International Journal of Pharmaceutical research and Applications
Volume 8, Issue 6, Nov.-Dec. 2023, pp: 635-644 www.ijprajournal.com ISSN: 2456-4494

# A review Article on: Drug design

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Date of Submission: 10-11-2023 Date of Acceptance: 25-11-2023

**Abstracts**
Drug design is a complex pharmaceutical science with a long history.Many achievements have been made in the field of drug design since The end of 19th century, when Emil Fisher suggested that the drug–Receptor interaction resembles the key and lock interplay. Gradually, Drug design has been transformed into a coherent and well organized science with a solid theoretical background and practical Applications. The development of a drug from an initial idea to Its entry into the market is a very complex process which can take Around 5-10 years and cost $1.7 billion. The idea for a new development can come from a variety of Sources which include the current necessities of the market, new Emerging diseases, academic and clinical research, commercial Sector, etc… Once a target for discovery has been chosen, the Pharmaceutical industries or the associated academic centres Work on the early processes to identify the chemical molecules With suitable characteristics to make the targeted drugs. The Recent outbreak of the deadly coronavirus disease 19 (COVID-19) Pandemic poses serious health concerns around the world. The lack Of approved drugs or vaccines continues to be a challenge and Further necessitates the discovery of new therapeutic molecules. The pharmaceutical industry is under pressure in developing cost effective new drug molecule from the previous knowledge and Established Quantitative Structure-Activity Relationships.

**Key words:-**CADD, QSAR, Lipinski rule, Quality of data, docking.

## I. Introduction:-

Developing a new drug from an original idea to the launch of a finished Product is a complex process which can take 12–15 years and cost in Excess of $1 billion. The idea for a target can come from a variety of Sources including academic and clinical research and from the Commercial sector. It may take many years to build up a body of Supporting evidence before selecting a target for a costly drug discovery Program. Once a target has been chosen, the pharmaceutical industry And, more recently, some academic centres would have streamlined a Number of early processes to identify molecules which possess suitable Characteristics to make acceptable drugs . Drug development and Discovery Includes preclinical research on cell-based and animal models and Clinical trials on humans, and finally move forward to the step of Obtaining regulatory approval in order to market the drug. Modern drug Discovery involves the identification of screening hits, medicinal Chemistry and optimization of those hits to increase the affinity, Selectivity (to reduce the potential of side effects), efficacy/potency, Metabolic stability (to increase the half-life), and oral Bioavailability. Once a compound that fulfills all of these requirements Has been identified, it will begin the process of drug development prior To clinical trials.[1] Drug discovery can be described as the process of identifying chemical Entities that have the potential to become therapeutic . A key Goal of drug discovery campaigns the recognition of new molecular Entities that may be of value in the treatment of diseases that qualify as Presenting unmet medical Needs. These diseases do not have definitively useful therapies and are actually or potentially life-threatening. Marketed drugs at this point Represent a relatively small number of drug target types. Drugs targeted Against G-protein coupled receptors, nuclear (hormone) receptors, and Ion channels represent Slightly less than50% of the marketed drugs. By far, drugs directed Against enzymes represent the largest portion of marketed drugs. Expansion into new types of drug targets may be necessary to fill Certain therapeutic voids, but a matter of great intellectual challenge is How to choose a target likely to be Of value, especially when venturing into less well-explored types of drug Targets.[2]

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**Principle:-**

Drug design is the inventive process of finding new medications Based on the knowledge of a biological target. In the most basic Sense, drug design involves the design of molecules that are Complementary in shape and charge to the molecular target with Which they interact and bind. Drug development and discovery Includes preclinical research on cell-based and animal models and Clinical trials on humans, and finally move forward to the step of Obtaining regulatory approval in order to market the drug. Modern Drug discovery involves the identification of screening hits, Medicinal chemistry and optimization of those hits to increase the Affinity, selectivity (to reduce the potential of side effects), Efficacy/potency, metabolic stability (to increase the half-life), and Oral bioavailability. [3]

