

Discovery and optimization of lead molecules in drug designing

Shivani Verma¹ and Rajesh Kumar Pathak²

¹Department of Chemistry, College of Basic Sciences & Humanities, G. B. Pant University of Agriculture and Technology, Pantnagar, India, ²School of Agricultural Biotechnology, Punjab Agricultural University, Ludhiana, India

16.1 Introduction

In 1948, the World Health Organization defined health as the complete status of physical, mental, and social well-being status, not only the absence of disease or infirmity (Sartorius, 2006). The abnormal condition displayed by a group of living organisms in association to represent a specified disorder or abnormalities of structure and function is called disease (Scully, 2004). Drug molecules are used to overcome the abnormal condition or function of an organism to the action on their particular target site. The discovery of drugs creates a driving force for the medicinal chemist to design new pharmaceutical active ingredients with therapeutic properties. In this whole scenario, pharmaceutical industry plays a crucial role in new drug development with understanding their biological chemistry (Durrant, 2001; Khanna, 2012; Mignani, Huber, Tomas, Rodrigues, & Majoral, 2016; Taylor, 2015). The discovery and development of a drug is a very vast, intense, time-consuming, and interdisciplinary area. The efficiency, specificity, and efficacy of drugs depend on their site of action, metabolic pathway, and pharmacokinetics parameters. Moreover, many drugs are failed due to less efficacy, poor selectivity, and unsuitable pharmacokinetics (Pajouhesh & Lenz, 2005). This chapter describes the role of computer-aided drug design (CADD) in lead molecule discovery and strategies of optimization in drug discovery processes. It also focused on different types of natural, synthetic, and semisynthetic lead molecules to design and create novelty for the effective and efficient drug library.

Conventional methods for drug discovery involve lead molecule identification, synthesis, and characterization to see the relevance between target sites and pharmaceutical action. It also involves clinical trials and approval. These processes take much time and cost for the synthesis of many compounds and experimental validation. Resolving these factors, the movement toward *in silico* chemistry and molecular modeling for computational drug designing are interesting approaches for the pharmaceutical industry (Rai, Pathak, Singh, Bhatt, & Baunthiyal, 2021; Wadood et al., 2013). CADD attracts the main attention due to their higher selectivity, efficiency, efficacy, lesser time-consuming process, lesser toxicity, and better to fit with different pharmacokinetics parameters (Makrynitsa, Lykouras, Spyroulia, & Matsoukas, 2018). The balance between their pharmaceutical chemistry and biological activity is the essential criteria for effective drug designing. With increasing the demand for drugs, the selection of biological active structure pays much attention. With today's increasing knowledge of structural biology and the power of computers; it becomes possible to use computational methods for the identification of active libraries to resolve the molecular obesity problem.

CADD technology helps to reduce the number of ligands for experimental assay via virtual screening (Pathak, Gupta, Shukla, & Baunthiyal, 2018; Tropsha & Bajorath, 2016). The high potential of virtual screening toward CADD gives an immense role in the finding of novel therapeutics molecules. It involves the investigation of the entire library based on scientific and literature knowledge to select a small set of active molecules. This leads to Hit-to-Lead molecule discovery. It also helps to decrease the molecular obesity for the discovery of novel biologically active lead molecules (Grzybowski, Ishchenko, Shimada, & Shakhnovich, 2002; Sliwoski, Kothiwale, Meiler, & Lowe, 2014). Fig. 16.1 shows the steps involved in the computational drug discovery process.

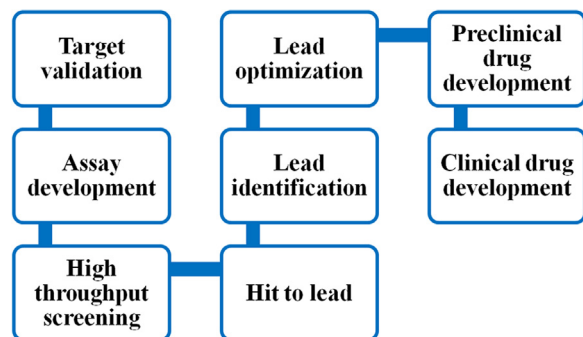


FIGURE 16.1 Process of drug discovery.

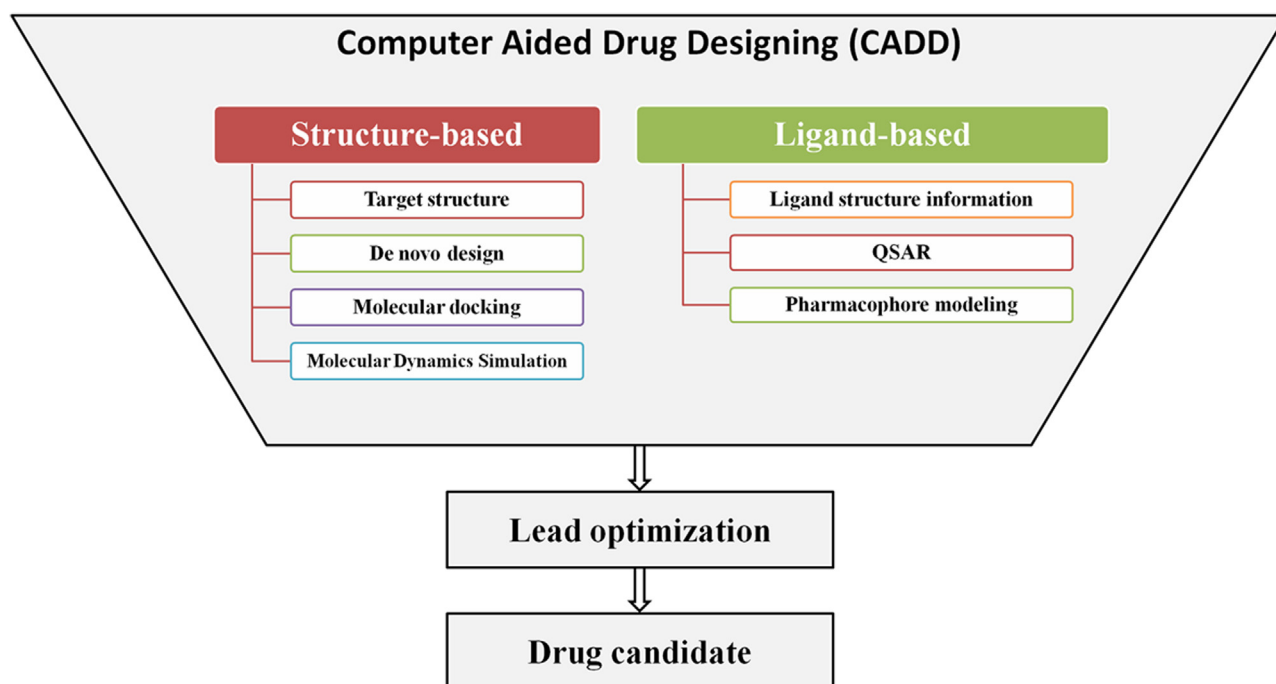


FIGURE 16.2 Computer-aided drug design techniques used in lead discovery and optimization.

