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A Review on Different Computational Approaches of In Silico Drug Design

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Abstract

The drug development and discovery is an extremely difficult, costly, and time-consuming process. because of the advancement of computational tools and procedures, the drug development discovery has been enhanced. For past few years' Computer Aided Drug Design (CADD), also known as In Silico screening has become a technique used in many phases of drug discovery and development. The purpose of this review is to focuses on focuses on the different types of approaches in the In Silico drug design such as Ligand Based Drug Design (LBDD), Structure Based Drug Design (SBDD) and Fragment Based Drug Design (FBDD). A literature review was performed to study about different In Silico methods. key articles were extracted from Pubmed, Elseiver, Embase, Google scholar using the terms In Silico methods, drug designing computer aided drug design as keywords for our search. Recent development in drug designing has paved way for faster recovery reducing morbidity and mortality rate. The use of In Silico methods comprehends in several stages of the discovery process and improves the chances of success. It allows access to a large amount of data that has been generated. It also combines vast quantities of complex biological data into usable knowledge. The article focused on several computational methods to which include. However, there are both risks and benefits which has to be further assessed. The three categories in the In Silico methods of drug designing were discussed in the study.

Keywords: *Computer aided drug discovery, Structure-based drug design, Ligand-based drug design, Drug development, Drug discovery.*

1. Introduction

The drug discovery process is extremely complicated, and it necessitates an interdisciplinary effort to develop a medicine that is both effective and economically viable. The development process is made up of several key components. It is a complex procedure that begins with the identification of a viable therapeutic target, followed by drug target validation, hit to lead discovery, lead molecule optimization, and preclinical and clinical research. [1,2] Drug design is a multidisciplinary field that anticipates a new era of drug development. It comprises the analysis of biologically active chemical effects based on molecular interactions, either in terms of molecular structure or physicochemical qualities. It investigates how drugs work, how they interact with protoplasm to elicit a specific pharmacological action or response, and how they are transformed, detoxified, metabolized, and removed by the organism. Despite the significant financial and time commitments required for the development of new pharmaceuticals, the success rate in clinical trials is only 13%, with a high drug attrition rate. [3]

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Drug failure at a later stage has been observed in the majority of cases (40-60%) due to a lack of optimal pharmacokinetic features on absorption, distribution, metabolism, excretion, and toxicity. [4] There are various parameters which have to be considered in designing of drugs; drug should be: safe and effective, bioavailable, metabolically stable, minimal side effects, selective target tissue distribution [5.6] Rational drug design and structure biology together works for the discovery of ideal therapeutic agents. Because of increased utility in recent years, computer aided drug design also known as In Silico screening which becomes a powerful tool in the drug discovery and development. In Latin "In Silicon" means performed using computers or via computer simulation. A computer plays an essential part in pharmaceutical, medical, and other scientific research, including the discovery of novel compounds in the search for improved therapeutic agents. [7] Computational power, when combined with modern analytical techniques such as X-ray crystallography, NMR, and other techniques, has boosted the applicability of CADD in the pharmaceutical industry, as multiple approved medications have been reported that owe their discovery in major part of CADD tools.

Importance of modern In Silico techniques are:

- The benefit of being able to deliver novel medication candidates faster and at a lesser cost.
- In several stages of the discovery process, it improves the chances of success.
- It allows access to a large amount of data that has been generated.
- It combines vast quantities of complex biological data into usable knowledge. [8]

2. In Silico Strategies on Drug Discovery/ CADD

In Silico strategies depends on the structural and other information available on the target (enzyme/receptor) and the ligands. The two main modelling methodologies in the drug design process include direct and indirect design. The indirect approach is based on a comparison of structural properties of known active and inactive compounds. The direct design considers the three-dimensional features of the target (enzyme/receptor) directly. [9]

Steps involved are:

- ❖ Target Identification Genetics
  -Molecular Biology
  -Bioinformatics
- ❖ Structure Determination - X ray crystallography
  - NMR spectroscopy
- ❖ Biological Assays - Molecular docking
  - Computer graphics
- ❖ Synthetic Chemistry - Peptidomimetics
  -Combinatorial chemistry [10]
- ❖ Pre-clinical and clinical trials

Structure-based and ligand-based drug design techniques are two types of CADD that have been widely employed in the drug development process to identify the lead compounds. While structure-based drug design is based on the three-dimensional structure of the target receptor and its active sites to understand the molecular interaction between the receptor and the ligand. [11]

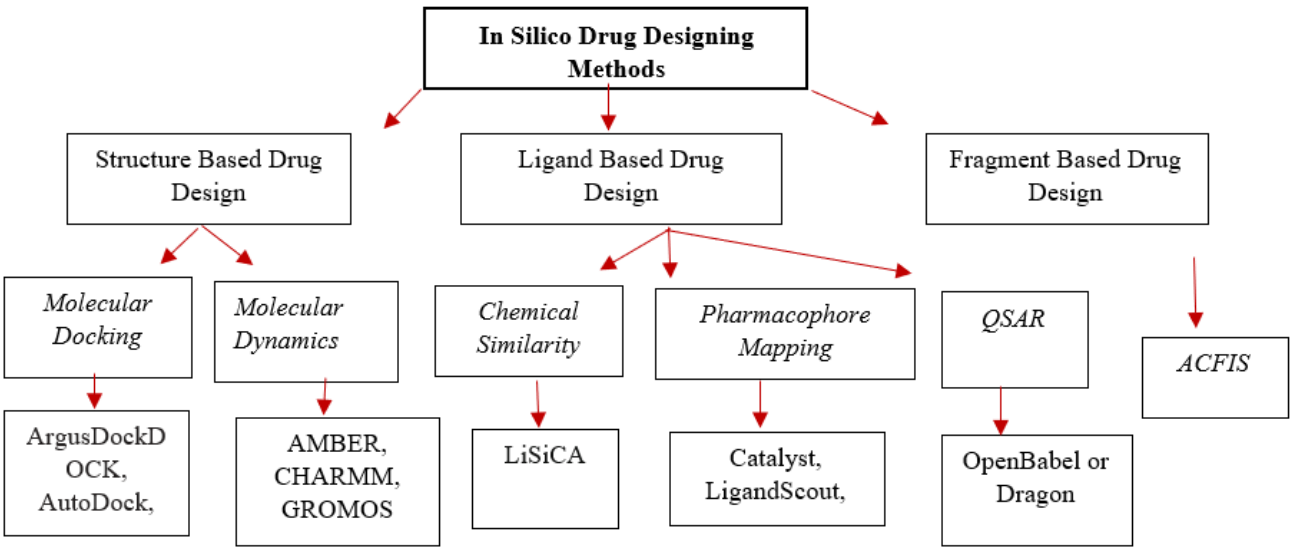

Fig 1: Schematic representation of types of drug design and softwares

The ligand-based drug-design (LBDD) strategy employs three basic strategies for finding novel compounds. The first is ligand chemical similarity, which is based on the selection of novel molecules with high chemical structure, binding affinity, and physicochemical qualities that are comparable to recognized active chemicals. The second method is pharmacophore mapping, which is used to identify functional groups that interact with targets in order to use this information to design more potent molecules. The third method is quantitative structure–activity relationship (QSAR), which correlates a number of features from a set of chemical compounds with their biologic activity for the studied target. [12]

Chemical Similarity

The purpose of this strategy is to explore chemical databases using molecular fingerprints of existing compounds and identifying new ligands by comparing their resemblance to existing ones.