Lipinski's Rule of Fives Lipinski's rule of five also known as the Pfizer's rule Of five or simply the Rule of five (RO5) is a rule of Thumb to evaluate drug likeness or determine if a Chemical compound with a certain pharmacological or biological activity has properties that would make it a Likely orally active drug in humans. The rule was Formulated by Christopher A. Lipinski in 1997, based on The observation that most medication drugs are relatively Small and lipophilic molecules. Components of the rule Lipinski's rule states that, in general, an orally active Drug has no more than one violation of the following Criteria:

- Not more than 5 hydrogen bond donors (nitrogen or Oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular mass less than 500 Dalton's
- An octanol-water partition coefficient log P not Greater than 5.[4]

**QSAR**:-

Quantitative structure–activity relationship (QSAR) analysis is a Ligand-based drug design method developed more than 50 years Ago by Hansch and Fujita (1964). Since then and until now, QSAR Remains an efficient method for building mathematical models, Which attempts to find a statistically significant correlation Between the chemical structure and continuous (pIC50, pEC50, Ki, Etc.) or categorical/binary (active, inactive, toxic, nontoxic, etc.) [5]

**Purpose of QSAR:-**

QSAR should not be seen as an academic tool to allow for the post Rationalization of data. We wish to derive the relationships between Molecular structure, Chemistry and Biology for good reason. From these Relationships we can develop models, and with luck, good judgment and Expertise these will be predictive. There are many practical purposes of a QSAR and these techniques are utilized widely in many situations. The Purpose of in Silico studies, therefore, includes the following: To predict Biological activity and physicochemical properties by rational Means. Comprehend and rationalize the mechanisms of action within a Series of chemicals.[6]

**History of QSAR:-**

Cross proposed a relationship which existed between the toxicity of Primary aliphatic alcohols with their water solubility. In 1868 Crum-Brown and Fraser published an equation which is Considerable to be the first generation formulation of a quantitative Structure-activity relationship, in their investigations of different Alkaloids. Systematic QSAR began with the work of on the narcotic Activity of various drugs. Hammett introduced a method to account For substituent effects on reaction mechanism. Taking Hammetts Model into account Taft proposed in 1956 an approach for Separating polar, steric, and resonance effects of substituents in Aliphatic compounds. Classical approach to QSAR/QSPR was led by The pioneering works of Hansch et al. in the development of linear Hansch equation.[7]

Approaches:-

The QSAR model construction is characterized by having specific Schemes for computing and choosing the molecular descriptors And explicit statistical procedures for formulating the resulting Models. Characterization of the QSAR group is done by designing the Model system in the lack of a definite structure intended for the Molecular target. Reformulating the conventional QSAR methods With refined mathematical tools and well-designed theoretical models, recently, three modern QSAR methods were introduced. First one being FB- QSAR (Fragment-Based two Dimensional QSAR), where as per the substitute being examined.

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the Molecular structures in a series of drug candidates are segregated Into a number of fragments. The physicochemical characteristics of Molecular fragments are compared with the bioactivities of drug Candidates with the help of two sets of coefficients out of which One is for the molecular fragments while the other for the Physicochemical characteristics. The second type is known as MF-3D-QSAR (Multiple Field Three Dimensional QSAR). In this QSAR Type, additional molecular potential field (thermodynamic and Non thermodynamic) is incorporated in CoMFA (Comparative Molecular Field Analysis) using two sets of coefficients, one for the Cartesian three dimensional space position and the other for Potential field. CoMFA (Comparative Molecular Fields Analysis).[8]

**Quality of data**

Data should come from the same assay protocol, and care Should be taken to avoid interlaboratory variability. Any bad Data points will tend to corrupt the proper correlation of Structure and activity. Rules of thumb for a good QSAR data Set are that the dose-response relationship should be smooth, The potency (or affinity) should be reproducible, the activity Range should span two or more orders of magnitude from the Least active to the most active chemical in the series, the Number of chemicals used to build the QSAR model should be Sufficiently large to ensure statistical stability, the activities of The chemicals should be evenly distributed across the range of Activity, and the chemicals selected for the training set should Possess enough structural diversity to span the range of Chemistry space associated with the biological activity under Study.