16.2 Principles of CADD

The CADD methods are depending on bioinformatics tools and databases and are based on structure- and ligand-based drug discovery approaches using computational and experimental techniques. It plays a vital role in lead identification and optimization, which leads to the discovery of novel molecules in very little time as compared to traditional methods (Fig. 16.2).

We use the structure-based drug designing (SBDD) approach when the structure of the target protein is available in PDB, or it can be model using sequence information (Schmidt, Bergner, & Schwede, 2014). In SBDD, novel small molecules are designed based on the 3D structure of the target binding site, and the binding affinity or interaction energies of ligands with the binding site are also kept in mind. The aim of SBDD involves molecular docking and binding affinity parameters (Anderson, 2003). First, molecular docking gives information about the orientation and geometry of both partners in which they coordinate in better form. Second, it gives the information regarding their binding parameters in which they bind efficiently to each other with noncovalent interaction, that is, H-bonding and hydrophobic bonding (Zoete, Grosdidier, & Michielin, 2009). Several computational programs, such as AutoDock, MOE, Discovery Studio, and Glide, are used for docking study (Morris et al., 2009; Trott & Olson, 2010). These software provide an estimated value of binding-free energy, which presents in the form of a score. The concept of drug designing is complementary to protein structure in terms of their geometry and distribution of charge. Recognition of efficient binding

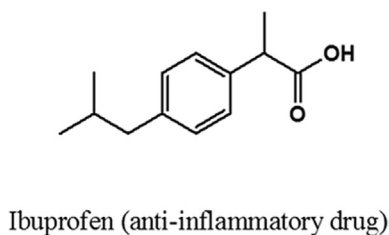
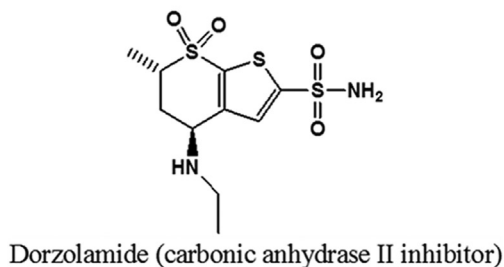
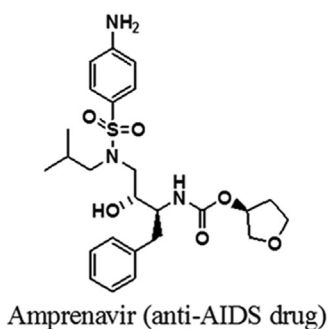
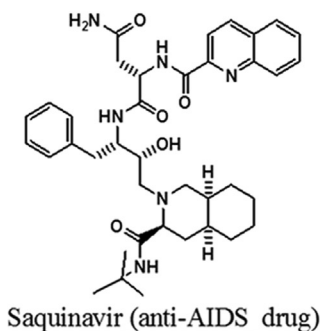


FIGURE 16.3 List of drugs designed based on the structure-based approach.

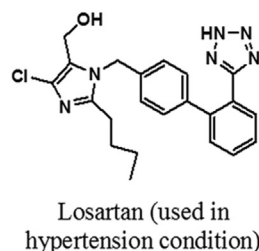
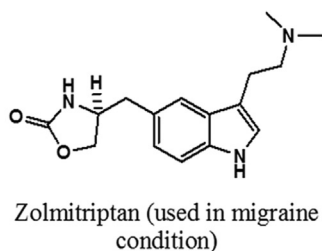
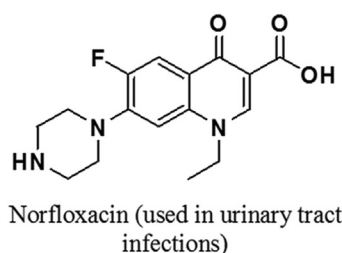


FIGURE 16.4 List of drugs designed based on the ligand-based approach.

affinity between two parties gives the better route for in silico designing and selection of drug libraries virtually. The designed combination should have improved drug and pharmacokinetics, and pharmacodynamics, that is, absorption distribution, metabolism, excretion, and toxicity (ADMET) (Jorgensen, 2010). The SBDD involves protein structure determination, comparative modeling, binding pocket identification, scoring function, knowledge-based scoring, force-based scoring function, protein–ligand docking algorithms, and structure-based virtual screening visualization of protein–ligand interaction diagram (Grant, 2009; Leelananda & Lindert, 2016; Pathak, Baunthiyal, Taj, & Kumar, 2014). Saquinavir, amprenavir, dorzolamide, and ibuprofen drugs were developed based on SBDD (Jorgensen, 2004) (Fig. 16.3).

Ligand-based designing approaches in the identification of small molecule, which binds to target site, efficiently play a key role in drug discovery. It is the alternative to SBDD. In the absence of knowledge of target structure, the ligand-based approaches are helpful. It involves pharmacophore modeling, QSAR (quantitative structure–activity relationship) and molecular similarity approaches (Acharya, Coop, Polli, & MacKerell, 2011). A pharmacophore is a small chemical entity that exhibits pharmaceutical activity. Pharmacophore modeling involves the study of small lead molecule interaction with the target site. These molecules are designed based on the hydrogen bond donor/acceptor capability, a residue of acid/base, and flexibility with the target pocket (Lin, 2000). It consists of the following processes: (1) based on database knowledge, identifying the lead molecule having the same type of interaction with target site; (2) designing of 2D and 3D structure of ligand; (3) building of pharmacophore model (4) based on the score giving the ranking of designed molecules and select the best structure which interacts with 3D structure of target protein; and (5) validating the molecule for further process (Mason, Good, & Martin, 2001). Norfloxacin, zolmitriptan, and losartan are the FDA-approved drugs that were designed via ligand-based drug discovery (Clark, 2006) (Fig. 16.4).