This technology is mainly relying on chemical data that is already available. Furthermore, the chemical similarity method considers the entire structure of the molecule, not only the functional groups that are important for biological activity. [13] The most common method for locating comparable ligands is to search databases for a number of different compounds and then pick those that have a high degree of similarity to a lead chemical. Following the selection of these compounds, they are put to the test to see if they have better biologic activity than the lead chemical. LiSiCA (ligand similarity using clique algorithm) is an example for LBDD virtual screening software that looks for similarities between a reference ligand and ligands in the database. [14] Another recently explored method is the use of poly pharmacology. This

method can be used to forecast the off-target effects of proposed chemicals. The studied chemicals bind to many molecular targets as a result of these off-target effects. The results can be exported for analyzing the similarity of the drug targets as well, by clustering those chemicals and comparing their similarity. The Tanimoto coefficient is used in this technique termed similarity ensemble approach (SEA) to compare a set of chemicals that interact with each target. [15]

Pharmacophore mapping

The CADD is used to screen Pharmacophores that consists of various scaffold-containing compounds but have the same 3-D functional group layout. The three-dimensional arrangement of chemical functional groups that is responsible for biological activity is known as a pharmacophore. The construction of a pharmacophore model has become a significant aspect of drug discovery, design, optimization, and development in recent years. [16, 17] Pharmacophore approaches are used to identify distinct types of molecules that have a similar layout. [18, 19] External data should be used to validate the created pharmacophore before it is used. Virtual screening starts in if an appropriate pharmacophore develops. [20,21] Noncovalent interactions or groups essential for intermolecular interactions, such as hydrogen bond donors or acceptors, electronegative or electropositive groups, positive- or negative-charged groups, aromatic rings, lipophilic or hydrophilic groups, and interatomic distances between those functional groups, are among the chemical properties of an effective pharmacophore. Both approaches of In Silico drug design uses the pharmacophore mapping methodology. In the instance of LBDD, the overall process requires building a pharmacophore framework uses the methods outlined. After exploring the literature or molecular databases, a collection of active ligands that interact with the target through the same mechanism is chosen. The ligands are layered with the most characteristics overlapping possible. [22] A large number of alternative ligand conformations are created for this purpose, and a subset of those conformers is employed during the superimposition. The structural flexibility of the compounds is always a consideration when creating a pharmacophore. To determine efficient conformers or the conformation space for an accurate pharmacophore model, different methodologies can be used, ranging from rigid to more flexible methods that use molecular dynamics (MD). [23]

For the superimposition of molecules, two approaches are commonly utilized. The first method is point-based approach, which is used to superimpose the various ligands feature by feature by minimizing their distances. The second method is property-based technique, uses molecular field descriptors to align the ligands. After the ligands are superimposed, an elucidation algorithm combines the common properties to generate the pharmacophore model. In most cases, more than one model can be created. The software calculates the highest score, that determines which model is most representative. The most common software packages for the ligand-based pharmacophore mapping include Catalyst, [22] LigandScout, [23] Phase [24] and Pharmer. [25]

Quantitative structure–activity relationship (QSAR)

When structural-based techniques aren't appropriate due to a lack of target macromolecule structure knowledge, the QSAR methodology is used. QSAR gives information on the link between chemical structure and biological activity in the form of a mathematical expression. [26] The QSAR method's main advantage is that it can detect properties of novel chemical compounds without requiring their production and testing. All of their properties, including structural descriptors of substances, physiological properties, and biological activities, have been linked in research. [27] The collection of active and inactive compounds against a certain biological target begins with a search in literature or databases for active and inactive compounds. This method necessitates a thorough understanding of each compound's activity. A variety of molecular descriptors should be used to create QSAR models. These descriptors are a set of characteristics that describe the chemical compounds' structural, physicochemical, and biological qualities. [26]
A model is created using this data in order to visualize the relationship between those descriptions and their biological activity. This mathematical modelling method generates a model that can be used to predict biological responses to novel ligands. The descriptors could be obtained from databases or computed from physicochemical and structural features including the number of atoms, atom kinds, interatomic distances, molecular mass, electronegativity, aromaticity, and other characteristics. More complicated calculations, such as molecular field descriptors and pharmacophore-based descriptors, may be necessary in other circumstances. More sophisticated approaches, such as the CoMFA and CoMSIA 3D-QSAR, typically use the latter. [27] OpenBabel or Dragon are common software for defining descriptors and are used in many descriptor calculations. [28,29] QSAR can be used in a number of different ways. The method has been used to improve molecular libraries used in high-throughput screening as well as identify novel ligands, in addition to anticipating the effect of novel ligands. Information gain and a general measure of correlation are the outcomes of the specific approach. [28]

