

Computational approaches in drug designing

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13.1 Introduction

In each step of the drug discovery and development, computational methods provide valuable and interesting resources. To explore the design and development of therapeutic agents, a computer-aided drug design (CADD) approach came into existence that uses various chemical, molecular, and quantum strategies for designing a potential drug candidate (Veselovsky & Ivanov, 2003). Structure–activity relationships (SAR) are the basis of many CADD strategies as it provides the information about the biological activity. CADD's principal aspects are to design and improve the biological activity of a drug, and also to understand the biological mechanism of action at the molecular level (Guha, 2013). Three major steps in the drug development processes are as follows: (1) to identify specific bioactive compounds and their molecular targets or hits, (2) testing of the compound using wet-lab experiments (preclinical, clinical I, II, and III trial), and (3) registration of drug compound to facilitate the marketing and therapeutic use (Sliwoski, Kothiwale, Meiler, & Lowe, 2014).

The objective of CADD approaches is to screen, optimize, and evaluate the activity of compounds against a drug target (Singh & Dwivedi, 2019; Yu & MacKerell, 2017). This virtual screening is intended to reduce the time, labor, and cost associated with drug development. The use of computational approaches, such as homology modeling, cavity prediction, big data mining and analysis, SAR, and virtual screening, made significant improvements in the process of drug discovery (Chan, Shan, Dahoun, Vogel, & Yuan, 2019; Yang, Wang, Byrne, Schneider, & Yang, 2019). The purpose of this chapter is to introduce CADD in a general way, covering key techniques and their applications, and future directions in the drug discovery process. Overall, CADD can be categorized into two main structure-based and ligand-based approaches (Fig. 13.1).

13.2 Computer-aided drug designing

In CADD, drug discovery may be focused on a ligand as well as the designing of candidate drug may be oriented on the cavity of the target molecule (Singh, 2020). Overall, CADD can be categorized into two main structure-based and ligand-based approaches. Some CADD-oriented drugs and their targets are listed in Table 13.1.

13.2.1 Structure-based drug design

The 3D structure of the target protein is known in the structure-based approach and interaction or affinity is measured for all the compounds tested after the docking procedure to construct a new drug molecule that possesses a very high affinity for the target protein. Structure-based drug design (SBDD) involves target protein structure analysis, identification of binding sites, or active sites, understanding of the molecular-level mechanism of action of active compound, and the evaluation of the thermodynamics and kinetics parameters used in ligand-target interaction (Sledz & Caffisch, 2018). SBDD goes through several processes before an optimized lead is obtained in clinical trials. Its first step consists