16.2.1 Case study: inhibition of lipoxygenases

Lipoxygenases (LOXs) (EC 1.13.11.12) are oxygen oxidoreductase nonheme iron-containing dioxygenase enzyme. It helps in the oxygenation process of polyunsaturated fatty acids like arachidonic acid (AA). AA is further metabolized

via LOX, epoxygenase, and cyclooxygenase pathways. This pathway is differentiated based on the position of oxygenation. Based on the insertion position (5, 8, 9, 12, and 15) of oxygen, LOXs divided into 5-, 8-, 9-, 12-, and 15-LOXs. Out of these, 5-LOXs predominant in nature and form 5-hydroperoxy eicosatetraenoic acid (5-HpETE). It acts as a precursor of peptide and nonpeptidoleukotriens synthesis. It acts as the main cause of asthma, rhinitis, and ulcerative colitis. Furthermore, it induces the growth of tumor cells and mitogenic processes. So, the inhibition of 5-LOXs is an essential criterion for the treatment of these disorders.

In this whole scenario, CADD plays an important role in lead molecule discovery and their optimization. The development of a therapeutic agent for LOXs inhibition has many challenges. The two principles of drug designing, such as structure-based and ligand-based tools, were used. In this study, the structure of LOXs was solved, and novel LOXs inhibitors were designed via *in silico* approaches. Zileuton acts as 5-LOX inhibitor, which is FDA approved and used in the treatment of asthma (Aparoy, Kumar Reddy, & Reddanna, 2012).

16.3 Discovery of the lead molecule

Any chemical compound that exhibits biological or pharmacological properties with therapeutic characteristics is called a lead molecule. The discovery of the lead molecule with good selectivity, efficiency, efficacy, and pharmacokinetic parameters is a challenging task. Sometimes, identified lead molecule wants some structural modification to enhance their biological properties. This process is called lead optimization. The investigated lead molecule must satisfy five characteristics to work as a bioactive drug molecule. These are potency, bioavailability, duration, safety, and pharmaceutical acceptability. Potency involves the capability of any molecule to exhibit desirable pharmaceutical properties in very few quantities. The transportation of drug molecules with multiple barriers to reach the target site is called bioavailability. Duration is the time between the entry of drug molecules and their pharmacological response. Safety rules include their toxicity parameters which indicate no side effects on the organism. Pharmaceutical action related with reasonable synthetic pathway, solubility, chemical stability, dissolution rate, etc. So, these all factors are important in drug discovery programs and their knowledge is necessary for optimization programs (Cheng, Korfmacher, White, & Njoroge, 2007).

Lead molecule discovery is based on traditional library screening, fragment-based screening, and virtual screening (Jain, 2004; Lavecchia & Di Giovanni, 2013). The aim of the rapid discovery of drugs involves target identification and validation. Following the target validation process, hit identification and lead discovery phases are developed for novel drug discovery. The physical and biochemical parameters are used to decide for change in the structural property of compounds to synthesize an effective lead molecule for drug development.

16.4 Types of lead molecules

Several natural leads are available in the databases as well as in the literature that possesses some biological activity against a biological target and may be used as a drug after some chemical modification. In pharmaceutical sciences, the lead molecules are divided into three categories, that is, natural, synthetic, and semisynthetic (Leisner, 2020).

16.4.1 Natural lead compounds

Nature gives a wide number of biologically active secondary metabolites that were used to cure a disease. Natural lead compounds were derived from natural products (NPs). NPs are secondary metabolites that are synthesized by the plants animal and microbes. These natural compounds are diverse in their structural properties and have several active ingredients. It gives new opportunities to develop a chemical library (Butler, 2004; Gorlenko, Kiselev, Budanova, Zamyatnin, & Ikryannikova, 2020; Mishra & Tiwari, 2011). It has been found that more than 80% of drugs were used to cure a disease, which are derived from natural compounds. Out of these, 40% of drugs based on NPs are approved by FDA (Maridass & De Britto, 2008; Newman & Cragg, 2012).

The pharmaceutical industry pays much attention to the discovery of natural lead molecules because of their lesser toxicity and herbal characteristics (Pan et al., 2013). In this process, plant, animal extract, microbial products, marine organisms, and fungi were used to isolate the biologically active molecule (Beutler, 2009; Dias, Urban, & Roessner, 2012). These isolated active molecules are further optimized and screened by using combinatorial chemistry to get efficient drug candidates (Cragg & Newman, 2013). From the approved data, it has been found that only 6% of unmodified drugs based on NPs were used and 28% of drugs are used with NP-based modified drugs. This survey concludes that structural modification of NPs based on the suitability of their target site creates new challenges in the pharmaceutical

