**Computer Aided Drug Designing – A Novel Approach Method**

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**ABSTRACT**

Today, there possesses different types of drugs against different diseases and various sophisticated technologies but still it is not enough to develop drugs instantly against a new emerging disease as drug designing and development is a complex and lengthy process and requires a huge amount of money. In 21st generation, other reliable methods are being used to speed up the drug discovery process following the combinatorial chemistry emergence, known as computer aided drug designing where drugs leads are being predicted among the huge number of molecules by checking the interaction between the target and various ligands and also their drug likeliness property through insilico approaches. It involves methods such as homology modeling de novo approach, virtual screening approach, molecular docking, QSAR, simulation and various others. All these are done using various softwares such as ChemDraw or other molecular structure drawing programs, descriptor generators such as DRAGON, MolConnZ, and OEChem, text editors such as UltraEdit, and EMACS, Databases such as ZINC, PubChem, and ChemDiv, all QSAR Program, Perl and Python modules, HiPCDock program, AutoDock3 program, AutoDock Tools package, OpenBabel program and many others. With the help of this softwares drug designing using insilico approach has minimized the cost and the time required as well as reduced the chance of failure or rejection of drugs at the clinical trial phases. Till date many drugs have been discovered using insilico methods for different diseases such as cancer, hypertension, diabetes which falls among the top category in the list of global causes of deaths along with various other diseases and even the diseases that are caused by pathogens.

***Keywords:***  *In-silico, Drug design, CADD, ADMET, QSAR*.

**INTRODUCTION**

The development and discovery of drugs is a complex, lengthy, time consuming and interdisciplinary course. It is also highly expense and bestows many challenges and changes since decades (Danishuddin & Khan, 2015). But new diseases and disorders are discovered eventually and even some leads to an emergency like that of the covid19. Thus, new potential drugs are of great demand to overcome and mitigate the risk of new diseases which requires multidisciplinary aspects to accomplish this challenging process. In recent times, the use of in-silico methods and molecular modeling for computer aided drug design has gained much popularity in this field due to its advantage of being cost effective and time saver over the traditional method of drug development. The traditional drug designing method is the one in which the foremost task is to identify suitable drug target molecules which include nucleic acids and protein receptors, ion channels transporters, enzymes. Traditionally, drugs were discovered by synthesizing compounds in a time-consuming multi-step processes against a battery of in vivo biological screens and further investigating the promising candidates for their pharmacokinetic properties, metabolism and potential toxicity (Kapetanovic, 2008). Such a development process has resulted in high attrition rates with failures attributed to poor pharmacokinetics, lack of efficacy, animal toxicity, adverse effects in humans and various commercial and miscellaneous factors. Today, the process of drug discovery has been revolutionized with the advent of genomics, proteomics, bioinformatics and efficient technologies like, combinatorial chemistry, high throughput screening (HTS), virtual screening, de novo design, in vitro**,** in silico ADMET screening and structure-based drug design (Kapetanovic, 2008).

In silico drug design represents computational methods and resources that are used to facilitate the opportunities for future drug lead discovery. Bioinformatic techniques hold a lot of prospective in target identification (generally proteins/enzymes), target validation, understanding the protein, evolution and phylogeny and protein modeling. It not only accelerates drug target identification and drug candidate screening and refinement, but also facilitate characterization of side effects and predict drug resistance. One of the major thrusts of current bioinformatics approaches is the prediction and identification of biologically active candidates, and mining and storage of related information. It also provides strategies and algorithm to predict new drug targets and to store and manage available drug target information. Fast expansion in this area has been made possible by advances in software and hardware computational power and sophistication, identification of molecular targets, and an increasing database of publicly available target protein structures. CADD is being utilized to identify hits (active drug candidates), select leads (most likely candidates for further evaluation), and optimize leads, i.e. transform biologically active compounds into suitable drugs by improving their physicochemical, pharmaceutical, ADMET/PK (pharmacokinetic) properties (Kapetanovic, 2008). Virtual screening is used to discover new drug candidates from different chemical scaffolds by searching commercial, public, or private three-dimensional chemical structure databases. It is intended to reduce the size of chemical space and thereby allow focus on more promising candidates for lead discovery and optimization. The goal is to enrich set of molecules with desirable properties (active, drug-like, lead-like) and eliminate compounds with undesirable properties (inactive, reactive, toxic, poor ADMET/PK) (Kapetanovic, 2008). In another words, in silico modeling is used significantly to minimize time and resource requirements of chemical synthesis and biological testing The rapid growth of virtual screening is evidenced by increase in the number of citations matching keywords “virtual screening” from four in 1997 to 302 in 2004 (Pozzan, 2006). In his 2003 review article, Green of Glaxo Smith Kline concluded that: “The future is bright. The future is virtual” (Green, 2003).

There are wide ranges of software that are used in in-silico drug design, Grid computing, window based general PBPK/PD modelling software, PKUDDS for structure-based drug design, APIS, JAVA, Perl and Python, in-silico drug design as well as software including software libraries along with different techniques like drug design visualization, homology, molecular dynamic, energy minimization molecular docking and QSAR etc. (Oa et al., 2013). In-silico drug design can take part considerably in all stages of drug development from the preclinical discovery stage to late-stage clinical development. Its exploitation in drug development helps in the selection of only a potent lead molecule and may thus thwart the late-stage clinical failures; thereby a major diminution in cost can be achieved (Oa et al., 2013).

