of diseases, they can be time-intensive methods for finding promising drug targets. Recently, genome-scale screening technologies, such as haploinsufficiency profiling (HIP), stable isotope labeling by amino acids in cell culture (SILAC), and target deconvolution have been developed to accelerate target identification.

HIP is a genome-wide screening assay for discovering drug targets by sensitizing cells to chemical compounds and identifying gene products associated with the viability of disease cell lines [30]. The HIP assay is advantageous in that thousands of genes can be evaluated simultaneously and that no prior knowledge of the pathophysiology of the disease is required.

In conventional drug discovery processes, it is often difficult to identify drug targets due to the complicated pathophysiology of many diseases. In this scenario, a reverse strategy can be applied: chemicals capable of modulating disease phenotypes can be screened, and corresponding target proteins can be found [31]. Diverse methods are employed for target deconvolution, such as protein microarrays, biochemical suppression, and affinity chromatography [31]. SILAC is an efficient reverse screening strategy that enables the unbiased, comprehensive, and robust identification of target proteins that bind to small molecule probes and drugs [32,33]. This technique was recently integrated with quantitative mass spectrometry-based proteomics and affinity chromatography, which enables more accurate identification of drug-protein interactions [32]. Despite the advantages of SILAC, it has several disadvantages that prevent its widespread and practical use: (i) isotope labeling is costly, (ii) sophisticated instruments, such as high-resolution mass spectrometers are required, and (iii) generating chemically immobilized drugs and ensuring their biological activity takes a long time [34].

3.2. Computational target identification

Experimental approaches are expensive and are generally conducted at low-throughput scale because of their complexity. To overcome these hurdles, *in silico* methods have been developed to identify potential drug targets [35]. Target proteins can be computationally predicted from experimental data [36,37], derived from the literature using text mining [38], or inferred from protein networks [39]. Several web servers such as Harmonizome [40] and the Open Targets Platform [41] provide lists of potential drug targets predicted using various databases. Alternatively, a reverse docking technique can be used to identify potential protein targets based on the concept that ligands with similar structures may bind to similar proteins with similar binding affinities, displaying similar biological effects [42–45].

The association-based identification of drug targets is a commonly used approach. For example, the Open Targets Platform [46] integrates diverse sources, including omics data, experimental results from animal models, and text-mined data from the literature. The platform then ranks genes according to their association with disease [46]. Several statistical and machine learning-based models, including TarFisDock [45], TargetHunter [47], PharmMapper [48], and Similarity Ensemble Approach [49], have been developed to predict the biological targets of a queried drug compound (Table 1). Ligand-based protein target discovery is commonly undertaken when no prior knowledge of pathophysiology is available [50]. Lavecchia reviewed various machine learning models designed to perform ligand searching using molecular descriptors and fingerprints representing the physicochemical properties of a chemical compound [51–56]. Given that descriptors and fingerprints are a quantitative representation of the chemical and physical characteristics of a compound, they are widely used in the development of predictive models [57]. A subtractive approach may help refine predicted targets. For example, potential drug targets to treat *Helicobacter pylori* infection can be identified by removing redundant enzymes, homologous enzymes to those of human or gut flora, extracellular enzymes, non-essential proteins, and other substances from the proteome of *H. pylori* [58]. Several freely available protein target databases are listed in Table 2.

3.3. Target validation

Once a target is identified, the next step is to confirm whether the modulation of the biological function of the target affects the disease phenotype [78]. There are various methods for modulating biological functions and evaluating predicted targets. Of these methods, small interfering RNAs (siRNAs) [79] are widely used because they can mimic drug effects by repressing translation, resulting in the temporary suppression of the target protein [80,81]. siRNAs allow investigation of the effects of target inhibition without inhibitors or prior knowledge of the protein structure [80]. However, for diseases with complex pathophysiology, such as neurological diseases, the degree of repression by siRNAs may affect cellular physiologies differently and may thereby result in contradictory outcomes [82]. In such cases, animal models in which the target gene is deleted or mutated can be more informative for target confirmation.

4. *In silico* methods for drug screening

The goal of drug discovery is to find small molecules that can modulate the function of an identified target protein and thereby modulate the disease phenotype. Furthermore, it is necessary to identify small molecules that possess effective pharmacokinetic properties and