Hologram quantitative structure activity relationship (HQSAR)

There is no need for exact 3D information on the ligands in Hologram QSAR which is a unique QSAR technique. The molecule is broken into a molecular fingerprint in this process, which encodes the regularity of incidence of

distinct sorts of molecular fragments. Simply put, the size of the fragment to be included in the hologram fingerprint determines the minimum and maximum length of the pieces. A creation of linear and branching fragments, ranging in size from 4 to 7 atoms, causes molecular holograms. [27]

Comparative molecular field analysis

CoMFA stands for comparative molecular field analysis, which is a new method of explaining structure-activity relationships. CoMFA is a well-known 3D QSAR approach that was developed in the 1970s. It provides CLogP values, which indicate how the solvent repellent constrains the ligands and also explains the ligands' steric and electrostatic properties. [28]

Comparative molecular similarity indices analysis

One of the most recent 3DQSAR techniques is CoMSIA. It's most commonly utilised in the drug development process to track down common uniqueness, which is essential for proper pharmacological receptor binding. The steric and electrostatic properties, hydrogen bond acceptors, hydrogen bond donors, and hydrophobic fields are all addressed in this method. [29]

Table 1: Properties of LBDD

Techniques	Effect on LBDD	Softwares
Chemical Similarity	• To explore chemical databases using molecular fingerprints of existing compounds and identify new Ligands. • Low-cost and effective • Method considers the entire structure of the molecule, not only the functional groups [13]	LiSiCA (ligand similarity using clique algorithm) [14]
Pharmacophore mapping	• Used to identify distinct types of molecules that have a similar layout. • Used in various scaffold-containing compounds but have the same 3-D functional group arrangement. [21]	Catalyst, [21] LigandScout, [22] Phase [23] and Pharmer. [24]
QSAR	• Gives information on the link between chemical structure and biological activity in the form of a mathematical expression. [26] • QSAR can be used when it lacks of target macromolecule structure knowledge. [27]	OpenBabel or Dragon [28]

2. Structure-Based Drug Design

The SBDD technique is divided into a number of steps. The initial step is to analyze the target's structure using methods such as X-ray crystallography, NMR spectroscopy, or homology modelling. Many proteins and nucleic acids have already solved 3D structures that have been published in databases and can be used for research. Multiple databases can be searched to locate potential ligands depending on the target's 3D structure. For biochemical and biological testing, the ones with the greatest affinity and specificity scores are chosen. The most promising chemical is then studied in complex, with the goal of producing a 3D structure for future optimization or even manufacture. The most prominent computational SBDD methods are molecular docking, molecular dynamics (MD), fragment based drug design (FBDD), and pharmacophore modelling. [30]

Molecular Docking

It's a molecular modelling docking technique that takes into account the preferred orientation of one molecule to another when they're connected together to form a stable complex. The process of a ligand binding to its receptor or target protein is referred to as "molecular docking." By analysing and modelling molecular interactions between ligand and target macromolecules, molecular docking aids in the identification and optimization of therapeutic candidates. Multiple ligand conformations and orientations are generated using molecular docking, and the most appropriate ones are chosen. [31] ArgusDock, DOCK, FRED, eHITS, AutoDock, and FRED are some of the molecular docking tools available. Molecular modelling entails using scoring algorithms to rank the affinity of ligands for binding to a receptor's active region. Compounds are docked into the active site and then scored to see which one is more likely to bind tightly to the target macromolecule in virtual high-throughput screening. Molecular modelling is the process of ranking the affinity of ligands for binding to a receptor's active area using scoring algorithms. [32]