**Development of Drug and Drug Candidate: An Insilco approach**

Regardless of the fact that a copious number of drugs are available in the market and have been routinely used against various diseases, the fight between humans and the emerging new diseases are ongoing and will be so for the foreseeable future. Thus, there is an immense need for the advancement in the drug discovery process and that is being met by the latest approach of drug designing i.e. Insilco approach which is also known as Computer aided drug design, which saves both time and money. In today’s world, employment of computer-aided drug discovery (CADD) techniques by top pharmaceutical companies and other research groups became very essential for the preliminary stage of drug discovery to expedite the drug development process in a more cost-efficient way and to minimize failures in the final stage. The use of rational drug design, as applied in CADD, provides a knowledge-driven approach that can yield valuable information about the interaction pattern between protein and ligand (complex), as well as the binding affinity. Furthermore, the availability of supercomputers, parallel processing, and advanced software’s have greatly facilitated the rate of lead identification in pharmaceutical research. The main aim of the drug discovery process is to search for new drug molecules which can bind to a specific target known to be involved in causing a disease and change the target’s function (Baig et al., 2014). Computer Aided Drug Design (*in silico*) approaches have been widely employed in Lead Identification and Lead Optimization stages of drug development against various targets over the years. Drug Design can be categorized as two types: Analog based study and Structure based study based on the availability of three-dimensional structure of the target.

**Analog/Ligand based studies**

Analog based studies gather information from already existing drugs/ligands that are active against biological molecule (protein or DNA/RNA) of interest. Based on this information a set of rules is framed to either design a new ligand or modify an existing ligand in order to enhance biological activity (Sandala, 2013).

**Structure Based Studies**

Structure based approaches, based on the three-dimensional structure of the target overcome many of the limitations of analog-based studies. These methods help to develop a general theoretical description of the protein–ligand interactions that would enable and a prior design of new leads for a particular biological target (Marrone et al., 1997). The first success story in structure-based design is the antihypertensive drug captopril, an inhibitor of angiotensin converting enzyme (ACE).

Over the decades, these two types of CADD approaches continued to improve and evolve separately. However, combining different structure-based and ligand-based design strategies in the drug discovery effort have been established to be more effective than any single approach since both methods are able to complement their strengths and weaknesses.

**Methods Used in Computer Aided Drug Design and Development**

The current scenario of the drug discovery process involves several disciplines such as chemical and structural biology, computational chemistry, organic synthesis, and pharmacology. Accordingly, it is comprised of several stages:

**(a)** *Target identification* involves the discovery and isolation of individual targets to investigate their functions and association with a specific disease (Anderson, 2003).

**(b)** *Target validation* is the stage where the drug target is linked to the disease of interest, as well as their capacity to regulate biological functions in the body after binding to a partner molecule

**(c)** *Lead identification* entails the discovery of a synthetic chemical that shows a degree of potency and specificity against a biological target and is assumed to have the makings of a drug that can cure the intended.

**(d)** *Lead optimization* covers the improvement of potency and other significant properties through iterative cycles of evaluation of the lead compound(s) and their analogs (Macalino et al., 2015). Thus, both in vitro and in vivo experiments are conducted to prioritize and select candidates with optimum potential for development as a safe and efficient drug. Moreover, structure-activity relationships (SARs) are developed to determine pertinent pharmacokinetic and pharmacodynamic properties that can be applied to analogs that will be synthesized for evaluation (Andricopulo et al., 2009).

**(e)** *Preclinical stage* involves drug synthesis and formulation research, in vivo animal studies for potency and toxicity, and characterization of mechanistic toxicity (Macalino et al., 2015).

**(f)** *Clinical trials* include three phases that investigate safety, adverse side-effects, dosage, efficacy, and pharmacokinetic and pharmacological properties of the candidate drug on human volunteers (Silverman and Holladay, 2014).

Insilco approaches of drug designing are categorized into structure-based and ligand-based (enzyme/receptor) for the generation or screening of potential ligands (modulators), followed by methods. The structure-based approach consists of using the 3D structure of the target synthesis, biological testing, and optimization. In contrast, ligand-based approach consists of subjecting a collection of molecules with diverse structures and known potency to computational modeling methods to develop theoretical predictive models. These models are then used for structural optimization to enhance potency and for identification of new chemical entities through virtual screening of a large chemical database (Macalino et al., 2015).

**Structure-based drug design (SBDD)**

In SBDD, the knowledge acquired from the binding site of a 3D macromolecule structure is used to design and evaluate ligands based on their predicted interactions with the protein binding site. Thus, identification of a valid drug target and the acquisition of its structural information are the first vital steps in SBDD. Research from structural and computational biology aided in the generation of protein structures with the use of X-ray crystallography, nuclear magnetic resonance (NMR), cryo-electron microscopy (EM), homology modeling, and molecular dynamic (MD) simulation (Macalino et al., 2015). SBDD can be divided into two categories: the de novo approach and the virtual screening approach. De novo drug design exploits information from the 3D receptor to find small fragments that match well with the binding site. These fragments should be linked based on connection rules to ensure synthetic accessibility, providing a structurally novel ligand that can be synthesized for further screening (Macalino et al., 2015). On the other hand, virtual screening (VS) uses available small molecule libraries to identify compounds with specific bioactivity to act as replacements for existing ligands of target biomolecules or to discover compounds for unexplored known targets with available structural information (Andricopulo et al., 2009).