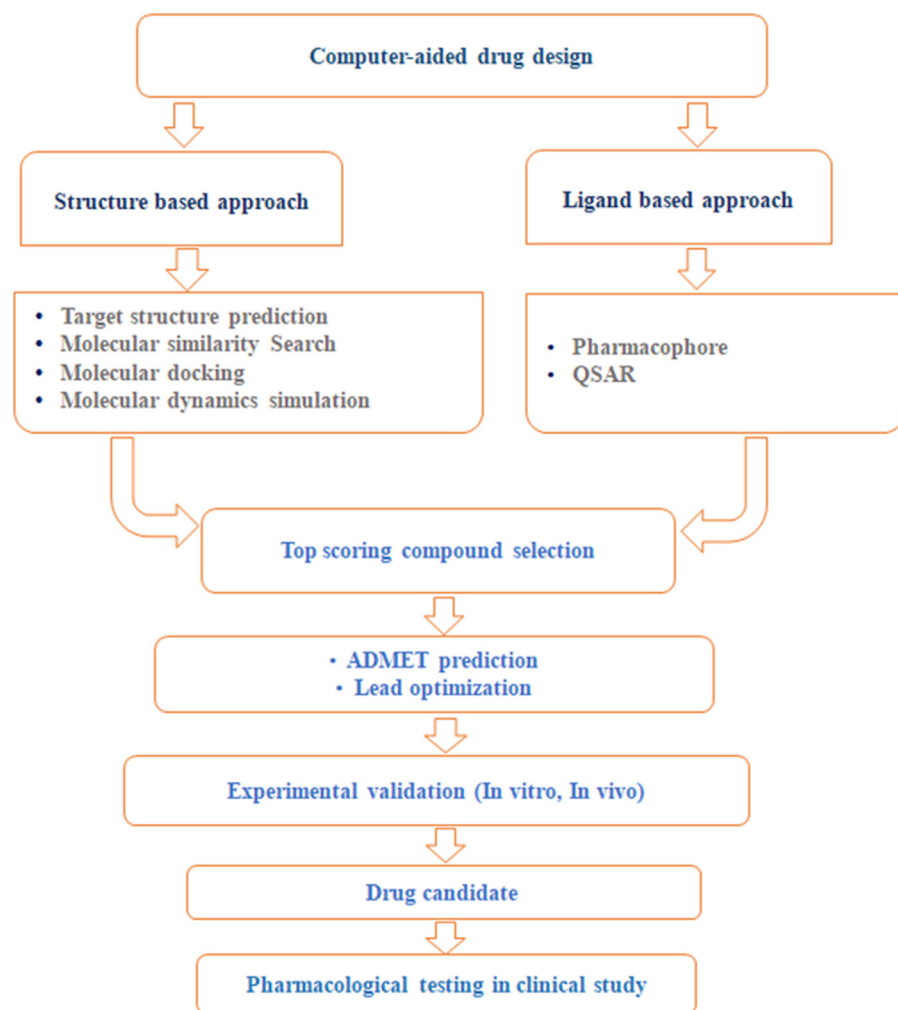


FIGURE 13.1 Drug discovery and development process using computer-aided drug design approach.

TABLE 13.1 Some drugs based on the computer-aided drug design approach, related disease, and their drug target.

Drug	Disease	Target	References
Oxymorphone	Potent opioid analgesic	Agonist of mu-opioid receptor	Sloan (2008)
Saquinavir	AIDS	Inhibitor of HIV-1 and HIV-2 proteases	Van Drie (2007)
Captopril	Hypertension	Inhibitor of angiotensin-converting enzyme	Talele, Khedkar, and Rigby (2010)
Zanamivir	Influenza A and influenza B	Inhibitor of neuraminidase	Kim et al. (1997)
Dorzolamide	Glaucoma and ocular hypertension	Inhibitor of carbonic anhydrase	Balfour and Wilde (1997)

of separation, purification, and structure determination of the target protein with X-ray crystallography, nuclear magnetic resonance spectroscopy, or homology modeling. After binding site information, a vast set of compounds are evaluated for their binding affinity and interaction at the active site of the target protein, and some potential binding ligands are screened against the target. A vast set of chemical compounds are evaluated and screened based on the steric, hydrophobic, electrostatic interactions of these compounds with the active site of a target protein. In further evaluation, top-scoring compounds are analyzed using biochemical assays.

The second cycle consists of the analysis and assessment of the protein stability in the complex with one of the most positive leads of its first cycle. The chosen lead compound can undergo several chemical modifications to improve its efficacy as a drug. After several subsequent cycles, such as lead synthesis, additional lead optimization, and protein and optimized lead compounds' binding analysis, the optimized compounds usually display a notable improvement in target specificity and binding affinity (Anderson, 2003).

13.2.2 Ligand-based drug design

The 3D structure of the target protein is not known in the ligand-based drug design (LBDD), but the characteristics of ligands that bind to the target site are known. Pharmacophores developed from a set of ligands possess all the structural components and features required to generate biological responses against a disease. Searching and identification of biologically active compounds or enhancing the bioactivity of known molecules are some of the main priorities of these approaches (Singh & Pathak, 2020). Similarity searching using a compound or its characteristics as an input feature, and development of the quantitative structure–activity relationship (QSAR) model for bioactivity predictions are the important approaches used in LBDD (Shim & Mackerell, 2011). The two fundamental techniques of LBDD are as follows: first, the searching and retrieval of chemical compounds considered to be similar to a known ligand with a certain extent of similarity and, second, the development of the QSAR model from a set of known ligands to predict the biological activity of new compounds. QSAR approach is also widely used to screen new ligands with the desired biological activity, hit-to-lead, and lead to drug optimization. QSAR analysis also guides the necessary changes required in a compound to improve the pharmacokinetics or toxicity parameters.