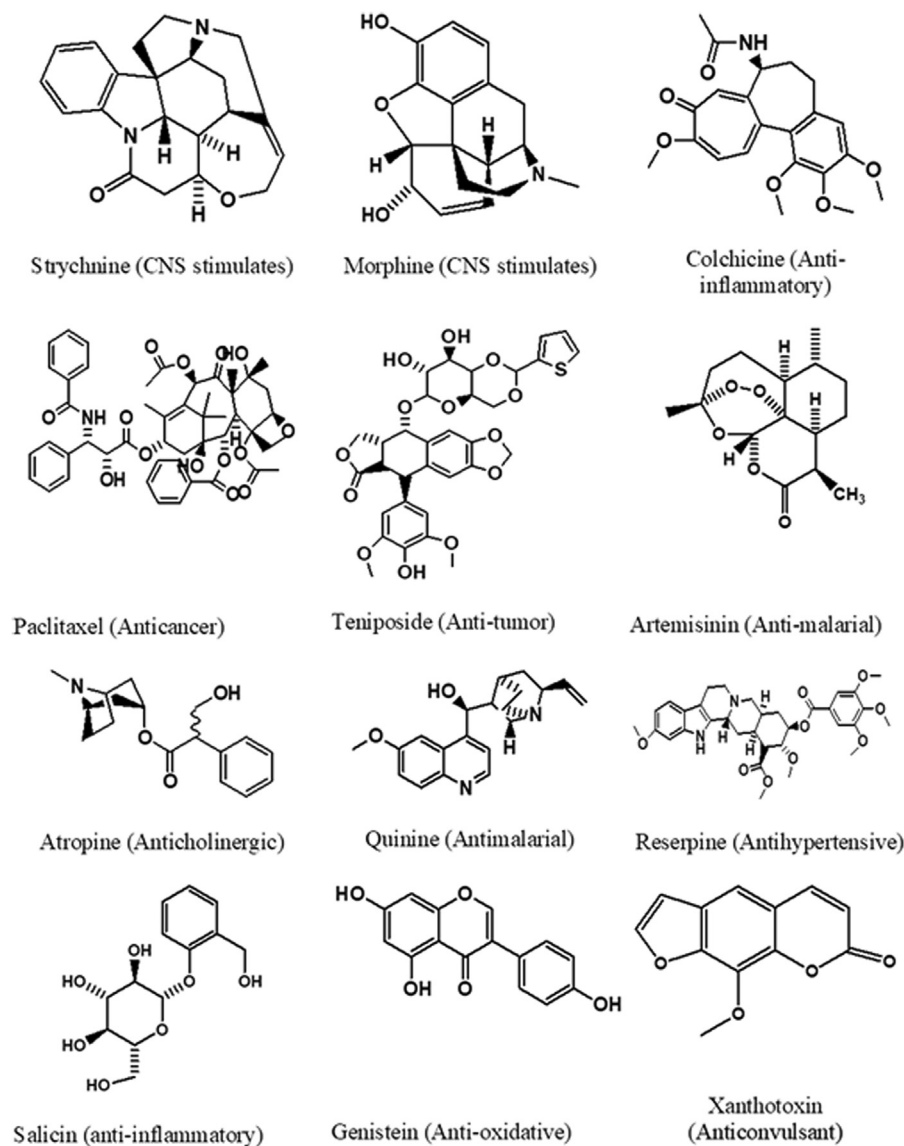


FIGURE 16.5 List of natural drugs and their applicability.

industry (Khazir, Mir, Mir, & Cowan, 2013; Lachance, Wetzel, & Waldmann, 2010). Molecule weight and partition coefficient are two key descriptors that play an important role in designing of new structure drug molecule (Pascolutti & Quinn, 2014). The discovery of natural lead molecules includes multidisciplinary collaboration involving computational chemistry and combinatorial chemistry (Singh, 2018). In the 21st century, CADD plays an immense role in designing effective and efficient drug libraries with therapeutic properties. It gives information about perfect coordination between the lead and target site interaction followed by pharmacodynamics parameters (Sidhu, Bhangu, Pathak, Yadav, & Chhuneja, 2020; Thomford et al., 2018). Fig. 16.5 represents the 2D structure of some natural lead compounds used for the treatment of various diseases.

16.4.2 Synthetic lead molecules

Synthetic lead molecules are those that design synthetically with the combination of organic synthetic chemistry and combinatorial chemistry. FDA-approved 36% of drugs derived synthetically were used for medical purposes. The design of lead molecules depends on their suitability, flexibility, affinity, stability, and toxicity at the target site (Flick et al., 2017). These parameters also help to synthesize the multitarget ligand. Designing a molecule having similar structural properties with NPs is more trending in CADD technology. With these molecules, drug likeliness properties

with efficiency and toxicity parameters were satisfied simultaneously. First, the chemical diversity is used to improve the selectivity against the target. Sometimes, the minute difference in structure creates a problem in interaction with the target, and a drug does not bind selectively to a target for which it was designed, which in turn leads to undesired response and toxicity. To overcome this problem, combinatorial chemistry is used to select the perfect library of lead molecules via chemical structural diversity. The target-oriented designing of molecules has also improved the effectiveness of the drug (Clemons et al., 2011; Gerry & Schreiber, 2018; Schreiber, 2000; Trosset & Carbonell, 2015). Recently, the pharmaceutical industry focused on some drugs, such as sulfonamide and sulfones, to improve pharmacological potential and to minimize toxicity (Fox et al., 2017; Greenwood, 2008). A list of some synthetic drugs that approved based on their ADMET parameters is shown in Fig. 16.6.

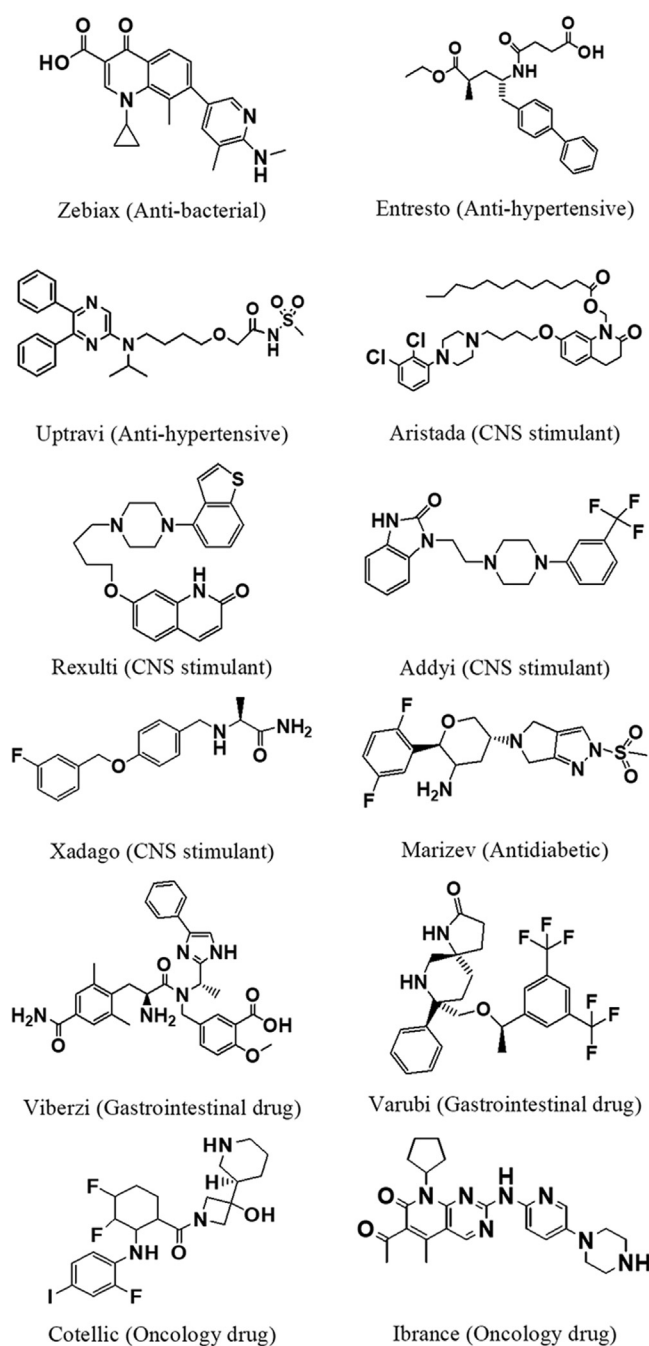


FIGURE 16.6 List of some synthetic drugs and their applicability.