**Homology Modelling**

Homology modelling is also recognized as comparative modelling of protein and it is a method that allows to generate an unknown atomic resolution model of the "target" protein from its amino acid sequence and an experimental three-dimensional (3D) structure of a related homologous protein (the "template"). Homology modelling involves the recognition of one or more identified protein structures probably to show resemblance with the structure of the query sequence, and on the making of an alignment that maps residues in the query sequence to residues in the template sequence. It has been reported that the protein structures are more conserved than protein sequences amongst homologues, but sequences have less than 20% sequence identity and can have very different structures (Ahmad, 2013). The proteins which are related with evolution have similar sequences and naturally occurring homologous proteins have similar protein structure. It has been revealed through the research that the evolutionarily protein three-dimensional structure is more conserved than expected because of the sequence conservation to generate a structural model of the target using the sequence alignment and template structure. Since the protein structures are more conserved than DNA sequences, detectable levels of sequence similarity usually involve substantial structural similarity (Ahmad, 2013). Bioinformatics software tools are used to generate the 3D structure of the target on the basis of the known 3D structures of templates (Park et al., 2008). The Modeller is a popular tool in homology modelling, and SWISS-model repository is a database of protein structures created with homology modelling (Ahmad, 2013).

**Virtual High-Throughput Screening**

Virtual screening is a computational technique where large libraries of compounds are evaluated for their potential to bind specific sites on target molecules such as proteins, and well-matched compounds tested. The research in the drug discovery process involves virtual screening (VS) which is a computational method used for the rapid exploration of large libraries of chemical structures in order to identify those structures that are most likely to bind to a drug target, usually a protein receptor or enzyme (Ahmad, 2013). Virtual screening plays a vital role in the drug discovery process. The term "virtual screening" is relatively new as compared to the more general and older concept of database searching. Walters, et al. define virtual screening as "automatically evaluating very large libraries of compounds" using a computer program (Bohacek et al., 1996). It is clear from above definition that VS has been a numbers game at large scale and it is focusing to find out answers of questions like how can we screen down the huge chemical space of over 1060 possible compounds to a practicable number that can be synthesized, purchased, and tested. Although filtering the whole chemical universe might be an interesting question, more practical VS scenarios focus on designing and optimizing targeted combinatorial libraries and enriching libraries of available compounds from in-house compound repositories or vendor offerings. It is less expensive than High-Throughput Screening, Faster than conventional screening, scanning a large number of potential drugs like molecules in very little time. HTS itself is a trial-and-error approach but can be better complemented by virtual screening (Ahmad, 2013).

**De novo design**

De novo is a Latin expression meaning "from the beginning". Active site of drug targets when characterized from a structural point of view will shed light on its binding features. This information of active site composition and the orientation of various amino acids at the binding site can be used to design ligands specific to that particular target. Computational tools that can analyze protein active site and suggest potential compounds are extensively used for *de novo* design methods. Many promising approaches with the goal of ligand design have been reported (Aparoy et al., 2012). Murcko provided a detailed analysis of computer aided ligand design methods and distinguished them as six major classes:

1. **Fragment location methods:** To determine desirable locations of atoms or small fragments within the active site.
2. **Site point connection methods:** To determine locations (“site points”) and then place fragments within the active site so that those locations are occupied by suitable atoms.
3. **Fragment connection methods:** Fragments are positioned and “linkers” or “scaffolds” are used to connect those fragments and hold them in a desirable orientation.
4. **Sequential buildup methods:** Construct a ligand atom by atom, or fragment by fragment.
5. **Whole molecule methods:** Compounds are placed into active site in various conformations, assessing shape and/or electrostatic complementarity.
6. **Random connection methods:** A special class of techniques combining some of the features of fragment connection and sequential buildup methods, along with bond disconnection strategies and ways to introduce randomness.

Over the years various *de novo* methods especially whole molecule methods like docking have become integrated within disciplines that include chemistry, pharmacology, molecular biology and computer modeling. Electrostatic and solvation terms critical for evaluating correct binding energies, are difficult and slow to calculate. Advances in algorithm sophistication are providing better and better approximations for these parameters (Gane & Dean, 2000). Finally, it is clear from the recent literature that the drug design process has become an essential part of drug discovery projects.

**Binding site prediction or identification**

The ideal binding site is a concave region containing several chemical functionalities that interact with a ligand to achieve the desired result (activation, modulation, or inhibition) (Anderson, 2003), (Kalyaanamoorthy & Chen, 2011). Proteins co-crystallized with their substrates or known inhibitors, as well as mutation studies identifying key residues for interaction, provide beneficial knowledge in SBDD. However, when no information about the binding site is available, additional analyses are needed in order to perform structure-based rational drug discovery (Macalino et al., 2015). Currently, several in silico approaches have been reported in a number of papers and are available for the recognition of binding regions in proteins. The binding site of a small molecule compound can be predicted using available tools such as PASS. Q-SiteFinder, LIGSITEcsc SiteMap, FPocket, ConCavity, MED-SuMo, MDPocket, FTMAP, POOL, and many others. Alternatively, specific approaches that can identify peptide binding sites include PepSite, PeptiMap, and PEP-SiteFinder (Saladin et al., 2014). Lastly, difficulties in detecting allosteric sites can be alleviated by recently developed open-access web servers such as SPACER, a systematic assessment of a number of available web servers and stand-alone protein–ligand binding site prediction programs was published previously. The report detailed that while these methods can be valuable in finding putative binding sites, the predictive quality of the algorithms used may be dependent on several factors, including template similarity and the size of the ligand (K. Chen et al., 2011).