13.3 Computational approaches

Computational methods and tools for drug discovery and development have grown explosively over the last 40 years, especially in recent decades with the incredible development of biology, biomedicine, and computer technology. Mostly in the postgenomic era, computational resources have been used in almost every stage of drug discovery and development due to the availability of a vast number of chemical compounds with their bioactivity data and pharmacological profile as well as an experimentally verified molecular drug target, which has completely transformed the drug discovery process. To date, some commercially available drugs, such as imatinib, zanamivir, and nelfinavir, are designed using molecular modeling approaches (Prieto-Martínez, López-López, Eurídice Juárez-Mercado, & Medina-Franco, 2019). Computational methods are widely used in all stages of CADD, including target identification to lead discovery, through lead optimization to preclinical or clinical studies (Table 13.2).

13.3.1 Molecular modeling

Molecular modeling makes use of structural knowledge to predict the 3D structure of a target protein based on its sequence similarity to homologous structures (template). This approach requires only protein sequence information to model the 3D structure of a protein (Mirjalili & Feig, 2013; Tiwari et al., 2011). Thus, for example, the structural determination of therapeutic targets is very important to proceed for the SBDD. In the homology modeling approach, the accuracy of modeled target structure depends on the selection of template and template–target similarity, the higher the similarity between template and target, the higher will be the accuracy of the modeled structure. Several structure modeling tools and software, such as modeler, Swiss Model, I-TASSER, ROSETTA, and ROBETTA, are available that are based on homology modeling, threading, or ab initio methods. Critical assessment of Protein Structure Prediction (CASP) is a bi-annual collaborative project to evaluate the state of the art in protein structure modeling (Moult, Pedersen, Judson, & Fidelis, 1995). It gives research groups an ability to review existing approaches of structure prediction critically and offers the research community and software users an unbiased evaluation of the state of the art in protein structure modeling. More than 100 study groups from around the world regularly participate in CASP, and it is not unusual for entire groups to postpone their other studies for months while concentrating on having their servers ready for the experiment and carrying out the comprehensive predictions (Kryshtafovych, Schwede, Topf, Fidelis, & Moult, 2019). Several tools, such as Verify 3D, ProCheck, and WhatCheck, are available to assess the accuracy of the modeled protein structure.

TABLE 13.2 Some tools/software and databases used in computer-aided drug design.

Name	Description	URL
SwissDock	Web integration of the EADock DSS program, which enables small molecules to be docked on the basis of a manually curated protein–ligand interaction database	http://www.swissdock.ch/
SwissModel	Server for homology modeling	https://swissmodel.expasy.org/
USR-VS	A webserver for ligand-based virtual screening powered by ultra-fast shape recognition techniques	http://usr.marseille.inserm.fr/
Hex Server	Protein–protein docking, based on the shape and electrostatics of targets	http://hexserver.loria.fr/
ZDOCK	Protein–protein docking server to measure energy on protein poses based on Fourier transformation	http://zdock.umassmed.edu/
UFSRAT	Virtual screening, based on the similarity	http://opus.bch.ed.ac.uk/ufsrat/
T-COFFEE	Server for homology modeling	http://tcoffee.crg.cat/
PUMA	A server that performs many chemical space analyses and the variety of small molecules	https://www.difacquim.com/d-tools/
AutoDock	Docking tools	http://autodock.scripps.edu/
Gold	Protein–ligand docking software	https://www.ccdc.cam.ac.uk/solutions/csd-discovery/Components/Gold/
Glide	Ligand–receptor docking software from Schrödinger	https://www.schrodinger.com/products/glide
FlexX	It is a fast and flexible docking software suited for virtual screening	https://www.biosolveit.de/FlexX
Dock	Molecular docking software	http://dock.compbio.ucsf.edu/
FRED	Fast exhaustive docking software	https://www.eyesopen.com/oedocking
ICM	Docking of a protein with a ligand, peptide, or protein	http://www.molsoft.com/docking.html
Binding Database	Database of binding affinity for protein–ligand complexes	https://www.bindingdb.org/
PubChem	Database of compounds with structure, 2D and 3D properties, and bioactivity, assays	https://pubchem.ncbi.nlm.nih.gov/
Human metabolome data	It is a freely available electronic database contains 114,266 metabolite entries	http://www.hmdb.ca
DrugBank	Compound database of many drugs and targets	https://www.drugbank.ca/
Protein data bank	Database of 3D structures of proteins, other biomolecules, and complex with others	http://www.pdb.org
Pharmacogenomic data	An interactive tool for researchers to investigate how genetic variation affects the response of drugs	http://www.pharmgkb.org
Comparative toxicogenomic database	Contains the information about how environmental exposures affect human health	http://ctdbase.org
BRENDA	Set of manually compiled enzymatic data from 82,568 proteins	https://www.brenda-enzymes.org/
Chemspider	Chemical compound database with searching and analysis facility	http://www.chemspider.com/
ChEMBL	Compound database with chemical features, activity values, and target information	https://www.ebi.ac.uk/chembl/
GLIDA	G-protein coupled receptors and their ligands information with searching facility	http://pharminfo.pharm.kyoto-u.ac.jp/services/glida/
HEMD	Provides information about the epigenetic targets and their chemical modulators, or ligands information	http://mdl.shsmu.edu.cn/HEMD/