Based on the dynamic features of the ligand–receptor complex, molecular docking approaches can be categorised into three types. Both the ligand and the target are rigid bodies in rigid-body docking, and they adopt a fixed shape. The receptor remains constant, while the ligand is tested in a small search space in various positions and orientations and is used in a variety of computational research projects. Structure-based virtual

screening (SBVS) is an In Silico method for testing multiple ligands from a database against a specific target during the early phases of drug discovery. During SBVS, commercially available compounds from a vast library are evaluated for their binding capabilities on a target with a known 3D structure as potential hit compounds. SBVS is an expanded docking approach in which many ligands, rather than simply one, are docked to the target. In SBVS, three phases are followed: first, the target and library of compounds are prepared for docking, then the most favourable binding site for each compound is determined, and finally the docked structures are ranked. The library size varies from thousands to millions of chemicals such as ZINC, and new software has cut docking time in half. [33]

Quantum Mechanics

According to a recent analysis, the application of QM approaches to all phases of CADD is likely to become a reality. Simultaneously, the growing interest in QM in CADD has prompted more methodological development of QM methods, particularly QM approaches for docking, scoring, improving known lead compounds, and unravelling reaction mechanisms. For instance, QM simulations were used to study significant variations in binding affinities when a CH2 linker was converted to a carbonyl. [34]

The methods for quantifying energies and optimizing structures belong to the first class, whereas the approaches for computing molecular characteristics belong to the second. The methods in the first class are the most basic and well-known QM applications. They can be used directly to evaluate the reactivities of physiologically active compounds, which are always accompanied by energy transfer and molecular structural alteration. However, present computational capacity is insufficient to do direct ab initio QM calculations of macromolecules with precision comparable to in-vitro experiments. As a result, the acceleration of QM approaches for macromolecules, such as linear scaling algorithms and hybrid quantum/molecular mechanics (QM/MM), will unavoidably play a key role. [33]

ONIOM

In biological research, having a thorough grasp of enzyme processes at the atomic and electronic levels is critical. [34] The computing expenses of ab initio QM approaches have limited their adoption because this would require solving the quantum mechanics (QM) of molecules. Several researchers employed a hybrid method, in which they used a molecular mechanics (MM) force field for the entire system and an ab initio (QM) treatment for the site of interest. By using this QM/MM method they were able to address various elements of the biological systems analysed, such as electrical characteristics, interaction sites, and even conformational changes in protein active sites. An advanced application for QM/MM approach is the ONIOM method. ONIOM stands for “our own N-layered integrated molecular orbital and molecular mechanics”. It models large molecules by specifying multiple layers inside the structure that are treated at varying accuracy levels. The ONIOM approach can treat relatively large molecules in this fashion, and it can be used in a variety of fields of research, including organic and enzymatic reaction mechanisms. Building the model and then mapping the enzymatic chemical process are the two primary processes in the modelling method. [33]

Molecular dynamics

Fischer's key–lock paradigm's target–ligand model has been supplanted in recent years by the induced-fit model and conformational selection. The use of MD modelling is critical when attempting to link the flexibility of a bio molecular system to ligand recognition. Additionally, MD simulation is an effective tool for identifying additional druggable sites, such as allosteric, that are not detectable by conventional structural methods, resulting in the development of more effective pharmacological drugs. [34] MD is a Newtonian mechanics-based computer simulation technique. The atoms and molecules are allowed to interact for a set amount of time, providing a picture of the system's dynamic evolution while expressing atom and molecule motions using a potential energy function. A trajectory of conformations of a protein alone or in complex with other molecular entities in a biological environment is determined as a function of time during MD simulations. MD simulations serve as a link between theory and reality. MD is frequently used to understand experimental results on the structure and function of proteins. [35] Molecular interaction potentials, which are normally parameterized by quantum chemical calculations or experimental data, determine the forces operating on the system. The contribution of each sort of interaction to the general function is determined by the set of parameters (the force-field). Among the several force-fields available, AMBER, CHARMM, and GROMOS are the most commonly utilized in molecular dynamics simulations. [36]