**Molecular docking**

In the field of molecular modeling, docking is a technique which envisages the favored orientation of one molecule to a second, when bound to each other to form a stable complex. Molecular docking denotes ligand binding to its receptor or target protein. Molecular docking is used to recognize and optimize drug candidates by examining and modeling molecular interactions between ligand and target macromolecules. Molecular docking is used to generate multiple ligand conformations and orientations and the most appropriate ones are selected. There are several molecular docking tools available that includes ArgusDock, DOCK, FRED, eHITS, AutoDock and FTDock. Molecular modeling involves scoring methods that are used to rank the affinity of ligands to bind to the active site of a receptor. In virtual high-throughput screening compounds are docked into the active site and then scored to determine which once more likely to bind tightly to the target macromolecule (A Wadood et al., 2013).

**Molecular dynamic (MD) simulation**

Molecular dynamics is an effective procedure and depends on the molecular motion simulation by solving Newton's equations of motion for each atom and increasing the speed and position of each atom by a small increase of the time duration. MD simulations characterize alternative method to sample configuration space, based on the above-mentioned rule. That is shared with temperatures using "reasonable" (a few hundreds or thousands of degrees), this means that only the local area around the sampled point, and only relatively small barriers (a few tens of kJ / mol) overcome. Generation may be different (local), minimum may be accomplished by selecting configurations appropriate times during the simulation and thus minimize these structures. MD methods utilize the inherent dynamics of the system to search deformation modes of low energy and can be used for sampling of the conformational space of large confined system (A Wadood et al., 2013).

**Ligand- Based Drug Design**

In cases where 3D structure of the target protein is lacking, information taken from a set of ligands active against a relevant target (receptor or enzyme) can be used to identify significant structural and physicochemical properties (molecular descriptors) responsible for the observed biological activity. Here, there is an assumption that structurally similar compounds display similar biological response and interaction with the target. The compound set should encompass a wide range of concentration (at least 4 orders of magnitude) to generate a reliable ligand-based screening model. Common ligand-based design techniques are quantitative structure–activity relationships (QSARs) and pharmacophore-based methods (Macalino et al., 2015).

**Quantitative-Structure Activity Relationship (QSAR)**

QSAR studies are based on the premise that changes in bioactivity which are associated with structural and molecular variations in a set of compounds (Macalino et al., 2015). A statistical model is generated from this correlation to develop and mathematically predict the biological property of novel compounds (Melo-Filho et al., 2014). Several restrictions are required to generate a reliable QSAR model: **(a)** the bioactivity data should be of sufficient number (minimum of 20 compounds with activity) and acquired from a common experimental protocol such that the potency values are comparable, **(b)** proper selection of compounds for the training and test sets, **(c)** molecular descriptors for the ligands should have no autocorrelation to avoid over-fitting, **(d)** the model should be validated using internal and/or external validation to determine its applicability and predictivity (Macalino et al., 2015). Comparative molecular field analysis (CoMFA) (Cramer et al., 1988), which was established more than three decades ago, is still one of the most widely used 3D-QSAR method. More recent 3D-QSAR strategies include Topomer CoMFA (Cramer, 2003), spectral structure activity relationship (S-SAR), adaptation of the fields for molecular comparison (AFMoC) and comparative residue interaction analysis (CoRIA). Despite its notable successes in the drug discovery field, 3D-QSAR still has numerous shortcomings that can be solved by more advanced multidimensional QSAR strategies in the form of 4D, 5D, and 6D-QSAR. 4D-QSAR was developed to address ligand conformation and orientation in the target binding site, while 5D-QSAR incorporates issues like receptor flexibility and induced fit effects (Macalino et al., 2015). Finally, 6D-QSAR takes note of the solvation effects to include its critical role in receptor-ligand interaction (Damale et al., 2013). Advances in computational power and software performance has also been applied in improving QSAR model development and validation through Discovery Bus (Cartmell et al., 2005) and Auto QSAR. In both methods, hundreds of highly predictive statistical models can be objectively discovered, updated, and validated by continuously integrating new machine learning agents and descriptors into the system (Macalino et al., 2015).

**Pharmacophore modeling**

Pharmacophore screening aims to identify compounds containing different scaffolds, but with a similar 3D arrangement of key interacting functional groups (Vuorinen & Schuster, 2015). Binding site information can be incorporated into the pharmacophore model by exploiting the bioactive conformation of candidate compounds. Pharmacophore modeling is also often performed in the molecular alignment stage of QSAR modeling studies (Melo-Filho et al., 2014). Several commonly used programs for automatic pharmacophore generation include Discovery Studio, PHASE b) LigandScout and MOE. These softwares and other algorithms have already been extensively reviewed (Vuorinen & Schuster, 2015). Accordingly, generating a model with well-balanced sensitivity and specificity is important to reduce false negative and false positive results, respectively. Spatial constraints can be employed in areas occupied by inactive compounds and refined to avoid making the model too restrictive. Furthermore, features not consistently observed in active compounds should be made optional or removed from the model. After model refinement, validation studies must be performed to determine the sensitivity and specificity of a model against an external test set (Vuorinen & Schuster, 2015). In the absence of both receptor 3D information and a set of active ligands, it is possible to create sequence-derived 3D pharmacophore models. From the concept similar receptors can bind with similar ligands. Pharma3D can use homology models and 3D crystal structures to detect common sequence motifs for ligand biomolecular recognition in protein families and create a single-feature pharmacophore database. This approach has been successfully applied in virtual screening for GPCR (family A). Sequences displaying the same motifs can theoretically distinguish the same ligand functionality at an analogous spatial location. With this, the sequence motifs linked to specific single-feature pharmacophores are identified and used to generate the 3D pharmacophore model. In spite of its limitations, this is an attractive technique for drug targets that have limited or no receptor and ligand information available (Macalino et al., 2015).