13.3.2 Binding site and cavity prediction

The binding site is one of the important regions in a 3D structure of a protein target. During protein–ligand interaction analysis, the user has to focus on the region in the protein structure where a ligand can bind and occupy its best pose. Binding site information can be taken from published literature as well also from the analysis of protein–ligand complex available in the structure databases. The binding site residues in the cavity of protein, therefore the cavity prediction tools can provide the probable location of the binding site in a protein. Several cavity prediction tools, such as CastP, Q-SiteFinder, and COACH, have been designed that are based on evolutionary, energy-based, or geometric-based approaches. In an evolutionary-based approach, it is considered that evolutionarily related proteins will have nearly the same binding site as it is conserved during evolution. Geometry-based methods are based on the features, such as shape, hydrophobic surface, compactness, and charged surface residues, whereas energy-based approach uses a probe to find the favorable binding regions on protein.

13.3.3 Computational ligand designing and searching

Big data analysis plays a significant role in medicinal chemistry. The volume and velocity of available data are defined by the compilation of large quantities of data generated daily and exchanged by public databases, such as the Enamine REAL Database (Klingler et al., 2019), ChEMBL (Gaulton et al., 2017), and PubChem (Kim et al., 2019). Many data repository interfaces (e.g., PubChem) collect data from various sources and then curate the data for its accuracy and acceptability. Techniques, such as high-throughput screening and combinatorial chemistry, can be used to screen a vast set of compounds in a short time. The availability of a vast amount of diverse chemical structures and computational tools for different CADD analyses has reduced the time required for drug discovery and development.

CADD has two key applications: (1) search for new possible active compounds, such as the identifying of hits, and (2) improve the biological activity or ADMET property of active compounds, such as the hit to lead optimization. Virtual screening is used for the identification of hit compounds from a vast set of the compound database using computational approaches (Siju et al., 2017). Experimental evaluation of screened compounds is essential. A second phase or more screening steps are undertaken when the experimental assessment has been carried out. The experimental facts of the prior steps should be considered in the screening of the molecules in the second or even more round of screening. Virtual screening and interaction studies for screening purposes are much beneficial, cost effective, and widely accepted. Virtual screening offers the selection of a better potential ligand for a target using docking methodologies (Yuriev, Holien, & Ramsland, 2015).