**Descriptor selection**

Many types of chemical structure descriptors are available From commercial software. Obtaining a statistically robust Model is very much dependent on how well the selected Descriptors can encode the variation of activity with structure. The more that is known at the molecular level about the Biological mechanism of action of the chemicals, the better the Chemist is able to select among the wide variety and types of Specific molecular descriptors. Commercially available Molecular modelling programs often include statistical tools to Help in evaluating which descriptors best encode structureactivity variation.

**Statistical methods**

It is also critical that the QSAR method selected to develop the Structure-activity correlation be suitable. Although the Relationship between a molecular descriptor and biological Activity may be linear or nonlinear, it is still common practice Today to use linear approaches such as multiple (or Multivariate) linear regression (MLR) or partial least squares (PLS) regression to construct the QSAR model. For nonlinear Modelling, the Polynomial Neural Network (PNN) offers an alternative that combines the best features of Artificial Neural Networks (ANNs) and MLR/PLS by providing the inherent nonlinearity of the ANN with the desired analytical regression Equation furnished by MLR and PLS.[9]

**CADD:-**

Drug discovery is a multistep process that begins with the Identification of suitable drug target, validation of drug target, hit to Lead discovery, optimization of lead molecules, and preclinical and Clinical studies. The application of rational drug design as an Integral part of CADD provides useful insights into the Understanding of the binding affinity and molecular interaction Between target protein and ligand. Additionally, lead identification In pharmaceutical research has been facilitated by the availability of Supercomputing facility, parallel processing, and advanced Programs, algorithms, and tools. Furthermore, recent Advancements in artificial intelligence (AI) and machine learning Methods have greatly aided in analyzing, learning, and explaining The pharmaceutical-related big data in the drug discovery process. Different methods employed in the identification of new Inhibitors from chemical databases include pharmacophore Modelling, quantitative structure-activity relationship (QSAR), Molecular docking, quantum mechanics, and statistical learning Methods. [10]

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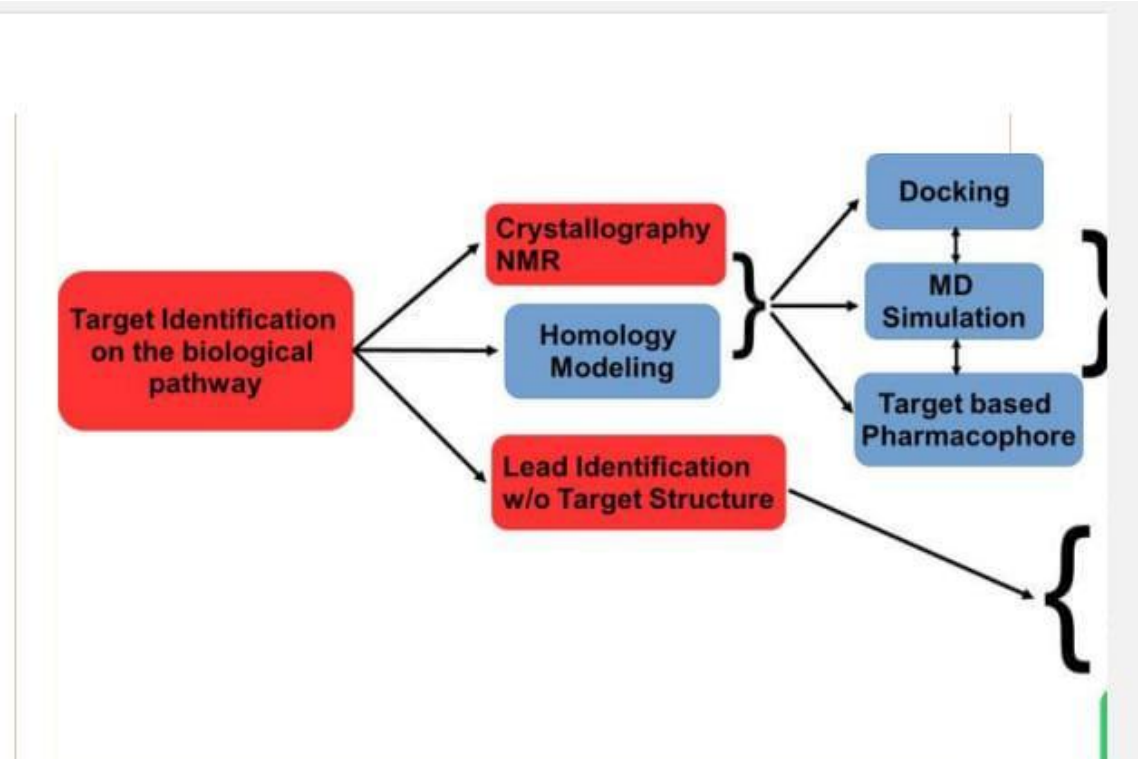