**Compound Selection**

Generally, compound selection (“cherry picking”) is done before proceeding to in vitro and in vivo assessment of lead potency. As mentioned in the Docking and Scoring section, one of the serious limitations of the current scoring functions include incorrectly ranking compounds, which lead to difficulty in identifying true hits. Apart from re-scoring poses and creating a consensus list of hits, an alternative strategy is to assess the interaction of a ligand in the binding pocket and identify compounds displaying similar interaction patterns (Macalino et al., 2015). The Automatic analysis of Poses using Self-Organizing Map (AuPosSOM) (Bouvier et al., 2010) can be employed for pose clustering and ranking of virtual screening hits. Their strategy is based on the assumption that specific contacts between an active compound and its target are necessary to display the desired activity. In addition, clustering is also often performed to search for common scaffolds among the hit compounds and to select a representative compound per cluster. Evaluation of structurally diverse compounds is a more cost- and time-efficient manner to investigate a large chemical space (Vuorinen & Schuster, 2015).

**Specificity Target**

Specificity is a vital criterion in the search of efficient drugs. Nevertheless, frequent occurrence of false positives due to aggregation, ligand promiscuity, and compound reactivity is still observed during the experimental evaluation of lead candidates, impeding drug discovery and development. The use of surfactants in screening assays minimizes compound aggregation (while reactive compounds are identified by using reactive group filters to improve hit list quality (Roche et al., 2002). Additionally, pan-assay interference compounds (PAINS) filter can take out compounds that are frequent hitters in various HTS experiments, and thus cannot be used as specific inhibitors.

However, the use of PAINS should be considered carefully since this filter was developed based on a limited number of HTS data and may not be applicable to other screening experiments (Macalino et al., 2015).

**Molecular Properties Prediction**

Molecular property is a complex balance of various structural features which decide a particular molecule is similar to the known drugs. In the development of drugs intended for oral use, good drug absorption and appropriate drug delivery are very important. The molecular structure is at the basis of physicochemical, drug metabolism, pharmacokinetics (DMPK), and toxicity properties (Mannhold & Kubinyi, 2009). Nearly 30% of oral drugs fail in the process of development due to poor pharmacokinetics. Properties at low and highly variable bioavailability are definitely the main cause stopping further development of the drugs. High oral bioavailability is an important contemplation for the development of bioactive molecules as therapeutic agents (Sandala, 2013). Therefore, the bioavailability related prediction of properties such as solubility, lipophilicity, good drug absorption, low polar surface area, sum of hydrogen bond donors and acceptors, molecular weight, LogP (portion coefficient) are important before actual synthesis to reduce the chemical expenses and valuable time. An in-Silico model for predicting oral bioavailability is very essential, it can be achieved with an appropriate balance between solubility and partitioning properties. The molecular properties of compounds can be calculated using Mol inspiration, Osiris and Mol Soft Software. Lipophilicity and solubility parameters can be calculated using ALOGPS program (Sandala, 2013). Drug like properties have been associated with oral drug–likeness include **(i)** Oral bioavailability **(ii)** Appropriate toxicity to pass a phase–I clinical trials **(iii)** Minimal potency for interacting with a therapeutic target **(iv)** Aqueous solubility **(v)** Permeability **(vi)** Pharmacokinetic viability **(vii)** Blood-brain barrier permeability. A practical definition of oral drug likeness, namely those compounds that are able to interact with a receptor, display profiles of known drugs and have good ADME properties. The World Drug Index derived well accepted “Rule-of 5”. Molecular size can be an additional limiting aspect in oral absorption. Compounds are most likely to have poor absorption when MW > 500, Clog P > 5, number of H - bond donors > 5 and the number of H - bond acceptors > 10. In general lead – like properties are lower than drug - like properties. Thus, MW < 350 and Clog P < 3 should be good starting points for leads. A “Rule - of - 3 ” has been proposed for screening of small fragments, which says the good lead fragments have MW ≤ 300, Clog P ≤ 3, H - bond donors and acceptors ≤ 3, ClogP ≤ 3 and the number of rotatable bonds (RTB) ≤ 3, PSA ≤ 60 Molecular size and H- bonding are two major components of log P. Octanol – water partition (log P) and distribution (log D) coefficients are broadly used to make estimates for membrane penetration and permeability, including gastrointestinal absorption (Sandala, 2013).