13.3.4 Pharmacophore modeling

A further technique of CADD to recognize drug-like novel compounds from a vast chemical space allows us to discover a new drug by optimizing many pharmaceutical properties necessary for an effective drug (Devi, Sathya, & Coumar, 2020). A pharmacophore is the set of steric and electronic characteristics required to ensure better interactions with a particular biological target and also able to generate its biological response (Wermuth, Ganellin, Lindberg, & Mitscher, 1998). In other terms, “a pharmacophore is the arrangement of a molecule’s characteristics that are accountable for a biological effect.” A pharmacophore is formed by a set of characteristics features rather than specific chemical classes. Since the development of the past century, pharmacophore techniques have been among the primary tools for drug discovery. For developing a better pharmacophore model, ligand-based and structure-based methodologies have been introduced. Pharmacophore models are widely used in virtual screening, de novo design, and lead optimization. The pharmacophore model represents the key set of features involved in the interaction with a biological target as it is derived from a vast set of ligands extracting common pharmacophore features using clustering (Fig. 13.2). The pharmacophore model can be used for searching compound libraries based on pharmacophore features, de novo designing of ligands, and optimizing the bioactivities of a lead compound. Many pharmacologically potential and well-recognized drug targets with uncertain active site geometries have been reported during the recent period of drug design. Several tools, such as MOE, Ligand-Scout, Phase, and Catalyst/Discovery Studio, are available that provide the facility to build a Pharmacophore model, and some tools have also facility to build a pharmacophore model and then use it to search many other compounds that possess the same pharmacophore (Liao, Sitzmann, Pugliese, & Nicklaus, 2011).

13.3.5 Molecular docking

Molecular docking is a technique that predicts the preferred orientation, affinity, and interaction of a ligand in the binding site of a protein. Information of the preferred orientation in turn may be used to predict the strength of binding

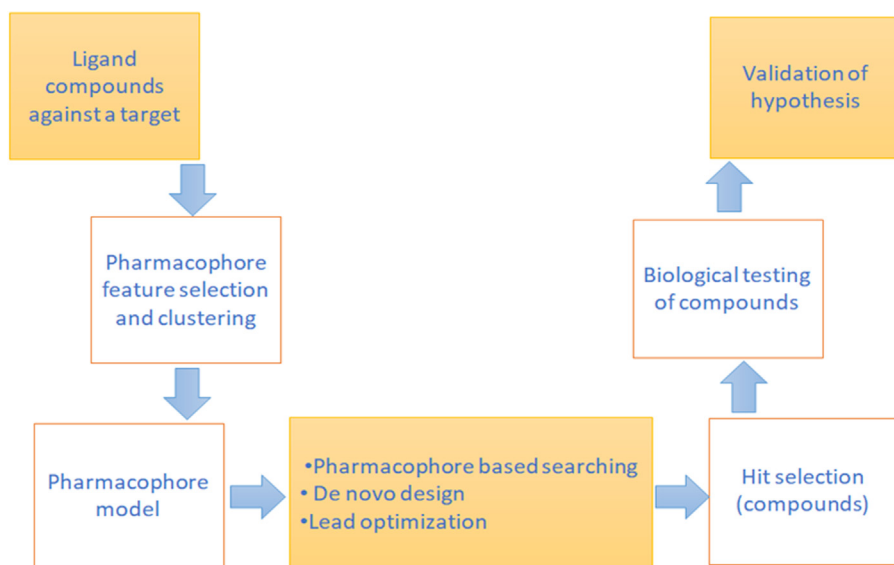


FIGURE 13.2 Pharmacophore modeling, its applications, and experimental validation of pharmacophore hypothesis.

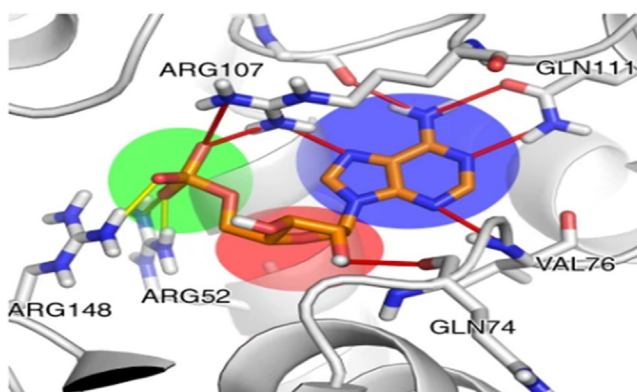


FIGURE 13.3 Interaction view of uridilate kinase with AMP, showing labeled residues with their positions.