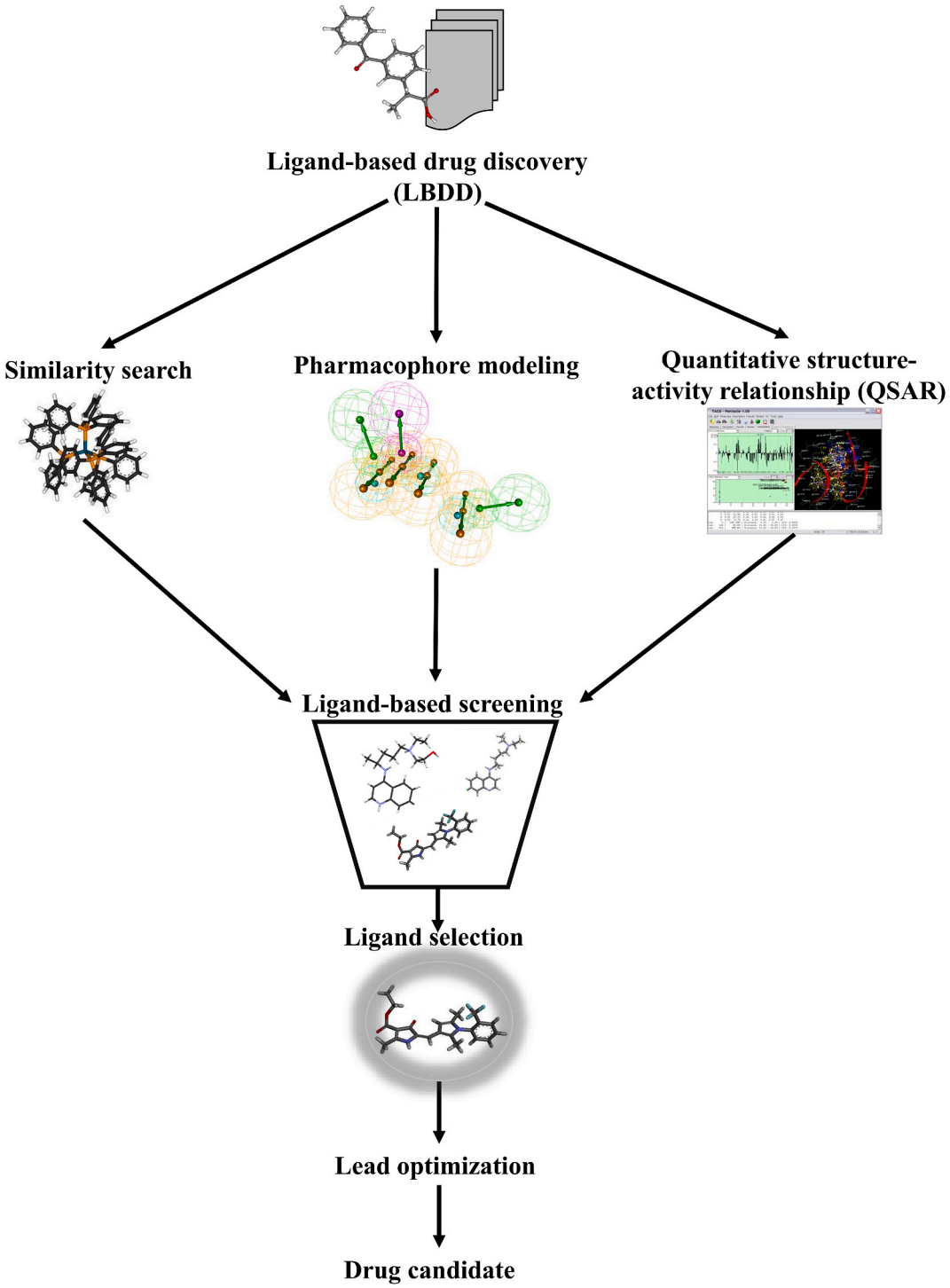

Fig. 1. Ligand-based drug discovery workflow. Known active compounds are used to predict new potential compounds from a large number of chemical compounds using a similarity search, pharmacophore modeling, or QSAR modeling. Predicted compounds are then subjected to virtual lead optimization and biological property assessment to identify new drug candidates.

low toxicity. Drug discovery involves a long, expensive, and risky cascade of complicated steps, including drug candidate identification, candidate validation, pharmacokinetics, and preclinical toxicity assessments. Traditional drug research and development (R&D) is expensive and time-consuming. On average, the standard period before a drug reaches the market is 10–12 years, and the estimated cost of discovering each successful drug is anywhere from $800 million to $1.8 billion USD [2,83].

The first hurdle in drug discovery is to screen for chemical compounds to find those that are pharmacologically effective. Generally, the hit rate of experimental HTS ranges between 0.01% and 0.14% [84]. Deficiencies in ADME-Tox are another significant hurdle and account for 40%–60% of drug failures in the later stages [85,86]. *In silico* drug discovery technology has played a significant role in the pharmaceutical industry for many years [87–89]. The main benefits of *in silico* drug discovery are cost and time efficiency. In addition, it can be applied to all stages from drug screening to preclinical and clinical stages [90], which remarkably reduces the failure risk in drug discovery processes.

Table 3
Compound databases available for virtual screening.

Database	Description	URL	Ref.
Asinex	- Contains 91,473 lead-like compounds for virtual screening	http://www.asinex.com/	[95]
ChemBridge	- Contains 1.3 million diverse and target-focused compounds	https://www.chembridge.com/	[96]
Zinc15	- Contains 230 million purchasable compounds for virtual screening	https://zinc15.docking.org/	[97]
BindingDB	- Contains 1.2 million binding affinity data entries on 5500 proteins and over 520,000 drug-like molecules	http://bindingdb.org	[98]
PubChem	- Contains 11 million unique small compounds and 99,361 tested target proteins	https://pubchem.ncbi.nlm.nih.gov/	[99]

Recent advances in machine learning algorithms, accumulated knowledge bases, and available synthetic chemical compound libraries enable computational methods to virtually screen a large number of chemical compounds and then rapidly evaluate their ADME-Tox properties [91,92] to find drug candidates with high potency and low toxicity.

4.1. Ligand-based drug screening

LBDD approaches utilize prior knowledge on active drugs—such as their structural, physical, and chemical features—to predict new drug compounds with similar biological effects [93] (Fig. 1). Prediction of drug compounds is based on the similarity of features (e.g., aromaticity, hydrogen bond acceptors, hydrogen bond donors, hydrophobicity, anion, and cation residues) between chemical compounds, under the assumption that compounds sharing high structural and physicochemical similarities are more likely to have similar biological activity [93]. LBDD is usually employed when the 3D structure of the target protein is not known. Methods such as pharmacophore modeling and QSAR provide useful information about target-ligand interactions in the absence of knowledge of the protein structure [94]. For virtual chemical compound screening, a number of compound libraries are publicly available (Table 3).