**Two Types of CADD:-**

1) structural Based drug design
2) Ligand Based drug design

**1. Structural based drug design:-**

The underlying principles of structure-based drug design are the Accessibility of the therapeutic target protein's three- dimensional Structures and the characterization of the binding site cavity (Kawato et al., 2015). A new era of SBDD in drug discovery and Design has begun by disclosing many biological molecules' three dimensional (3D) structures (Middleton, 2007; Hosfield et al., 2003; Lavecchia and Di, 2013). SBDD has emerged as a possible Means of generating and optimizing ligands in the pharmaceutical Industry (Park et al., 2012; Jorgensen, 2004; Gurung et al., 2021). Preparation of the target, identification of the binding site, Molecular docking, virtual screening and molecular dynamics are the basic steps of SBDD.

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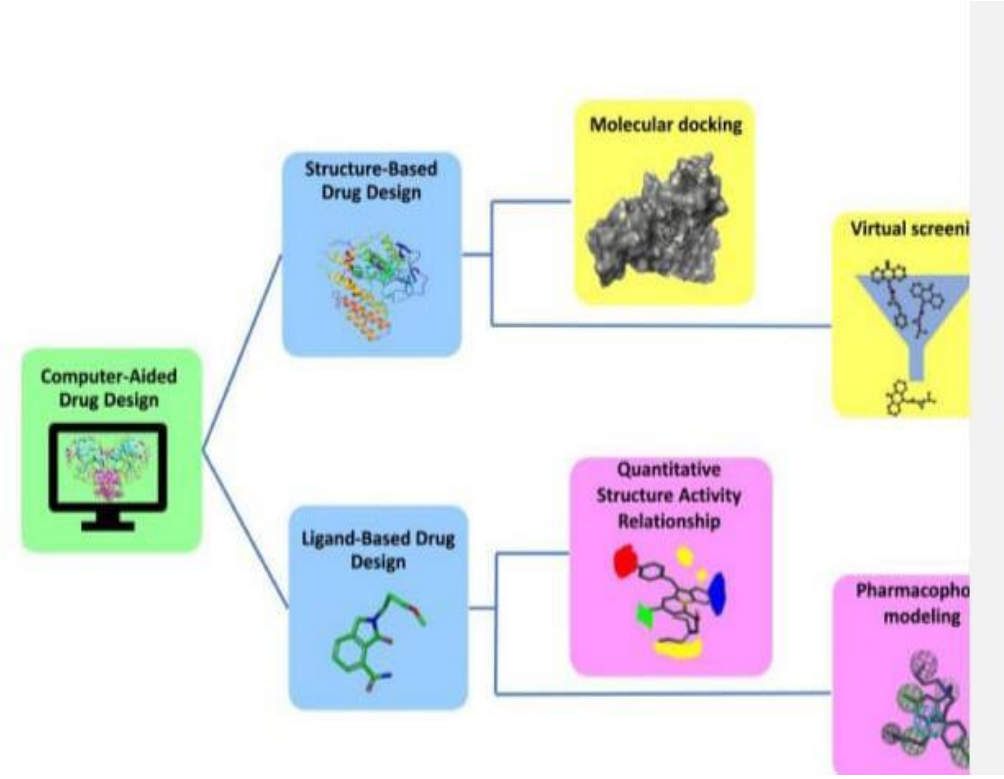