affinity between a drug target and ligand molecule using scoring functions (Lengauer & Rarey, 1996). The most interesting case is the protein–ligand interaction because of its applications in medicine. In CADD, macromolecules are generally considered rigid, and some software provides flexibility to certain residues while running docking. During docking, it is assumed necessary to take dynamics into account for a protein target. Toward this, molecular dynamics methods have been used that emphasize the application of quantum chemistry, statistical mechanics, and the features of the electrical potential (force field) (Ganesan, Coote, & Barakat, 2017). Several docking tools, such as AutoDock, AutoDock Vina, Gilde, DOCK, GOLD, FlexX, and Surflex, and many docking servers, such as ZDOCK, HDOCK, ClusPro, and SwissDock, are available for molecular docking purposes. Several parameters, such as ligand center and the number of torsions, binding residues, grid parameters, flexible residues, algorithm, iteration, pose, and result oriented settings, are defined before proceeding for docking. Molecular docking is used for virtual screening, binding affinity, and binding free energy calculations and also for tracing out and visualizing various types of bonded and non-bonded interaction between the ligand and amino acid residues of a protein (Singh, Gupta, Kesharwani, & Misra, 2013). Interaction view of uridilate kinase with adenosine monophosphate (AMP) shows residues Arg52, Gln74, Val76, Gln111, Arg107, Gln11, and Arg148 that belongs to the ligand-binding region (Fig. 13.3) (Majewski, Ruiz-Carmona, & Barril, 2019).

13.3.6 Molecular dynamics simulation

Molecular dynamics simulation (MDS) is used for the computational simulation of a molecular system alone as well as also in a complex form with another molecule, that is, for a protein–ligand complex. The advantage of MDS analysis

is that it considers the role of many physical parameters, such as temperature, pressure, solvent, and ions, that are not included in docking tools (Singh & Dwivedi, 2016). MDS analysis provides a clear picture of the dynamic behaviors of systems and the physical motions of molecules and atoms. For a given time duration, the atoms and molecules are allowed to interact and their trajectory analysis is done to provide a glimpse of the system's dynamic evolution. The adaptation of the laws of motion to molecules and other principles of molecular mechanics and interactions is taken into considerations during MDS. A variety of simplifications are needed in MDS, such as bonds are portrayed as loops and a molecule is regarded as a series of spheres. Charges, bonded interactions, nonbonding interactions, polarization, and torsions are parts of the parameter set used in MDS (Vanommeslaeghe, Guvench, & Mackerell, 2014).

MDS has a wide range of applications, such as binding energy and interaction analysis, mutational analysis, and understanding the impact of physical parameters, such as temperature, pressure, solvent, ions, water on the molecular system, and protein folding and unfolding dynamics (Arcon et al., 2017; Clark et al., 2016). MDS scalability recently allows for modern approaches which can address challenges beyond protein versatility. The distinct techniques include pH-REMD, an enhanced sampling method used to assess the atmosphere of active positions and right side chains pKa (Sabri Dashti, Meng, & Roitberg, 2012), and QM/MM, a hybrid technique for modeling electronic changes based on ab initio and physical changes using molecular mechanics (Aldeghi, Heifetz, Bodkin, Knapp, & Biggin, 2016). CHARMM, Desmond, Amber, Gromacs, and many other tools are available for MDS analysis of a protein alone or its complex with an inhibitor/drug or biomolecules. In MDS analysis, dynamics and behaviors of a molecular system are explained on the basics of some parameters, such as root means square deviation, root means square fluctuation, the radius of gyration, free energy, H-bonding dynamics, and protein–ligand contact plot.

13.3.7 Quantitative structure–activity relationship

Chemical knowledge extraction and processing approach for some kind of use in the physical or biological sciences shall be included in the chemoinformatics as well as in the relevant analytical methods for the discovery of pharmaceutical compounds. Molecular similarity search and QSAR methods are among the most common chemoinformatics approaches (Leach & Gillet, 2007). In CADD, the QSAR methods are used for the estimation of the biological activity of a compound based on the QSAR model developed from a set of known ligands. QSAR model defines a relationship between physicochemical properties and biological activity of a set of compounds. QSAR models are derived from a set of ligands (training set: 80%) that are active against a particular target protein. Internal validation of the QSAR model is done using a test set (20% data), and external validation can also be performed using data from other experimental sources (Fig. 13.4). There are many 1D, 2D, 3D, etc., descriptors, such as the spatial, electronic, and