16.4.3 Semisynthetic drugs

Semisynthetic drugs are those that start from a natural source as starting material and end with chemical products. These are hybrid of natural and synthetic drug. From ancient times, NP-based drugs are efficient and effective for the treatment of diseases; but they have become less effective with respect to time, a due mutation in the target structure. To overcome this problem, the modification in their structure is essential to give a new direction in pharmaceutical chemistry. It generates semisynthetic drugs and maintains their natural properties. The designing of these drugs is more focused on because it directly associated with natural compounds. The modification can be done based on the structural properties nature of the functional group present in the molecules. Generally, the modification occurs in macrolides, polycyclic glycopeptide, anthracyclines, oligomycin, heliomycin, and other entities. Macrolide-based antibiotic drugs are clarithromycin and azithromycin exhibiting antimicrobial properties via inhibition of protein synthesis. Glycopeptide-based semisynthetic antibiotic drugs are telavancin, oritavancin, and dalbavancin (Olsufyeva & Yankovskaya, 2020). The first semisynthetic drug penicillin was discovered in 1928 by Alexander Fleming. It is derived from *Staphylococcus* bacteria and acts as an efficient antibacterial agent (Clarke, 2015). Besides, antibacterial semisynthetic drugs were developed for the treatment of bacterial infection caused by *Mycobacterium tuberculosis* (Lee, 2016).

16.5 Lead optimization and strategies

Lead optimization involves in which any lead molecule (biologically active) can be modified structurally and maintains its physicochemical properties, thermodynamic, pharmacokinetic parameters, and toxicity (Jorgensen, 2009). When any chemical compounds to be biological or pharmacological active with some chemical and physical properties present active oral drug as per Lipinski rule. Lipinski rule of five is used to evaluate the drug-likeness of newly discovered or designed molecules. According to this rule, for oral active drugs, the molecule should contain 5 or less than 5 donor hydrogen bonds and 10 acceptor hydrogen bonds. Molecular mass should be less than 500 Da and its partition coefficient (log *P*-value) not higher than 5 (Lipinski, Lombardo, Dominy, & Feeney, 2001; Wenlock, Austin, Barton, Davis, & Leeson, 2003). Lead optimization not only depends on only binding parameters that exhibit information about drug efficiency but also depends on the metabolic process occurs in living organism after consumption of a drug (Korfmacher, 2003). The optimization of lead molecules was carried out by using organic synthetic chemistry and dynamic/kinetics parameters. Organic synthetic chemistry involves structure simplification, structure modification, functional group interconversion, and bonding strength/selectivity. Dynamic/kinetics parameters include thermodynamics, pharmacodynamics/kinetics, and improvement of ADMET properties (Fig. 16.7). The major approaches used in the optimization of lead molecules are discussed in the following sections.

16.5.1 By using organic synthetic chemistry

The response of the drug molecule as a pharmacological agent depends on the target structure and nature of the functional group present in the drug molecule. The suitable relation between binding sites and efficient biological responses is the effective criteria for the development of drug molecules. The slight changes in the designed molecular structure may lead to a change in their properties as a drug. Synthetic organic chemistry is the strong pipeline of the CADD technique (Campos et al., 2019). The proper guidance of structural chemistry for the designing of lead molecules gives an immense role in the pharmaceutical industry (Blakemore et al., 2018; Nadin, Hattotuwagama, & Churcher, 2012). The strategy to fit the connection with their structure and functional properties are most important for new drug development (Van Arnam & Dougherty, 2014).

To overcome the problem of molecular obesity, the design of the library includes different plans. These are diversity-oriented synthesis (DOS), target-oriented synthesis (TOS), biological-oriented synthesis (BOS), and functionally oriented synthesis (FOS). These libraries help to find out the more active molecule and structure-specific molecules. TOS is used in the discovery of drugs by the synthesis of the small molecule, based on preselected target protein whereas DOS is used to identify the similar therapeutic protein target sites and more efficient drug molecule. TOS planned efficiently with retrosynthetic analysis. These are based on stereo selective organic synthetic chemistry. Retro synthesis involves the study of a structural element of the product rather than the structure of the reactant for the transformation of the synthetic procedure. This gives immense knowledge about the structure simplification by the organic chemist (Fig. 16.8). In contrast, DOS is related to the collection and study of a large biological active molecule with complexity and diversity to the target protein site (Fig. 16.9). Complexity and diversity of molecule play essential dynamics with protein–ligand interaction because in many cases simplicity of molecules disturbed binding parameters.

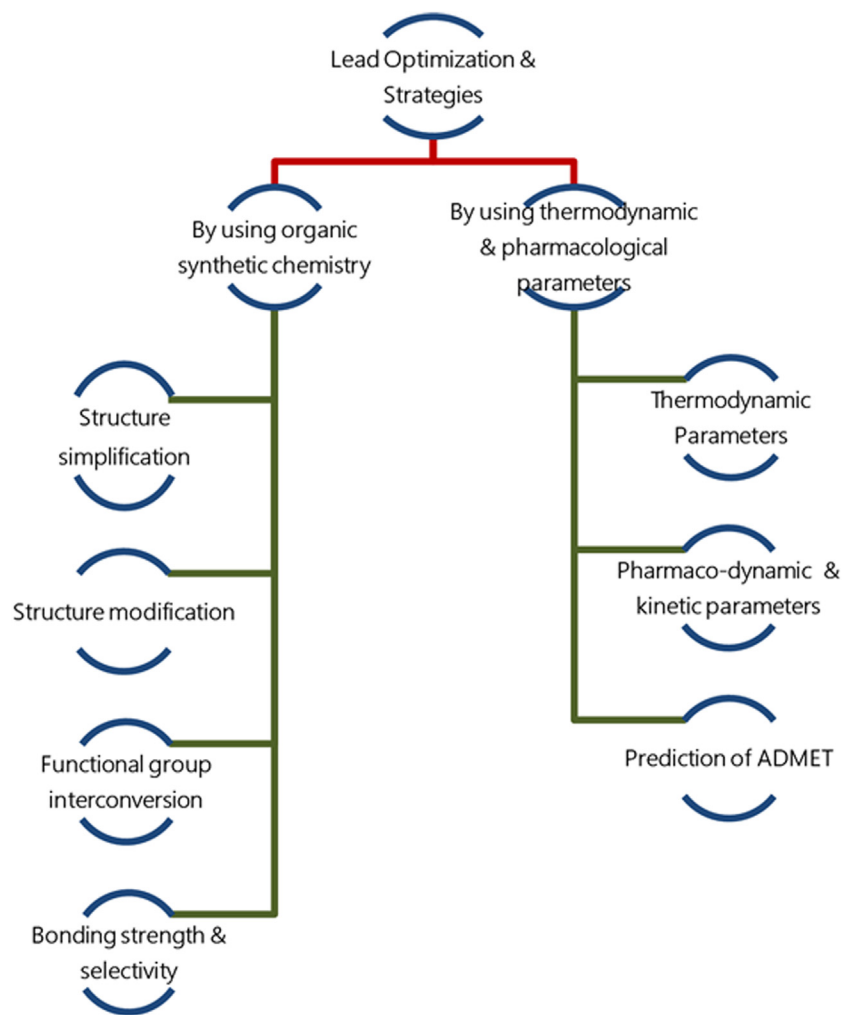


FIGURE 16.7 Strategies and approaches used for the lead optimization.