MD has limitations, regardless matter how valuable it is. We can highlight the enormous computational cost necessary by large-scale simulations, which typically involve thousands of atoms when studying ligand-receptor complexes. Some of the conformational changes made by receptors during chemical recognition happen on time scales that are beyond the computational capabilities of the system. Despite its flaws, MD can make a significant contribution to SBDD, especially when paired with other molecular modelling techniques like molecular docking. [37]

Table 2: Properties of SBDD

Techniques	Effect on SBDD	Softwares
Molecular docking	• The process of a ligand binding to its receptor or target protein is referred to as "molecular docking." • Aids in the identification and optimization of therapeutic targets. [31] • Multiple ligand conformations and orientations are generated	ArgusDock, DOCK, FRED, eHITS, AutoDock, and FRED [32]
Molecular dynamics	• An effective tool for identifying additional druggable sites, such as allosteric. [34] • Frequently used to understand experimental results on the structure and function of proteins. [35]	AMBER, CHARMM, and GROMOS [36]

Structural Water

In molecular docking and SBDD, crystallographic water is a significant challenge. These molecules are tightly linked to the receptor and have been seen in many crystallographic structures of the same protein. At least one water molecule is involved in ligand-receptor recognition in approximately 65 percent of crystallographic protein-ligand complexes. Structural water is usually found in deep pockets of the receptor structure, facilitating numerous hydrogen bonds between the ligand and the protein binding site. These molecules can be displaced by the intended ligands or considered part of the target structure in SBDD and docking efforts. The entropy of releasing a crystallographic water molecule from its binding site is favorable, but the process results in a loss of enthalpy. [38] To compensate for the enthalpy loss, a specific moiety of the ligand can be selected to make analogous hydrogen bonds with the protein to replicate the interaction network of the displaced water. Alternatively, structural water can be explicitly added in docking experiments, allowing the ligand and the target binding site to form highly favorable hydrogen-bonding networks. Free energy perturbation calculations utilizing Monte Carlo statistical mechanics simulations, which estimate the binding free energy for a specific water molecule and allow the discriminating between displaceable and strongly-bound structural water, are one of these methodologies. Analysis of geometric characteristics of the protein environment around each crystallographic water molecule is another technique. [39] One of these approaches combines the HINT free energy scoring function with the Rank algorithm, which calculates the amount and quality of possible hydrogen bonds for a given water molecule. HINT analyses the interaction energy between each crystallographic water molecule and its surroundings based on the chemical characteristics and accessibility of possible hydrogen bond donors and acceptors, as well as the binding site's hydrophobic features. Rank looks for probable donor and acceptor partners for each water molecule and creates a rating scheme that ranges from molecules that don't interact via hydrogen bonds with non-water elements to molecules that make four geometrically ideal hydrogen bonds. This method can be used to determine whether an optimally coupled structural water molecule should be replaced or kept in the SBDD and docking procedures. In addition to using such algorithms, a comparison of structural water in multiple crystal structures should be performed to reduce the possibility of accidentally discarding or keeping a single water molecule. [40]