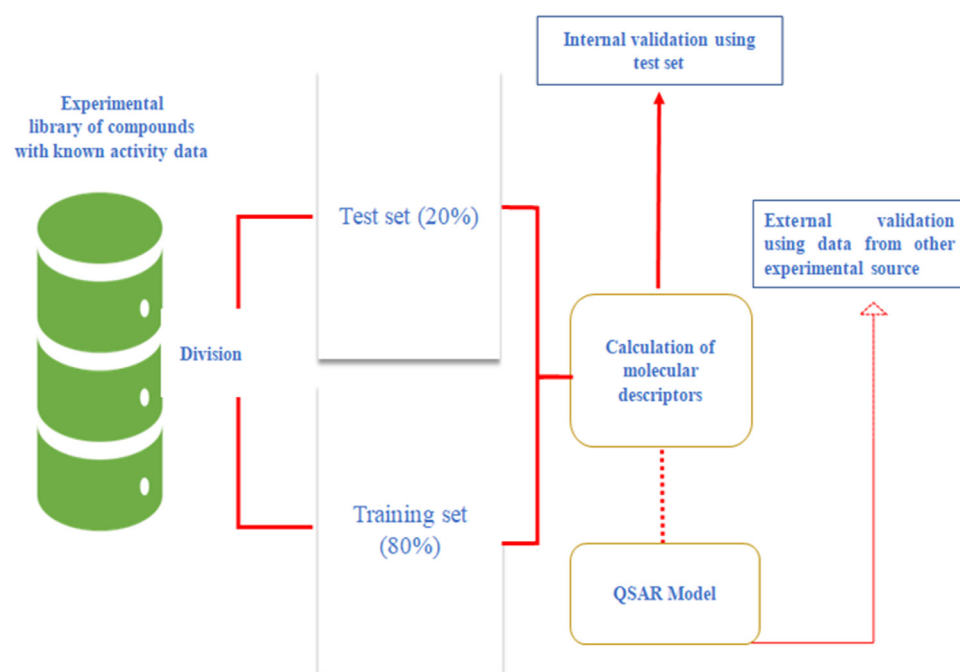


FIGURE 13.4 Quantitative structure–activity relationship model generation from compound activity data, internal validation of the model using the test set, and external validation using data from other experimental sources.

conformational features, and many more others that are used as input to predict the biological activity of a new compound. Though several descriptors, including the number of H-bond acceptors, are easier to compute based on molecular connectivity, more specialized measurements may be needed for the calculation of other descriptors. Noticeably, it is important to obtain descriptors that can relate to the chemical reactivity of drugs, such as the Highest Occupied Molecular Orbital and the Lowest Unoccupied Molecular Orbital energy using quantum chemical equations (Bredas, 2014; Griffith & Orgel, 1957).

Clustering, artificial neural networks, regression, and multivariate data analysis (partial least square, principal component analysis) approaches are used to establish a relationship between biological activity and structural properties. A small difference in structural property leads to a significant change in biological activity. QSAR allows a vast range of chemical products to be prioritized as an *in silico* technique in terms of their desired biological activity and also reduces the number of chemicals for *in vivo* research. QSAR analysis also suggests the chemical and structural changes required in a lead molecule to optimize its activity suitable for a drug. Some tools, such as Gusar, BioPPSy, ChemDes, and PHASE, are used for developing the QSAR analysis.

13.3.8 Lead optimization

A variety of structure or ligand-based approaches, such as ring or chain modification, the addition of linkers, and others, are used to increase the potency and minimize side effects of known compounds. Problems with the ADME-related issues may reduce the success rate of the drug in a clinical trial. QSAR and machine-learning techniques are used to overcome not only ADME but also toxicity- and efficacy-related issues (Caldwell & Yan, 2014). Several computational approaches help in chemical designing and modification of existing lead to improve the binding interaction, specificity, selectivity, efficacy, and ADME/T properties of a drug. During lead optimization, several chemical changes or modification strategies, such as ring substitution, ring contraction/expansion, chain substitution, chain extension, and group insertion/deletion substitution, are used to produce a chemical structure that satisfies most of the features required in a drug (Singh, 2018).