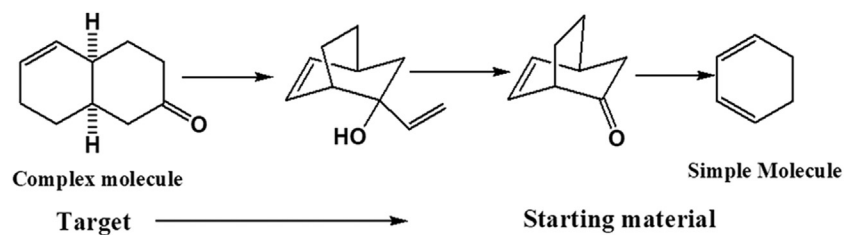


FIGURE 16.8 Target-oriented synthesis and retrosynthetic analysis of complex molecule (focused libraries) to simple lead molecules (building blocks). Example of retrosynthesis: phthalascidin (anticancer agent) and neocarzinostatin chromophore (antiproliferative actions).

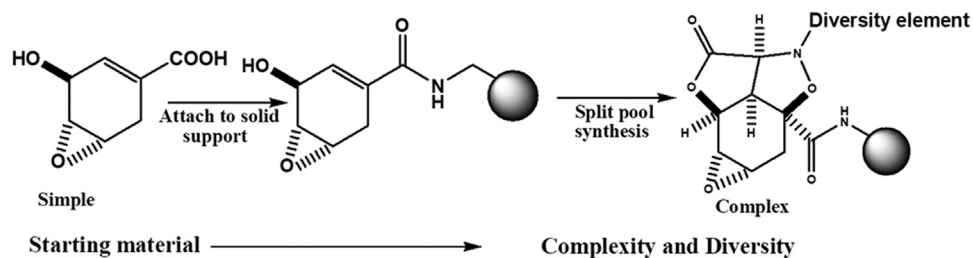


FIGURE 16.9 Simple building block to the complexity and diverse structure by diversity-oriented synthesis.

It affects the therapeutic properties of the drug molecule. TOS and DOS are complementary to each other. The selection criteria of techniques depend on the lead molecule structure and target site (Rodriguez, 2012; Tan, 2005). BOS is related to the study of the identified compound as its biological importance. FOS is associated with structural and chemical biology. FOS aims to design the derivative with a small effect on the biological properties of the parent molecules (Wender, Verma, Paxton, & Pillow, 2008; Wetzel, Bon, Kumar, & Waldmann, 2011).

16.5.2 Structure simplification

To resolve the problem of molecular obesity, simplification of structure with the same or higher potency leads to attention in the pharmaceutical industry. The necessary conditions for reoptimization of the drug are synthetic difficulty, unfavorable physiochemical profile, and higher toxicity. With these difficulties, simplification of structure with favorable functional parameters is the important criteria. Simplification of drug structure occurs by structure affinity relationship (SAR)-based design, structure-based design, and pharmacophore-based design. It has been found that structure simplification with suitable functional group entity improves synthetic accessibility as well as pharmacokinetic parameters. Natural products are more complicated in structure. So, these techniques are most useful for natural biologically active molecules (Wang, Dong, & Sheng, 2019). Some examples of simplified biological active analogs of NPs are given in Table 16.1.

16.5.3 Structure modification

Modification of the structure of lead molecule leads to optimize the binding affinity with binding site amino acid which present in the receptors. Hydrophilic compounds are those having a stronger affinity toward polar compounds. Synthetic chemistry is used to optimize the structure of molecules through modification, in the functional group which makes the molecule, more efficient than their native structure (Waring, 2010). Another factor associated with rigidification makes the molecule stable in one conformation and it helps to find out a better understanding to fit in the binding pocket. RAF kinases are used as a target protein for the designing of the drug molecule. The study reveals that rigidification of pyrazolopyrimidine via ring closure improves the selectivity against RAF kinase and helps in designing efficient anticancer agents (Fig. 16.10) (Assadieskandar et al., 2019).

16.5.4 Functional group interconversion

Functional group interconversion is related to change in structural properties via suitable functionalization to make a drug more effective, less toxic, and highly efficient. During lead optimization, many functional group interconversion reactions are used to develop a more effective candidate drug. These are electrophilic reaction, deprotonation, aromatic nucleophilic substitution, amide formation, Suzuki–Miyaura reaction, etc. From the survey, it has been found that, in the overall process of drug discovery, functional group interconversion plays an 8% role in lead optimization. Click chemistry, multicomponent reactions, macromolecule synthesis based on NPs, and activity-directed synthesis are involved in strategies that involve lead molecule identification and optimization (Boström, Brown, Young, & Keserü,

TABLE 16.1 Natural product-derived simplified active compounds and their application.

S. no.	Natural products	Simplified biological active analogs	Application
1.	Morpholine	Butorphanol, pentazocine, pethidine, methadone	μ and κ opioid receptor agonist and antagonist
2.	Halichondrin B	Eribulin, mesilate	Antitumor Activity
3.	Myriocin	Fingolimod	Immunosuppressive Activity
4.	Trichostatin A	Vorinostat	Histone deacetylase inhibitor
5.	Schisandrin C	Bicyclol	Antihepatitis B activity
6.	Staurosporine	Ruboxistaurin, enzastaurin	Protein kinase C inhibitor
7.	Asperlicin	Devazepide	Cholecystokinin receptors antagonist

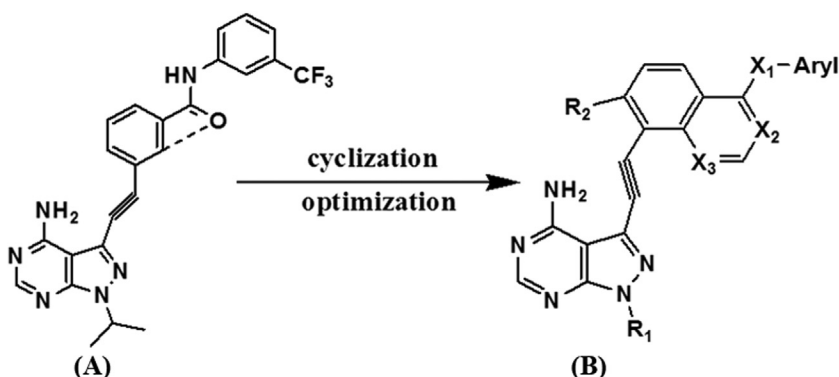


FIGURE 16.10 Rigidification of pyrazolopyrimidine entity for efficient RAF kinase inhibition: (A) Nonselective kinase inhibitor and (B) highly selective and potent B-RAF inhibitor.