**Absorption, distribution, metabolism, excretion, and toxicity (ADMET) test**

High attrition rates due to poor pharmacokinetic profiles produces the need to determine the ADMET properties of leads in the early stages of drug screening. However, experimental evaluation of pharmacokinetic properties of millions of compounds is not a viable option in terms of money and time. Thus, in order to quickly assess the drug-likeness of a lead compound prior to extensive experimental testing, virtual screening can be employed to filter hits and eliminate compounds with undesirable qualities (Bajorath, 2002). Similar to QSAR, in silico ADMET filters are derived from chemical or molecular descriptors and are used to predict drug-like characteristics of compounds. The simplest and most well-known models include Lipinski Rule of Five (Lipinski et al., 1997), Rule of Three for fragments (Congreve et al., 2003) and Veber rules (Veber et al., 2002). Publicly available web servers like ChemBioServer and Free ADMET Filtering-Drugs2 (FAF-Drugs2) (Lagorce et al., 2008) and (Lagorce et al., 2011) can be used to filter a large compound database or a list of potential leads. ChemBioServer has the capability to display compounds and graph molecular properties, filter compounds based on different chemical qualities, steric clashes, and toxicity, perform substructure search, cluster compounds, and recommend a representative for each group. Alternatively, FAF-Drugs2 features various pre-defined filters that the user can choose from, like the ones mentioned above, along with others such as central nervous system (CNS) Filter and reactive group filter. In addition to these, pharmacophore models generated from inhibitors that cause toxicity can also be used to identify compounds with unfavourable moieties. To address the issue of drug metabolism, reactivity models such as those implemented in SMARTCyp are helpful. SMARTCyp is a free web service and downloadable program that predicts sites in 2D compound structures that are likely to undergo Phase I CYP450-mediated metabolism (Macalino et al., 2015). It calculates the reactivity of ligand fragments using quantum chemical computations and the accessibility of atoms in the molecule to determine possible sites of metabolism. Alternatively, MetaSite also makes use of a similar algorithm to identify potential metabolic reactivity sites, but with 3D configuration of the compound as the query input. In the application of these in silico ADMET models, we should keep in mind that these tools are more helpful in the qualitative analysis of hits or compound sets rather than accurately predicting the quantitative values (Macalino et al., 2015). These methods are beneficial in the prioritization of an identified class of compounds for in vitro or in vivo assessment or evaluation of a particular descriptor and SAR (Gleeson & Montanari, 2012).

**DISCUSSION**

Drugs are chemicals that prevent disease or assist in restoring health to diseased individuals. As such they play an indispensable role in modern medicine. In the distant past, designing a new drug by changing the molecular structure of an existing drug was a slow process of trial and error. Now, a computer can display the molecular structure of any drug from a list of thousands in a database. With only very slight molecular changes, the original drug may be significantly changed in a variety of ways that influence absorption, metabolism, half-life, therapeutic effect, or side effects. The computer can also identify those chemicals that would probably not be successful in treating a particular disease before time and money are invested in extensive testing. Using computers to manipulate chemicals at the molecular level and design new drugs is based on molecular pharmacology, the study of the chemical structures of drugs and their interactions at the molecular level within a cell and even within DNA in the nucleus. Traditionally, drugs are discovered by synthesizing compounds in a time-consuming multi-step process against a battery of in vivo biological screens and further investigating the promising candidates for their pharmacokinetic properties, metabolism and potential toxicity (Anh Vu et al., 2015).

Thus, drug discovery and development is a very complicated, time consuming process and there are many factors responsible for the failure of different drugs such as lack of effectiveness, side effects, poor pharmacokinetics, and marketable reason. Beside this expenditure of this process has amplified ominously during the past thirty-four years. Therefore computer-aided drug design (CADD) approaches are being widely used in the pharmaceutical industry to accelerate the process. The cost benefit of using computational tools in the lead optimization phase of drug development is substantial. On an average, it takes 10-15 years and US $500-800 million to introduce a drug into the market, with synthesis and testing of lead analogs being a large contributor to that sum (Basak, 2012). Therefore, it is beneficial to apply computational tools in hit-to-lead optimization to cover a wider chemical space while reducing the number of compounds that must be synthesized and tested in vitro. The computational optimization of a hit compound involves a structure-based analysis of docking poses and energy profiles for hit analogs, ligand-based screening for compounds with similar chemical structure or improved predicted biological activity, or prediction of favorable affinity or optimize drug metabolism and pharmacokinetics (DMPK) or absorption, distribution, metabolism, excretion, and the potential for toxicity (ADMET) properties. The comparably low cost of CADD compared with chemical synthesis and biological characterization of compounds make these methods attractive to focus, reduce, and diversify the chemical space that is explored (Sujit. G, n.d.).

Till now many drug and drug candidates have been discovered through insilico method against various diseases. Even some drugs are repurposed via drug repurporsing method and is being used for more than one disease which saves time and also cost as it had already gone through various procedures insilico as well as clinical and thus few methods can be skipped. In the recent days with the advancement of technologies insilico approach can be more effectively and efficiently used in drug designing resulting in discovery of drugs and fighting against the newly emerging disease. In this study we could found various insilico designed drugs starting from captropil against hypertension, and others like imatinib for leukemia, boceprevir for hepatitis C leading to the present-day repurposed drugs against the corona virus such as Sofasuvir, Remdisivir.

**CONCLUSION**

Drug discovery and development is an interdisciplinary, expensive and time-consuming process. Scientific advancements have changed the way of generating novel bioactive molecules. Advances in computational techniques and in parallel hardware support have enabled in silico methods. Computational methods have relentlessly helped in designing new, safe and effective therapeutics. Successful implementation of software-based techniques has provided an opportunity to identify in vitro biologically active agents without much effort. Since the development of insilico methods, many drugs have been designed. The in-silico methods has led to the development of new drugs in mitigating the new emerging diseases within a short span of time and cost. As such captopril was the first ligand-based ACE inhibitor designed through in silico. Later many other novel drugs have been developed. Thus, insilico methods have reduced the problems of drug designing by saving time and money and led to discovery of many drugs and drug leads.