Protein-Protein Interaction Inhibitors and Molecular Docking

Interactions between different kinds of proteins affect a lot of cellular and metabolic processes. Defective protein-protein interactions (PPIs) are linked to a variety of illnesses, including cancer. As a result, this sort of intermolecular event is a particularly appealing target in drug development. Small-molecule drugs that directly compete with one of the protein partners are known as PPI inhibitors. [38] Recent results, such as the creation of AMG-232, an MDM2-p53 inhibitor, have expressed concern on the assumption that targeting PPIs is an inadequate method in drug design. The identification and characterization of binding sites, as well as the assessment of their potential for interacting with small-molecule drugs, is a major problem for SBDD and molecular docking in the field of PPIs. Unlike ligand-protein binding cavities, the contact surfaces where two proteins interact are drastically different. PPI binding sites, in general, are generally flat surfaces with no single large, well-defined pocket; rather, they are made up of a larger number of smaller pockets. Several computational approaches have been developed to find such binding sites and assess their drugability, the most notable of which are the freely available web-based applications Q-SiteFinder and ANCHOR. [39]

Q-SiteFinder is an energy-based approach for predicting protein binding sites, based on the notion that each interface pocket's amenability to SBDD is determined by its interaction energy (measured by a methyl probe). The interaction energy of the different pockets at the interface is classified, allowing an assessment of the locations where a ligand could interact and optimise the binding energy. The algorithm constructs a volume envelope, which is a region where the computed Van der Waals interaction energy remains below a set threshold, according to this procedure. The pockets where a potential ligand might have a good

interaction with the receptor surface are indicated by these volume envelopes. [41] To find possible binding pockets with drugable features, the ANCHOR algorithm searches for amino acid side chains deeply buried at protein-protein interfaces (anchor residues). The approach determines the change in the solvent Accessible Surface Area (SASA) for each amino acid side-chain following binding for a given PPI interface, as well as a measure of their contribution to the total interaction free energy. The probed residues are not classified as anchor or non-anchor by ANCHOR; instead, they are ranked in decreasing order of SASA by ANCHOR. The top ranked residues can be seen using a web-based application that provides an interactive interface for visualizing the surrounding environment's features, such as the presence of hydrogen-bonding networks. [42]

3. Fragment-Based Design

Researchers working with high-molecular-weight lead compounds have an issue of poor solubility and, as a result, unsatisfactory pharmacokinetic qualities. Scientists presented an FBDD technique to circumvent this barrier. FBDD is based on the discovery of soluble organic compounds with low molecular weight and chemical complexity (less than 150 Da) that target a sub pocket inside a broad binding site. Because they are simple and easy to handle, these fragments are the beginning points for 'hit to lead optimization.' Repetitive actions, such as adding functional groups or joining distinct fragments, are used to improve the selected pieces. [43] The Rule of Three must be followed for a chemical compound to be classified as fragment. According to this criteria, fragments must have a molecular weight of less than 300 Da, a cLogP of 3, and a number of hydrogen bond donors and acceptors of 3. [44] Fragment library design, fragment screening, and fragment elaboration are the three stages of the FBDD approach. The first stage involves designing or synthesizing a library of compounds that obey the rule of three, while toxic, unstable, and reactive fragments are left out. The ability of segments of the library to bind to a target molecule is next examined experimentally or computationally (docking and pharmacophore screening) utilizing biophysical approaches such as NMR spectroscopy, X-ray crystallography, and fluorescence-based thermal shift. [45] Experimentally validated fragments are chemically combined for potency augmentation into lead compounds in the final stage. [46] This process has resulted in the development of clinical candidates for a variety of targets, with Zelboraf (PLX4032) being the first FDA-approved medicine created utilizing the FBDD method. [47]

Conclusion

The field of In Silico drug discovery tools is quickly expanding, and it has been expanded by sophisticated tools used in research and the pharmaceutical industry. Advances in such tools, combined with a range of software, have resulted in a number of techniques, based on the experimental data available on the pharmacological target. The computational methods discussed here, SBDD and LBDD, each have their own set of benefits and drawbacks. We offer these approaches, divided into three categories, in this article, and give an overview of the most often employed strategies in the never-ending quest for small molecules in the drug development sector.

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Conflict of Interest

The authors declare no conflict of interest

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