2018). Functional group interconversion correlated with SAR. It (1) improves affinity with target site, (2) increases flexibility, (3) decreases lipophilicity, and (4) enhances the functionality of lead molecule. Based on the SAR, various $\sigma 2$ receptors are designed to improve their antiproliferative activity. These designed lead molecules are based on morphans, benzamides, indoles, and *N*-cyclohexylpiperazines structures (Abate, Perrone, & Berardi, 2012).

16.5.5 Bonding strength and selectivity

Electrostatic interaction, hydrogen bonding, van der Waals force, and hydrophobic interaction are weak type intermolecular interaction, which acts as a stabilizing agent between drug–receptor entities (Barratt et al., 2005; Hubbard & Haider, 2010; Kenny, 2009; Matthews, 2001) and helps in binding efficiency and efficacy of the drug. It depends on the orientation and length of the hydrogen bond. The selection of lead molecules and target sites depends on the chemical nature of both candidates for donor and acceptor accessibility. It gives pharmacological interest to demonstrate their therapeutic values. The electrostatic potential is the energy associated with the charge around both sides (receptor and donor entity). It defines the potency of the molecule to attach with the target site (Bhosale, Shaikh, Coutinho, & Saran, 2007). Hydrophobicity is a nonpolar type of interaction that increases the affinity between the drug and the target site. The parameters of hydrophobicity also play important role in designing the structure of the lead molecule (Patil et al., 2010).

16.5.6 Using thermodynamic, pharmacodynamics, and pharmacokinetic parameters

Besides synthetic chemistry, the optimization of lead compounds can be done by using thermodynamic-, pharmacodynamic-, and pharmacokinetic-based parameters. It is also recognized as a key strategy and is discussed in the following sections.

These parameters are related to Gibbs free energy, binding-free energy, entropy, and enthalpy changes when the interaction between two entities (drug and target site) occurs (Freire, 2008). Suitable functional groups of a ligand that exhibit the appropriate efficiency will decide their thermodynamic parameters. These come under rational drug designing (Holdgate & Ward, 2005; Thoppil, Choudhary, & Kishore, 2016). The entropy factor followed with the second law of thermodynamic maintains the structural property of lead molecule as well as connection suitability (Dini, Guarini, Morrone, & Marzilli, 2012; Uehara, Sakane, & Bertolotti, 2008) and contributes the favorable condition for binding (Chaires, 2008). These parameters play an important role to address the interaction based on associated energy and connection between ligand and target for the drug discovery. Binding strength depends on thermodynamics. It will give a better understanding of the flexibility, strength, and suitability of lead molecules during protein–ligand interaction (Judy, Choudhary, & Kishore, 2016).

Pharmacodynamics act on the lead molecule and provide information about drug toxicity (T) whereas, pharmacokinetics gives the information about absorption, distribution, metabolism, and excretion (ADME) of the lead molecule in biological systems. The action and transportation rate of drug molecules depends on their pharmacodynamics and pharmacokinetics parameters. The small changes in the structure of the lead molecule will change the whole property of pharmacokinetics and dynamic. Based on the survey, it has been found that pharmacokinetics parameters play a 39% role in the failure of a new drug. To improve the efficiency and efficacy of a drug by reducing its toxicity, it is important to understand these parameters for the development and optimization of the drug molecule. The coordination

between these parameters gives a better understanding of reactivity, action point, and safety factors with their target sites (Walker, 2004).

Absorption involves the entering of drug molecules into blood circulation. It enters the body via the lung, skin, or gastrointestinal tract. Absorption depends on the pathways of transportation in the blood and the concentration of the drug. After absorption, the transfer of lead molecule occurs from one site to another within the whole body is called distribution. It depends on the solubility and binding affinity; furthermore, the metabolism of the drug molecule takes place. Maximum metabolism occurs in the liver (Gunaratna, 2000). It involves various processes, such as dealkylation, hydration, oxidation, and reduction, and it depends on the metabolic activity of the cell inside the environment. Excretion is the elimination process of a drug or its metabolic product from the body. Highly polar compounds are removed easily through urine (Carrillo, 2011). Any drug molecule having lesser toxicity is more efficient to cure disease. These all factors give an alert toward the success or failure of the designed molecule as a drug. The optimization of ADMET properties of drugs is a challenging task; it can be optimized during experimental/preclinical and clinical studies by mixing some other chemicals/preservatives and applied using different concentrations to evaluate their ADMET nature.

16.6 Computational lead optimization

Computational methods, tools, and database resources hold immense potential in lead discovery and optimization. Several methods and tools like databases have been developed for this purpose. The scoring functions and search algorithms are used for the identification of lead molecules using different software packages available for molecular docking and virtual screening, that is, AutoDock vina, Glide, etc. The major database resources are PubChem, ChemSpider, and ZINC holding the structure and properties of molecules utilized in the drug discovery program. Besides, the DrugBank database has FDA-approved drugs and plays a key role in drug repurposing as a new lead for the treatment of other diseases. The ADMET prediction tools are also playing a vital role in evaluating the drug-likeness of molecules. Based on computational evaluation of putative molecules, it will be further subjected to chemical drawing tools like ChemSketch, MarwinSketch, etc., to modify or replace a targeted functional group for improving their biological activity (Fig. 16.11), followed by experimental validation. The key disadvantage of any drug molecule is toxicity, many drugs comeback from the market to the lab for further investigation and optimization due to their toxic nature. The major toxic effects are carcinogenicity, cytotoxicity, teratogenicity, phospholipidosis, and reproductive toxicity. To prevent toxicity, medicinal chemists should consider the toxicity data during lead optimization. The major strategies used for minimizing or removing the toxic effect of lead are: (1) eliminate substructures that cause toxic responses; (2) synthetic modifications to eliminate any possibly toxic substructures from the lead molecules; (3) during lead optimization, prevent the insertion of toxic substructures; (4) screening of toxic compounds through reactive metabolite assays; (5) obstruct the functional group undergoing bioactivation by a nonbioactive functional group; (6) Insertion of a bulky substituent near the metabolism site to prevent metabolic activation; and (7) substitution with a metabolism-resistant substituent or metabolized by a nonreactive species. The structural changes will improve the drug-likeness of molecules leading to the development of safe drugs (Agnihotry, Pathak, Srivastav, Shukla, & Gautam, 2020; Pathak, Singh, Sagar, Baunthiyal, & Kumar, 2020).