**REFERENCES**

1. Ahmad, A. (2013). In-silico drug design: An approach which revolutionarised the drug discovery process. *Oa Drug Design and Delivery*, *1*.
2. Anderson, A. C. (2003). The process of structure-based drug design. *Chemistry & Biology*, *10*(9), 787–797. https://doi.org/10.1016/j.chembiol.2003.09.002
3. Andricopulo, A. D., Salum, L. B., & Abraham, D. J. (2009). Structure-based drug design strategies in medicinal chemistry. *Current Topics in Medicinal Chemistry*, *9*(9), 771–790. https://doi.org/10.2174/156802609789207127
4. Anh Vu, L., Thi Cam Quyen, P., & Thuy Huong, N. (2015). In silico Drug Design: Prospective for Drug Lead Discovery. *International Journal of Engineering Science Invention*, *4*(10), 60–70. www.ijesi.org
5. Aparoy, P., Reddy, K. K., & Reddanna, P. (2012). Structure and ligand based drug design strategies in the development of novel 5- LOX inhibitors. *Current Medicinal Chemistry*, *19*(22), 3763–3778. https://doi.org/10.2174/092986712801661112
6. Baig, M. H., Ahmad, K., Adil, M., Khan, Z., Khan, M., Lohani, M., Khan, M., & Kamal, M. (2014). Drug Discovery and In Silico Techniques: A Mini-Review. *Enzyme Engineering*. https://doi.org/10.4172/2329-6674.1000123
7. Bajorath, J. (2002). Integration of virtual and high-throughput screening. *Nature Reviews. Drug Discovery*, *1*(11), 882–894. https://doi.org/10.1038/nrd941
8. Basak, S. C. (2012). Chemobioinformatics: the advancing frontier of computer-aided drug design in the post-genomic era. In *Current computer-aided drug design* (Vol. 8, Issue 1, pp. 1–2). https://doi.org/10.2174/157340912799218507
9. Bohacek, R. S., McMartin, C., & Guida, W. C. (1996). The art and practice of structure- based drug design: A molecular modeling perspective. *Medicinal Research Reviews*, *16*(1), 3–50. https://doi.org/10.1002/(SICI)1098-1128(199601)16:1<3::AID-MED1>3.0.CO;2-6
10. Bouvier, G., Evrard-Todeschi, N., Girault, J.-P., & Bertho, G. (2010). Automatic clustering of docking poses in virtual screening process using self-organizing map. *Bioinformatics (Oxford, England)*, *26*(1), 53–60. https://doi.org/10.1093/bioinformatics/btp623
11. Cartmell, J., Enoch, S., Krstajic, D., & Leahy, D. (2005). Automated QSPR through Competitive Workflow. *Journal of Computer-Aided Molecular Design*, *19*, 821–833. https://doi.org/10.1007/s10822-005-9029-8
12. Chen, K., Mizianty, M. J., Gao, J., & Kurgan, L. (2011). A critical comparative assessment of predictions of protein-binding sites for biologically relevant organic compounds. *Structure (1993)*, *19*(5), 613–621. https://doi.org/10.1016/j.str.2011.02.015
13. Congreve, M., Carr, R., Murray, C., & Jhoti, H. (2003). A “rule of three” for fragment-based lead discovery? *Drug Discovery Today*, *8*(19), 876–877. https://doi.org/10.1016/s1359- 6446(03)02831-9
14. Cramer, R. D. (2003). Topomer CoMFA:  A Design Methodology for Rapid Lead Optimization. *Journal of Medicinal Chemistry*, *46*(3), 374–388. https://doi.org/10.1021/jm020194o
15. Cramer, R. D., Patterson, D. E., & Bunce, J. D. (1988). Comparative molecular field analysis (CoMFA). 1. Effect of shape on binding of steroids to carrier proteins. *Journal of the American Chemical Society*, *110*(18), 5959–5967. https://doi.org/10.1021/ja00226a005
16. Damale, M., Harke, S., Khan, F., Shinde, D., & Sangshetti, J. (2013). Recent advances in multidimensional QSAR (4D-6D): A critical review. *Mini Reviews in Medicinal Chemistry*, *14*. https://doi.org/10.2174/13895575113136660104
17. Danishuddin, M., & Khan, A. U. (2015). Structure based virtual screening to discover putative drug candidates: Necessary considerations and successful case studies. *Methods*, *71*(C), 135–145. https://doi.org/10.1016/j.ymeth.2014.10.019
18. Foote, B. S., Spooner, L. M., & Belliveau, P. P. (2011). Boceprevir: Un inhibidor de proteasa para el tratamiento de hepatitis C crónica. *Annals of Pharmacotherapy*, *45*(9), 1085–1093. https://doi.org/10.1345/aph.1P744
19. Gane, P. J., & Dean, P. M. (2000). Recent advances in structure-based rational drug design. *Current Opinion* *in Structural Biology*, *10*(4), 401–404. https://doi.org/https://doi.org/10.1016/S0959-440X(00)00105-6
20. Gleeson, M., & Montanari, D. (2012). Strategies for the generation, validation and application of in silico ADMET models in lead generation and optimization. *Expert Opinion on Drug Metabolism & Toxicology*, *8*, 1435–1446. https://doi.org/10.1517/17425255.2012.711317