4.1.1. Similarity searches

Compound similarity searches are common and effective methods to identify new compounds that are similar to known active compounds. These methods are based on the idea that molecules with similar physicochemical properties are more likely to have similar biological activity [100,101]. Recently, many potent compounds have been identified using a similarity search approach [102]; for example, agonists for a G-protein-coupled receptor (GPR30) were developed with this method [103].

4.1.2. Pharmacophore modeling

Pharmacophores are sets of electronic and steric features that are essential for a compound to be recognized by a protein target [104]. Pharmacophore models are used as a query to screen compound libraries to identify chemicals with similar structural features and physicochemical properties. To identify pharmacophores, structurally diverse active ligands are computed to generate energetically stable conformations, and then their structures are arranged and superimposed to identify similar functional groups common to the active ligands. Chemical compounds containing these pharmacophores could be new drug candidates. There are several tools for pharmacophore modeling: Ligand Scout [105], 3D-pharmacophore modeling software (HipHop) [106], 3D QSAR pharmacophore generation software (HypoGen) [106], and the commercial pharmacophore modeling platform (PHASE) [107].

Pharmacophore modeling has been utilized to identify more potent drug compounds [108–110]. For instance, novel inhibitors against the bacterial DNA gyrase B, a bacterial type II topoisomerase, as a potent antibacterial drug have been developed from the molecules in the ZINC database by pharmacophore modeling [111].

Table 4
Tools for QSAR modeling.

Tools	Description	URL	Ref.
QSAR-Co	- Software for the development of robust multi-target classification-based QSAR models using a random forest technique or linear discriminate analysis	https://sites.google.com/view/qsar-co	[120]
Open3DQSAR	- 3D-QSAR model generation software for pharmacophore exploration by partial least square chemometric analysis	http://open3dqsar.sourceforge.net/	[121]
SYBYL-X	- Small molecular modeling, macromolecular modeling, and lead identification and optimization	https://chemweb.ir/downloads/sybyl-x-suite/	[122]
QSAR ToolBox	- A toolbox incorporating experimental data, theoretical knowledge, and computational tools from several resources; enables the identification of chemical compounds possessing similar structural characteristics	https://qsartoolbox.org/	[123]
McQSAR	- An extension of a genetic algorithm to generate QSAR models	http://users.abo.fi/mivainio/mcqsar/index.php	[124]

4.1.3. Quantitative structure-activity relationships

QSAR methods generate mathematical models that correlate the structural and physicochemical properties of compounds with their biological activity. QSAR was first developed by Hansch and Fujita in 1962 [112] and is a classic method in drug discovery. In this method, molecular descriptors representing the structural and chemical properties of compounds [113] are used to train QSAR models, and the trained models are then used to predict the biological activity of given chemicals to detect new drug candidates or to optimize lead compounds. For QSAR model construction [114], chemical compounds with known biological activities are collected, and these compounds are used for model training and evaluation. To improve the prediction accuracy, a structural diversity of compounds should be ensured. For model training, molecular descriptors (features) of the collected chemical compounds are computed, and then a mathematical formula (model) that best correlates the descriptors with biological activities is generated. The model is evaluated using holdout compounds that are not used for training the model.

Recently, 3D-QSAR approaches have been developed as an extension of the classical QSAR methods to overcome their limitations [115]. 3D-QSAR approaches can be classified into comparative molecular field analysis (CoMFA) [116] and comparative molecular similarity indices analysis (CoMSIA) [117]. CoMFA is a linear 3D-QSAR method that focuses on ligand properties like electrostatic and steric energies. CoMFA determines the bioactive conformation of each small molecule by the superimposition or alignment of molecules. Several pitfalls of the CoMFA method include its imperfect potential energy functions, that hydrophobicity is not well quantified, and that it is applicable only to *in vitro* data [118]. CoMSIA was developed to overcome these limitations by using an exponential functional form derived from the SEAL alignment algorithm [117] to compute steric and electrostatic grids and hydrophobic and hydrogen bonding properties. In CoMSIA, the distance-dependent similarity of a probe to the atoms of the molecules in the aligned dataset is evaluated at each grid node using Gaussian-type functions, and grid nodes falling within the molecular volume are also taken into account to avoid abrupt changes in grid-based probe-atom interactions [119]. Several online servers and tools are available for QSAR modeling including QSAR-Co [120] and Open3DQSAR [121] (Table 4).