16.7 Advantages of computational lead designing

In this whole scenario, CADD pays much attention because of three major factors. These are (1) screening of a large set of the molecule on target structure, which can be further evaluated by computational as well as experimental methods; (2) guiding the optimization of lead compounds based on their affinity, pharmacokinetic parameters, and toxicity criteria; and (3) helping in designing of novel compounds based on their structure to improve their functionality as a potential drug. CADD technique is very applicable for the modeling of the drug. Keeping in mind all the things computational chemistry and bioinformatics in addition to combinatorial chemistry address the various challenges associated with the drug discovery pipeline in less time and cost (Singh & Pathak, 2020).

16.8 Future perspectives

As per demanding aspects toward the cure of diseases, the potential drug designing has played more focused attention right now. The setups of the perfect combination of structural and functional properties are the challenging task to develop the active pharmaceutical ingredients. The potency of drugs not only depends on their efficiency, selectivity,

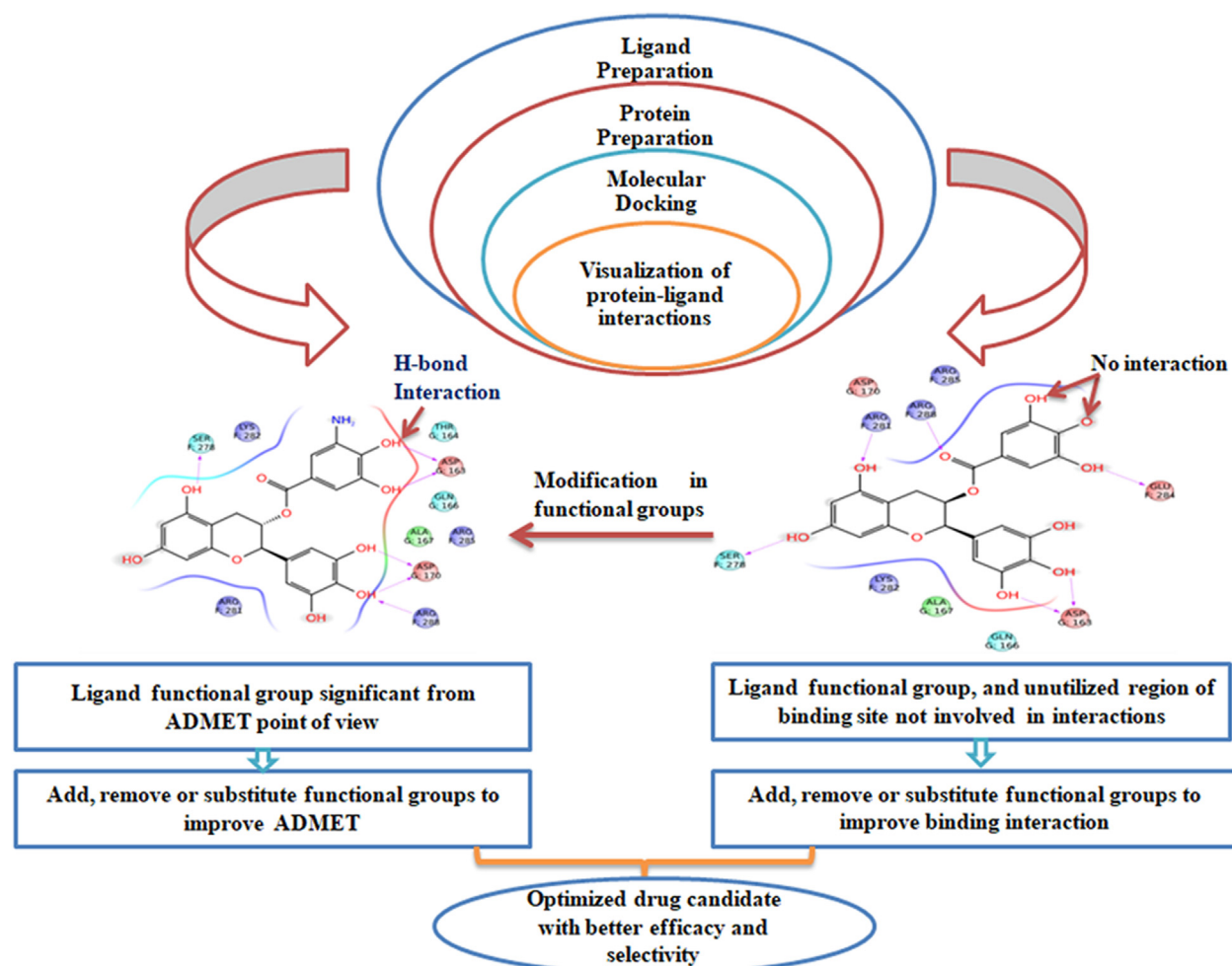


FIGURE 16.11 Lead optimization strategies for improving absorption, distribution, metabolism, excretion, and toxicity and binding interaction.

and efficacy but also depends on toxicity factors. CADD helps to develop new parameters to make the lead molecule more efficient and selective toward their target. SAR and mode of action also pay much attention to optimization processes of lead. Chemical diversity followed by DOS, TOS, BOS, and FOS is important to play role in drug designing to improve site-specificity and reduce toxicity. The selection of lead for optimization is based on ADMET screening. These parameters are important for lead optimizations as per our need, and further going for molecular dynamics simulation, binding energy calculation followed by in vitro and in vivo study in drug discovery program. In recent years due to advances in computational sciences and experimental techniques, it becomes easier and fast in the future. Therefore coordination within in silico, in vivo, and in vitro technologies plays a vital role in the pharmaceutical industry for the discovery of well-optimized drugs.

16.9 Conclusion

The computational study based on the identification of lead compounds, that is, compound holds drug-like properties against particular disease, is a resource taking and complicated process. After the identification of lead compounds, it takes much time to become a drug. There are multiple pipelines are involved from lead discovery to drug development *via* computational and experimental approaches. The optimization of identified lead as per our need in terms of affinity, efficacy, and potency is one key step in a drug-designing program. This chapter highlights the major strategies used for lead optimization, that is, structure simplification, structure modification, functional group interconversion, bonding strength and selectivity, thermodynamic parameters, and pharmacodynamics and pharmacokinetics parameters and their importance in drug designing for the discovery and development of novel therapeutics.

Conflict of interest

The authors declare that they have no conflict of interest.

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