13.4 Limitations

There are several theoretical limitations associated with the different approaches, such as modeling, cavity prediction, pharmacophore building, structure optimization, QSAR, and ADMET prediction. In general, the findings of any computer-aided theoretical framework must be tested in real systems (Schneider, 2010; Verkhivker et al., 2000). Before the potential compound to be licensed as an effective lead/drug, certain therapeutic necessities must be satisfied. CADD tools and software rely on theoretical principles/parameters, predefined algorithms, and codes. All CADD tools used for virtual scanning, QSAR, molecular dynamics, molecular docking, pharmacophore modeling, and other predictions have their advantages and limitations (Korb et al., 2012). Due to the availability of experimental data, the accuracy of CADD tools is being improved by including more knowledge, information, and parameters in the tool development process. Due to the unavailability of accurate, and quality data, many developed pharmacophore models are not very close to real-world solutions or do not satisfy the features required for physiological response. To overcome the many limitations of existing CADD tools, more experimental data and knowledge are required. Similarly, for better ADMET predictions, QSAR modeling, docking, and MD simulation calculations, more suitable, accurate, and validated algorithms need to be developed that can include all significant parameters related to a problem.

13.5 Recent trends in drug designing

Drug repurposing (also known as drug repositioning, reprofiling, or retasking) is a technique to find potential applications that are beyond the range of the actual medical indication for licensed or investigational drugs (Ashburn & Thor, 2004). This technique provides numerous benefits over designing an entirely new medication for a given indication. Here, the risk of failure is lower; since in preclinical models, the repurposed drug has already been shown to be reasonably effective in early-stage tests. Drug repurposing reduces the time required for drug development, since many of the preclinical tests, safety assessments, and the production of formulations have already been done. Combinatorial treatments and multitarget therapy are vital approaches for dealing with complex diseases in the area of polypharmacology. Combinatorial treatment consists of a blend of several drugs that are single-targeted. On the other hand, multitarget drugs are molecules with the ability to operate on multiple targets at the same time (Sanchez-Tejeda, Sanchez-Ruiz, Salazar, & Loza-Mejia, 2020). The design of multitarget drugs is a problematic mission. This can solve many issues

related to combinatorial treatments, such as metabolism of drugs (drug–drug interactions), and drug reactions at different pharmacokinetics stages: absorption, distribution, metabolism, and disposal (Rosini, 2014). Multitarget drugs have greater in vivo efficacy, and many in silico methods and techniques are constantly being used to design such drugs (Zhang, Pei, & Lai, 2017).

A standard approach used is the combination, or partial overlap of two pharmacophores in a certain molecule to bind to two or more targets (Talevi, 2015). The likelihood of combating multifactorial diseases is provided by binding to two or more targets at the same period. It is a promising area for multitarget drugs in neurodegenerative diseases. Ladostigil is a cholinesterase-monoamine oxidase-B inhibitor for the cure of Alzheimer’s disease and other neurological disorders (Van Der Schyf, 2011). Several anticancer medicines are generally called multitarget drugs because they suppress two or more kinases or receptors (Lu, Pan, Hu, & Wang, 2012). Dual ligands can be used for the treatment of tuberculosis, and a dual mode of action is helpful for the treatment of multidrug-resistant *Mycobacterium tuberculosis* (Chiarelli et al., 2018). Natural compounds offer a vast set of chemical diversity that can be used as a starting lead for the discovery and development of potential drug using optimization approaches (Kesharwani, Misra, & Singh, 2019).

13.6 Conclusion

CADD is a key component of multidisciplinary approaches that are being used for the development of the drug. One of the challenges for pharmaceutical companies is to develop drugs that well suits to patients with better efficacy and no side effects. Traditional approaches of drug discovery and development were very complex, time taking, and costly and were also full of risk of failure during clinical trials, but CADD approaches are very precise and efficient. CADD approaches have made significant improvement in compound searching based on similarity, target identification and structure prediction, binding site/cavity prediction and validation, understanding the protein–ligand interaction, screening the vast set of compounds, understanding the dynamics of protein–ligand binding under physiological conditions, predicting the ADMET properties, estimating the biological activity using QSAR, and guiding the necessary changes required in a lead for better efficacy and selectivity.

Conflict of interest

The authors declare that they have no conflict of interest.

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