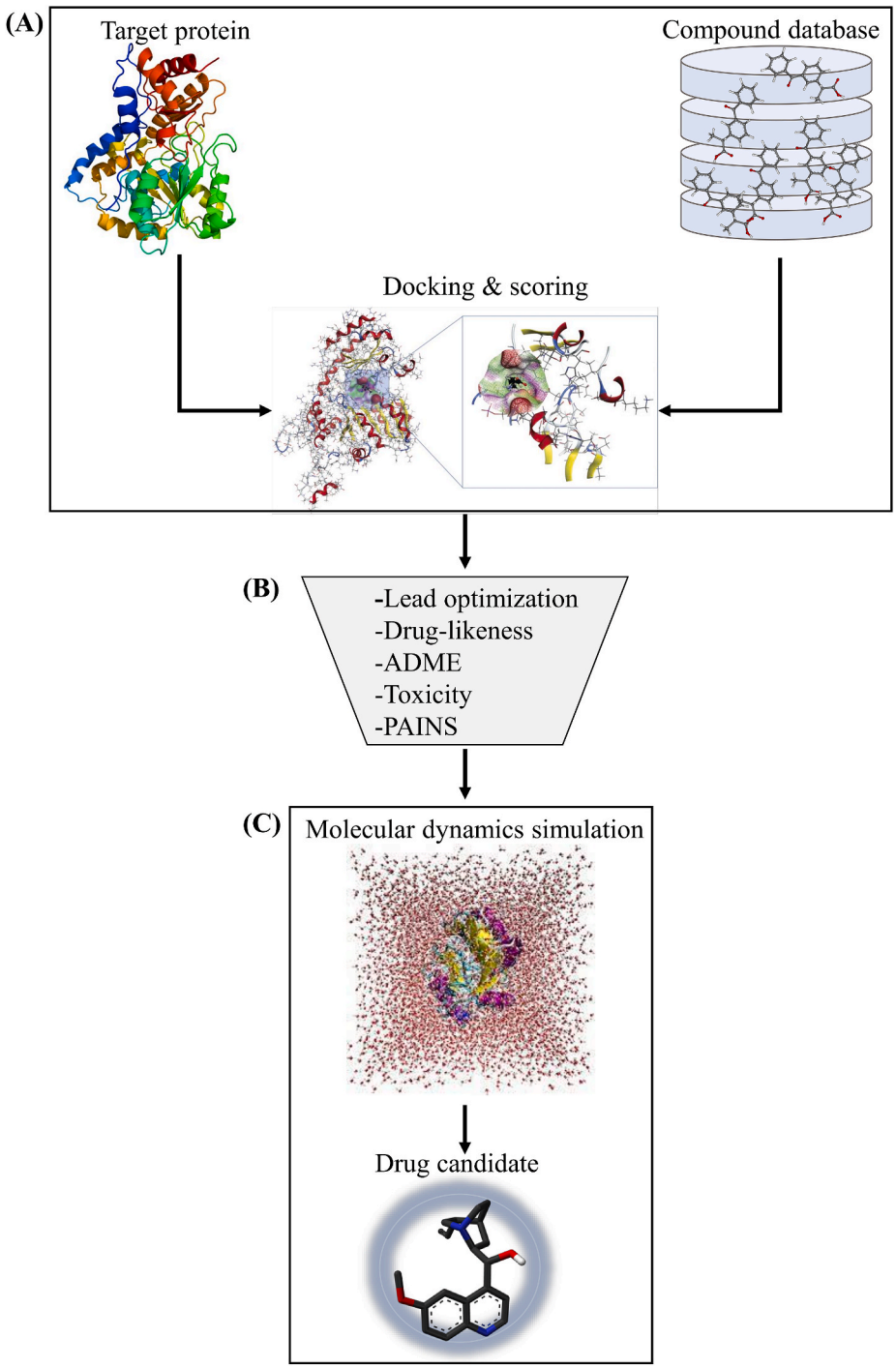

Fig. 2. Structure-based drug discovery workflow. (A) Compounds are docked on a target protein and are prioritized by their binding affinity and mode. (B) Hit compounds are structurally optimized and filtered by their physiochemical properties, determining ADME-Tox and other pharmacological characteristics. (C) Additional molecular dynamics simulations are performed to refine the designed chemicals, and finally, drug candidates are selected. These candidates are then subjected to experimental validation.

4.2. Structure-based drug discovery

Paul Ehrlich, a German researcher known for his vast contributions to pharmacology, stated that "corpora non agunt nisi fixate; " drugs will not act unless they are bound [125]. Unlike ligand-based drug discovery, SBDD approaches calculate the binding affinity between a ligand and a target protein, specifically a binding pocket, using the structures of the ligand and the target protein [126] (Fig. 2). This approach includes molecular docking, fragment-based docking, and molecular dynamic simulation for the prediction of binding affinity [127–129]. Many drugs that are in clinical trials or are FDA-approved were successfully developed using SBDD approaches [130]. Saquinavir and amprenavir were the first FDA-approved HIV-1 protease drugs developed with SBDD methods [131,132]. As a groundbreaking success in the early 1990s, these drugs improved the prognosis of HIV-infected patients [88]. SBDD methods have also been successfully employed to predict binding sites in AmpC β-lactamase, which was important for designing small molecules [11]. Another successful application of SBDD is FDA-approved dorzolamide, a carbonic anhydrase II inhibitor, that is used to treat glaucoma [133,134].

4.2.1. Target protein structure generation

The first step in SBDD is to obtain a high-resolution 3D structure of the target protein, which may be available in the Protein Data Bank (PDB) [135]. If the structure is not yet resolved, it can be predicted by leveraging other structures with similar sequences or from scratch.

Table 5
List of ligand binding site prediction tools.

Name	Description	URL	Ref.
CASTp 3.0	- CASTp allows the prediction of all surface pockets and interior cavities in a protein and provides a detailed description of all atoms involved in the pocket formation.	http://sts.bioe.uic.edu/castp/	[150]
SiteMap	- SiteMap uses a whole protein sequence to predict ligand binding sites and ranks the putative binding sites by SiteScore, a scoring function to access the site's propensity for ligand binding.	https://www.schrodinger.com/products/sitemap	[151]
Fpocket	- Fpocket is a fast method for pocket prediction and is also efficient for large proteins. It provides two programs: (i) tpocket is to test own scoring function and (ii) dpocket is to extract the pocket description.	http://fpocket.sourceforge.net/	[152]
3DLigandSite	- User can provide a sequence or 3D structure of a queried protein. This tool predicts the 3D structure of the sequence and uses it to identify homolog structures with bound ligands from the PDB. The superimposed structure of the query and homolog structure is used to predict the binding sites.	http://www.sbg.bio.ic.ac.uk/~3dligandsite/	[153]
PocketDepth	- PocketDept is a geometry-based and depth-based clustering method that predicts binding pockets with an accuracy of 96%.	http://proline.physics.iisc.ernet.in/pocketdepth/	[154]