21. Green, D. (2003). Virtual Screening of Virtual Libraries. *Progress in Medicinal Chemistry*, *41*, 61–97. https://doi.org/10.1016/S0079-6468(02)41002-8
22. Kalyaanamoorthy, S., & Chen, Y.-P. P. (2011). Structure-based drug design to augment hit discovery. *Drug Discovery Today*, *16*(17),831–839. https://doi.org/https://doi.org/10.1016/j.drudis.2011.07.006
23. Kapetanovic, I. M. (2008). Computer-aided drug discovery and development (CADDD): In silico-chemico-biological approach. *Chemico-Biological Interactions*, *171*(2), 165–176. https://doi.org/10.1016/j.cbi.2006.12.006
24. Lagorce, D., Maupetit, J., Baell, J., Sperandio, O., Tuffery, P., Miteva, M., Galons, H., & Villoutreix, B. (2011). The FAF-Drugs2 server: A multistep engine to prepare electronic chemical compound collections. *Bioinformatics (Oxford, England)*, *27*, 2018–2020. https://doi.org/10.1093/bioinformatics/btr333
25. Lagorce, D., Sperandio, O., Galons, H., Miteva, M. A., & Villoutreix, B. O. (2008). FAF- Drugs2: free ADME/tox filtering tool to assist drug discovery and chemical biology projects. *BMC Bioinformatics*, *9*, 396. https://doi.org/10.1186/1471-2105-9-396
26. Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.*, *23*, 3.
27. Macalino, S. J. Y., Gosu, V., Hong, S., & Choi, S. (2015). Role of computer-aided drug design in modern drug discovery. *Archives of Pharmacal Research*, *38*(9), 1686–1701. https://doi.org/10.1007/s12272-015-0640-5
28. Marrone, T. J., Briggs James M., and, & McCammon, J. A. (1997). STRUCTURE-BASED DRUG DESIGN:Computational Advances. *Annual Review of Pharmacology and Toxicology*, *37*(1), 71–90. https://doi.org/10.1146/annurev.pharmtox.37.1.71
29. Melo-Filho, C. C., Braga, R. C., & Andrade, C. H. (2014). 3D-QSAR approaches in drug design: perspectives to generate reliable CoMFA models. *Current Computer-Aided Drug Design*, *10*(2), 148–159. https://doi.org/10.2174/1573409910666140410111043
30. Oa, L., London, P., Commons, C., & License, A. (2013). *Wadood A , Ahmed N , Shah L , Ahmad A , Hassan H , Shams S . In- silico drug design : An approach which revolutionarised the drug discovery process . OA Drug Design & Delivery 2013 Sep*. *1*(1).
31. Park, D., Kim, J., Lee, Y., & Ahn, C. (2008). QSID Tool: a new three-dimensional QSAR environmental tool. *Journal of Computer-Aided Molecular Design*, *22*, 873–883. https://doi.org/10.1007/s10822-008-9219-2
32. Pozzan, A. (2006). Molecular Descriptors and Methods for Ligand Based Virtual High Throughput Screening in Drug Discovery. *Current Pharmaceutical Design*, *12*, 2099–2110. https://doi.org/10.2174/138161206777585247
33. Rasheed, O. F. A.-. (2019). *Molecular Docking Studies for Design, Synthesis and Characterization of New Imatinib Analogues*. *December*. <https://doi.org/10.35248/2153> 2435.19.10.616
34. Roche, O., Schneider, P., Zuegge, J., Guba, W., Kansy, M., Alanine, A., Bleicher, K., Danel, F., Gutknecht, E.-M., Rogers-Evans, M., Neidhart, W., Stalder, H., Dillon, M., Sjögren, E., Fotouhi, N., Gillespie, P., Goodnow, R., Harris, W., Jones, P., … Schneider, G. (2002). Development of a Virtual Screening Method for Identification of “Frequent Hitters” in Compound Libraries. *Journal of Medicinal Chemistry*, *45*(1), 137–142. https://doi.org/10.1021/jm010934d
35. Saladin, A., Rey, J., Thévenet, P., Zacharias, M., Moroy, G., & Tufféry, P. (2014). PEP-SiteFinder: a tool for the blind identification of peptide binding sites on protein surfaces. *Nucleic Acids Research*, *42*(Web Server issue), W221-6. https://doi.org/10.1093/nar/gku404
36. Sandala, A. (2013). *Rational design and synthesis of benzimidazole derivatives for the evaluation of biological activity*[. http://hdl.handle.net/10603/21288](http://hdl.handle.net/10603/21288)
37. Veber, D. F., Johnson, S. R., Cheng, H.-Y., Smith, B. R., Ward, K. W., & Kopple, K.D. (2002). Molecular properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry*, *45*(12), 2615–2623. https://doi.org/10.1021/jm020017n
38. Vetrichelvan, T., Jegadeesan, M., & Devi, B. (2002). Antidiabetic Activity of Alcoholic Extract of Celosia argentea LINN. Seeds in Rats. *Biological & Pharmaceutical Bulletin*, *25*, 526–528. https://doi.org/10.1248/bpb.25.526
39. Vuorinen, A., & Schuster, D. (2015). Methods for generating and applying pharmacophore models as virtual screening filters and for bioactivity profiling. *Methods (San Diego, Calif.)*, *71*, 113–134. https://doi.org/10.1016/j.ymeth.2014.10.013