Homology modeling assumes that proteins with a high sequence identity share similar 3D structural conformations and functions. Diverse tools and online resources for homology modeling are available; these tools include MODELER [136], SwissModel [137], Mod web [138], and Phyre2 [139]. If appropriate template structures are not available, an *ab initio* protein structure modeling approach can be utilized [140]. Template-free modeling techniques use energy functions to find the most stable (energetically lowest) conformations, and these approaches can predict short proteins (<100 amino acids) with a root mean square deviation (RMSD) of 2–5 Å [141–143]. Two major factors responsible for accurate structure predictions are an accurate energy function that finds the most thermodynamically stable conformation and an efficient search method to identify the lowest energy state via a large number of possible conformations. I-TASER [144], Robetta server [145], and QUARK [146] are some of the available web servers for *ab initio* structure prediction.

4.2.2. Binding site prediction

A binding site is a concave region or a small pocket of a protein where a ligand molecule binds to produce the desired output (activation, inhibition, or modulation) [11,147]. The structure of co-crystallized ligands with a protein can provide beneficial information for SBDD. If this structural information on binding pockets is not available, potential binding pockets can be predicted with *in silico* methods [148]. Although these tools can play a pivotal role in predicting putative binding sites, their prediction accuracy is influenced by various factors such as template similarity and the size of the pocket [149]. Several current binding site prediction tools are listed in Table 5.

4.2.3. Molecular docking

Once the 3D structure of a target protein is determined, the next step

Table 6
Molecular docking tools.

Tools	Description	URL	Ref.
GOLD	- GOLD predicts ligand binding conformations using a genetic algorithm and provides multiple scoring functions for ranking the predicted binding conformations, including GoldScore, ChemScore, and ASP fitness score.	https://www.ch.cam.ac.uk/computing/software/gold-suite	[160]
Glide	- Glide is a fast-docking method that uses a series of hierarchical filters and three different scoring functions (SP, XP, and HTV) to rank predicted ligand binding conformations in the binding cavity of a receptor.	https://www.schrodinger.com/glide	[161]
FlexX	- This method splits a ligand into fragments and places them into multiple regions of a binding pocket. The ligand is then built up and scored.	https://www.biosolveit.de/SeeSAR/#FlexX	[162]
DOCK	- This docking software provides several functions: ligand and receptor desolvation, ligand conformational entropy correction, Hawkins–Cramer–Truhlar GB/SA solvation, molecular dynamic simulation, and receptor flexibility during docking analysis.	http://dock.compbio.ucsf.edu/	[163]
AutoDock Vina	- AutoDock Vina is widely used and is known as a fast and accurate docking program. - It uses a variety of stochastic global optimization approaches, including simulated annealing, genetic algorithm, and particle swarm optimization, to speed up docking optimization. - It also allows receptor side chains to be treated as flexible during docking.	http://vina.scripps.edu/	[164]
HADDOCK	- HADDOCK is a flexible docking method for resolving multiple modeling problems and is applicable to the prediction of protein-ligand docking, protein-protein docking, and protein-nucleic acid docking.	https://wenmr.science.uu.nl/haddock2.4/	[165]
Surflex-dock	- Surflex-dock is a platform that provides several functions, such as molecular conversion from 2D to 3D, protein structure alignment and preparation, molecular docking for virtual screening, and ligand modeling.	https://www.biopharmics.com/	[166]
FITTED	- FITTED is a genetic algorithm-based docking program that can efficiently handle flexible macromolecules and the presence of bridging water molecules during docking analysis.	http://mgltools.scripps.edu/documentation/links/fitted	[167]
MOE	- MOE is integrative drug discovery software for efficient molecular modeling, QSAR model generation, virtual screening, and structure-based drug design.	https://www.chemcomp.com/Products.htm	[168]
FlipDock	- This method can dock a flexible ligand molecule into the binding site of a flexible receptor molecule.	http://flipdock.scripps.edu/	[169]
pyDOCK	- pyDOCK is a fast and efficient web server for rigid-body docking prediction that uses an advanced pyDock scoring algorithm.	https://life.bsc.es/pid/pydockweb/	[170]
Discovery Studio	- Discovery Studio is an integrative drug discovery platform for		[171]

(*continued on next page*)

Table 6 (*continued*)

Tools	Description	URL	Ref.
	molecular dynamic/quantum mechanics/molecular mechanics simulations, macromolecule design, structure-based and ligand-based drug discovery, and pharmacophore and QSAR modeling.	https://www.dsngine.com/discovery.studio	
ZDock	- This program enables the prediction of protein-protein interactions.	http://zdock.umassmed.edu	[172]
GEMDOCK	- GEMDOCK provides a highly accurate method for predicting ligand conformation and orientation within the binding site of a receptor by using its empirical scoring function.	http://gemdock.life.nctu.edu.tw/dock/	[173]
LigandFit	- LigandFit uses a cavity detection algorithm to detect active site regions and a Monte Carlo conformational search to generate ligand conformations within active sites.	https://www.phenix-online.org/documentation/reference/ligandfit.html	[174]
PatchDock	- PatchDock implements a geometry-based molecular docking algorithm to predict protein-protein and protein-ligand dock conformations.	https://bioinfo3d.cs.tau.ac.il/PatchDock/php.php	[175]
ClusPro	- ClusPro employs a fast Fourier transform-based docking method for fast and accurate peptide-protein docking prediction.	https://cluspro.bu.edu/publications.php	[176]

is to identify ligands with a high binding affinity via molecular docking. Molecular docking algorithms predict the preferred orientation of a given ligand within the binding pocket of a target protein and calculate their affinity by electrostatic interactions and van der Waals interactions [18,155–157]. With docking algorithms, a large number of ligands can be virtually screened to find those with a high binding affinity to the target protein. Docking methods can be classified as rigid docking and flexible docking [158]. Rigid docking considers only static physiochemical/geometry complementarities and does not allow flexibility between a target and a ligand [158]. This approach is generally adopted when many compounds are screened quickly during initial virtual screening. Flexible docking methods are used for the refinement and optimization of rigid docking results.

Docking methods can also assist in predicting protein-protein interactions and evaluating the affinity of complexes, thus enabling a better understanding of signaling pathways. Protein-protein interactions are responsible for cellular processes, and, therefore, predicting protein-protein docked complexes can help us gain an understanding of their functional mechanisms and roles in the cell [159]. Popular docking tools are listed in Table 6.

4.2.4. Fragment-based docking

Fragment-based docking has revolutionized the process of drug discovery with the aid of molecular docking. Drug compounds contain substructures (fragments), and some of these fragments, such as the pharmacophore, are essential for displaying biological functions, while some are only structurally used to assemble substructures. Conventional molecular docking approaches utilize the complete structures of chemical compounds to calculate their binding affinities with binding pockets. By contrast, fragment-based docking approaches detect fragments with a reasonable affinity that is generally low compared to entire ligand structures [177]. Then, the fragments are optimized to improve their binding affinity by adding functional groups to the fragment or joining with other fragments [178].

For fragment-based docking, the first step is to build a library of fragments that are structurally diverse [179]. In general, the "rule of three" is commonly used to construct druggable fragments [180]: a molecular weight <300 Da, a cLogP ≤ 3, hydrogen bond donors ≤ 3, and hydrogen bond acceptors ≤ 3 [178–180]. Next, potent fragments are screened based on their binding affinity computed as in conventional molecular docking algorithms. As the screened fragments generally include essential substructures, such as pharmacophores, their affinities are typically weak. Thus, to enhance their potency, screened fragments are modified by adding functional groups or other fragments. Zelboaf (PLX4032) was the first FDA-approved drug developed by a fragment-based docking approach [181], and 40 chemical compounds discovered by this approach have advanced to clinical trials to date [182,183].

4.2.5. Molecular dynamic simulation

Proteins are flexible, and their flexibility is important in ligand binding, but prediction of the motions of protein binding pockets and ligands involves high computational cost due to the complex atomic interactions between the target protein and ligand molecule. Molecular dynamics (MD) simulation was first introduced in the 1970s to overcome this limitation [184]. It involves solution of Newton's equation of motion to simulate atomic motions and to reduce the calculation complexity [185,186]. In terms of drug discovery, MD simulations enable an understanding of the structural features of proteins and the stability of protein-ligand complexes, which can be used to virtually screen chemical compounds. It also helps the identification of additional druggable binding sites such as allosteric sites and consequently leads to the design of more effective drug compounds [187,188].

In computational drug discovery, the best-docked complexes are generally subjected to MD simulations to confirm their binding. Briefly, protein and ligand topologies are generated with standard parameters using AMBER or CharmGUI [189,190]. The dynamics (atomic movement) of the complex are simulated using force fields in the AMBER [189], CHARMM [190], and GROMOS [191] simulation packages. Once the simulation is completed, the trajectories of atomic movements are analyzed by using the Xmgrace or Qtgrace tools for graphical analysis [192]. Usually, the root mean square fluctuation, the RMSD, the radius of gyration, and hydrogen bonding formations are analyzed to determine complex stability. The binding of the free energy of ligand-protein complexes can be calculated with the molecular mechanics/Poisson–Boltzmann surface area (MM/PBSA) and the molecular mechanics/generalized born surface area (MM/GBSA) because they are more accurate than most molecular docking scoring functions and less computationally expensive [193,194]. These methods have successfully reproduced experimental results and can thus improve molecular docking results [193]. The binding free energy includes several electrostatic energies, such as the van der Waals energy, internal energy summed from molecular mechanics, and the polar contribution toward solvation energy, and the energy can be calculated using the MMPBSA.py module in the AMBER package.

To further improve MD simulations, a more accurate molecular force field is required to simulate the movements of atoms in target proteins and ligands. However, this may also increase the computational burden, which limits simulations longer than a microsecond [195]. To resolve this limitation, recently, graphics processing units with a large number of cores have been used to increase the speed of MD simulations [196–198]. Conventional MD simulations are based on molecular mechanics (MM) [199], but quantum mechanics (QM) is required for a more accurate prediction of chemical reactions [200,201], which requires a high computational burden. Thus, a hybrid QM/MM approach has been used to understand the dynamic behavior of chemical reactions at the molecular level [200,202,203]. Typically, a QM potential function is used to predict the part of the protein that is directly involved in chemical reactions. The MM potential function is used for the remaining atoms in the system. This hybrid approach can provide reliable accuracy within a reasonable timeframe [200]. For decades, QM/MM methods have been further improved and used to study many biological and

Table 7
Servers for predicting the ADME-Tox properties of compounds.

Name	Description	URL	Ref.
PreADMET 2.0	- Provides numerical information on the ADME and toxicity of chemical compounds	https://preadmet.bmdrc.kr/preadmet-pc-version-2-0/	[213]
ALOGPS 2.1	- Predicts water solubility, LogP, and pKa(s) of compounds	http://www.vcclab.org/lab/alogps/	[214]
SwissADME	- Provides a user-friendly environment to compute physicochemical descriptors and ADME parameters	http://www.swissadme.ch/	[215]
DrugMint	- Predicts drug-like compounds	https://webs.iiitd.edu.in/oscadd/drugmint/	[216]
LightBBB	- Predicts blood-brain barrier permeability of compounds	http://bioanalysis.cau.ac.kr:7030/	[221]
CardPred	- Predicts hERG-related toxicity of compounds	http://bioanalysis.cau.ac.kr:7050/	[223]
ToxinPred	- Predicts and designs toxic and non-toxic peptides	http://crdd.osdd.net/raghava/toxinpred/	[224]
ProTox-II	- Predicts the toxicity profile of compounds	http://tox.charite.de/protox_II/	[225]
ToxiPred	- Predicts the toxicity of small compounds based on QSAR descriptors	http://crdd.osdd.net/oscadd/toxipred/	[226]
ADMETlab	- Computes ADME and toxicity features of compounds	http://admet.scbdd.com/	[227]

chemical reactions [204–208]. Several popular packages for MM/QM simulations include Gromacs [209], NAMD [210], AMBER [189], and CHARMM [190].

5. ADME-Tox assessment

Once drug candidates are discovered, the next step is to assess their pharmacokinetic properties, such as ADME-Tox. Due to advances in machine learning algorithms and accumulated datasets, ADME-Tox can also be predicted using computational methods.

It is estimated that 40%–60% of drug candidates are withdrawn in preclinical tests because of ADME-Tox concerns [85]. Drug compounds must cross various physiological barriers, such as the gastrointestinal barrier, the blood-brain barrier, and microcirculatory barriers, to reach the biological targets where they exert their pharmacological effects. They may require metabolic conversion for activation or may be converted into a toxic compound that can lead to adverse effects [211]. However, traditional experimental methods for ADME-Tox assessments remain laborious and costly.

A simple rule for assessing the drug-likeness of chemical compounds is Lipinski's "rule of five": a molecular weight <500 Da, lipophilicity <5, number of rotatable bonds <10, hydrogen bond donors <5, and hydrogen bond acceptors <10 [212]. Recently, instead of using this simple rule, more advanced prediction methods are becoming increasingly used to predict drug-likeness in terms of ADME-Tox properties. A number of machine learning-based models have been developed for the prediction of the pharmacokinetic properties of chemical compounds. These models include PreADMET [213], ALOGPS [214], SwissADME [215], and DrugMint [216]. For example, Schyman et al. constructed 15 models for the prediction of ADME-Tox properties using the variable nearest neighbor (vNN) method [26,27]. Furthermore, Abdul et al. developed a chemical toxicity prediction model using a decision tree algorithm. They identified an optimum number of features from thousands of features, and the model was used for toxicity screening [217,218]. Additionally, Yu et al. used a coevolutionary neural network algorithm to build an androgen receptor toxicity prediction model [219,220]. Interestingly, instead of commonly used molecular descriptors, they used 2D chemical structure images of compounds to train the model. Their model successfully classified androgen receptor agonists

Table 8
Approved and reported drugs developed by CADD approaches.

Drugs	Year approved or reported	Drug target/disease	Ref.
Captopril (Capoten)	1975/ approved	Angiotensin-converting enzyme inhibitor to treat hypertension and myocardial failure	[241]
Cimetidine (Tagamet)	1978/ approved	H_2-receptor antagonist to treat peptic ulcers	[242]
Dorzolamide (Trusopt)	1989/ approved	Carbonic anhydrase inhibitor used as an antiglaucoma agent	[243]
Imatinib (Gleevec)	1990/ approved	Tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia	[244]
Saquinavir (Invirase)	1995/ approved	HIV-1 protease inhibitor used to treat HIV/AIDS (1st generation)	[8]
Oseltamivir (Tamiflu)	1996/ approved	Influenza neuraminidase inhibitor for the treatment of influenza A and B	[245]
Indinavir (Crixivan)	1996/ approved	HIV protease inhibitor to treat HIV/AIDS (1st generation)	[9]
Ritonavir (Norvir)	1996/ approved	HIV protease inhibitor to treat HIV/AIDS (1st generation)	[10]
Zanamivir (Relenza)	1999/ approved	Neuraminidase inhibitor for the treatment of influenza A and B	[246]
Nelfinavir (Viracept)	1999/ approved	HIV protease inhibitor to treat HIV/AIDS (1st generation)	[247]
Lopinavir (Kaletra)	2000/ approved	HIV protease inhibitor used to inhibit HIV that is resistant to other protease inhibitors	[232]
Fosamprenavir (Lexiva)	2003/ approved	HIV protease inhibitor used to treat HIV/AIDS (1st generation)	[248]
Atazanavir (Reyataz)	2004/ approved	HIV protease inhibitor used to treat HIV/AIDS (2nd generation)	[7]
Tipranavir (Aptivus)	2005/ approved	A non-peptide HIV-1 protease inhibitor that is active against HIV strains resistant to other protease inhibitors	[233]
Erlotinib (Tarceva)	2005/ approved	Epidermal growth factor receptor (EGFR) kinase inhibitor used to treat pancreatic cancer	[249]
Sorafenib (Nexavar)	2005/ approved	Vascular endothelial growth factor receptor kinase inhibitor used to treat renal cancer, thyroid cancer, and liver cancer	[250]
Darunavir (Prezista)	2006/ approved	A non-peptide HIV-1 protease inhibitor used to treat 2nd-generation HIV/AIDS	[251]
Lapatinib (Tyverb)	2007/ approved	EGFR inhibitor used to treat ERBB2-positive breast cancer	[252]
1-(8-(benzo[d][1,3]dioxol-5-ylmethyl)-9H-purin-6-yl)guanidine	2011/ reported	Dipeptidyl peptidase IV inhibitor for diabetes therapy	[230]
Abiraterone (Zytiga)	2011/ approved	Androgen synthesis inhibitor used to treat prostate cancer	[253]
Crizotinib (Xalkori)	2011/ approved	Anaplastic lymphoma kinase (ALK) inhibitor used to treat pancreatic cancer	[254]

(*continued on next page*)

Table 8 (*continued*)

Drugs	Year approved or reported	Drug target/disease	Ref.
ZINC01807204 and ZINC02318494	2012/ reported	Inhibitors against KPC-2 β-lactamase to treat the multidrug-resistant bacterial infection	[255]
1-(3-Carboxypropyl)-4-(4-(3,5-difluorobenzyloxy) phenyl)-1H-pyrrole-2-carboxylic	2012/ reported	Potent inhibitor of β-ketoacyl-acyl carrier protein synthase III (*mt*FabH) to treat *Mycobacterium tuberculosis* infection	[256]
Compound 25h (4-(4-(3-methoxyphenoxy) pyridin-2-yl)morpholine), 26e (3-((2-methyl-6-phenylpyridin-4-yl)oxy) phenol), and 26k (4-(3-methoxy-5-methylphenoxy)-2-(4-methoxyphenyl)-6-methylpyridine)	2012/ reported	*Plasmodium falciparum* macrophage migration inhibitory factor tautomerase inhibitors to treat the malaria infection	[257]
(methyl2-(2-(((benzyloxy) carbonyl)amino) propanamido)-3-(4-hydroxyphenyl) propanoate)	2013/ reported	Inhibitor of an enzyme lipoate protein ligase B (LipB) to treat *M. tuberculosis* infection	[258]
NRB04248	2015/ reported	*M. tuberculosis* PknG (*Mt*PknG) inhibitor	[259]
Ribociclib (Kisqali)	2017/ approved	Cyclin-dependent kinase (CDK) 4 and 6 inhibitors to treat metastatic breast cancer	[260]
3,9-disubstituted eudistomin U derivative (compound 6p)	2018/ reported	*Staphylococcus aureus* DNA gyrase	[261]
Larotrectinib Sulfate (Vitrakvi)	2018/ approved	Tropomyosin-related kinase (Trk) inhibitor to treat various cancers	[262]
Apalutamide (Erleada)	2018/ approved	An antagonist of androgen receptor used to treat prostate cancer	[263]
Cladribine (Leustatin)	2019/ approved	Adenosine deaminase inhibitor to treat hairy cell leukemia and B-cell chronic lymphocytic leukemia	[264]
Erdafitinib (Balversa)	2019/ approved	Fibroblast growth factor receptor inhibitor to treat cancers	[265]
Zanubrutinib (Brukinsa)	2019/ approved	Bruton's tyrosine kinase inhibitor to treat mantle cell lymphoma	[266]
Selinexor (Xpovio)	2019/ approved	Nuclear export inhibitor to treat cancers	[267]

and inactive compounds. Shaker et al. developed a blood-brain-barrier permeability prediction model based on LightGBM, an advanced random forest algorithm, to screen for compounds to treat neuronal diseases [221,222]. Finally, Lee et al. developed a reliable human ether-a-go-go related gene (hERG) cardiotoxicity prediction model using a neural network algorithm [223]. A list of available tools and web servers for ADME-Tox predictions is provided in Table 7.

6. Successful applications of *in silico* drug design

The development of new therapeutic drugs is an expensive and time-consuming process. *In silico* technology has become essential in the contemporary pharmaceutical industry because it can reduce the time and resources required for drug discovery. Due to advancements in computational algorithms and accumulated knowledge databases, computational prediction tools have now been integrated into every stage of the drug discovery process. Computational drug discovery methods have been successfully used in the design and identification of drug compounds to treat various diseases, including cancer [228,229], diabetes [230,231], and viral [8,9,232,233] and bacterial infections [128,234–240]. Drugs developed by CADD thus far are listed in Table 8.

7. Conclusions

Over the past few decades, the *in silico* identification of disease-associated drug targets and therapeutic drugs has become increasingly efficient and accurate. Recently, *in silico* drug discovery has accelerated due to rapid advancements in computational methods and accumulating publicly available biological data. Chemical biology is involved in the elucidation of the biological functions of targets, while CADD techniques make use of structural information of either the drug target (structure-based) or ligands with known bioactivity (ligand-based) to facilitate the identification of promising drug candidates. CADD techniques are now an essential part of the drug discovery process due to their ability to fast-track drug discovery by leveraging existing knowledge on ligand-receptor interactions, structural optimization, and synthesis. Pharmacological properties such as adsorption, distribution, metabolism, excretion, and toxicity are the most important pharmacological features for successful drug development. Many machine-learning-based models have been also developed based on increasing amounts of biological data.

To date, numerous drugs identified using CADD techniques have successfully reached the market and are available to consumers. Nonetheless, further improvements are needed, especially in molecular docking scoring functions, in targeting receptors with little or no structural information, to incorporate molecular flexibility and solvent effects, for MD simulation force fields, and to increase computational efficiency. By alleviating these shortcomings of CADD approaches, the full potential of CADD can be achieved.

Author contributions

BS, SA, and DN: conceptualization. BS and JL: data curation. BS and CJ: methodology. DN: supervision. BS and DN: manuscript writing. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interests

There are no conflicts of interest to declare.

A conflict of interest statement

None declared.

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