**Types of virtual screening methods in CADD**

Virtual screening is now widely used in drug discovery and many Approved and marketed drugs have been discovered with the aid Of this computational technique .Two major virtual screening Classes dominate the technique namely structure-based virtual Screening (also known as receptor-based or target-based virtual Screening) and ligand-based virtual screening, which in turn arcomposed of other virtual screening methods mentioned before Structure-based virtualscreening.

**Virtual screening software programs and graphical user Interfaces used in CADD**

Several factors influence the frequency of use of a virtual Screening program including their availability on various Platforms or operating systems such as Linux, Mac or Windows.One of the greatest contributing factors regarding their use or Application is the availability or licencing .These range from Commercial, public freeware, freeware for academic use and open Source .

**Molecular dynamics simulations**

Molecular dynamics simulations are some of the most integral Calculations that follow virtual screening simulations. They should Be therefore considered as an advanced technique, Complementary to docking. They can also be applied prior to Docking for conformational sampling and clustering on a protein Molecule to cater for the conformational dynamics relating to Ligand binding . More prominently, MD simulations are employed To filter and validate the results obtained from protein–ligand.

**Density functional theory**

The density functional theory seems to be the least popular Computational method applied to complement virtual screening. The average application of this technique within the six-year Period under study accounts for a meagre 0.02%. This may indicate that this technique is highly specific to limited occasions Whereby certain intricate inter-molecular interactions and Reaction mechanisms need to be established Experimental evaluation/calibration Experimental evaluation is of paramount importance in virtual Screening application and assays can also be used for hypothesis Testing .It is crucial to calibrate theoretical results against Experimental as it serves as a benchmark upon which the Computational model can be evaluated and cross- validated .

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**CADD-linked drug discoveries**

Computer-aided drug design has come of age and it has greatly Influenced the development of several therapeutically crucial Small molecules (drug leads), many of which have led to the Successful development of commercially available drugs . The Application of computational methods in drug discovery has been Facilitated by the synergy between bioinformatics, computational Simulations and medicinal chemistry, resulting in an increase in Their use.[13]

**Preparation of the Target Structure:-**

With the rapid advancement in structural elucidation techniques Such as X-ray and NMR, the structures deposited and available in Protein data bank (PDB) have increased over the last few decades. Owing to the limitations of experimental techniques, many target Protein structures have not been solved to date.

**Identification of the Ligand Binding Site**:-

The information about the ligand-binding site is a prerequisite for Carrying out specific docking. The knowledge of the binding sites can Be extracted from the site-directed mutagenesis study or X-ray Crystallographic structures of proteins cocrystallized with substrates Or inhibitors.

**COMPOUND LIBRARY PREPARATION** :-

Chemical compounds can be selected from chemical databases such As ZINC (N=230 million purchasable compounds)PubChem (N=111 Million pure and characterized chemical compounds) MCULE (N=122 Million synthetically accessible compounds) (), ChEMBL (>1.6 million Distinct compounds) Drug Bank (N=14528 drug molecules) and ChemSpider ( N=25 million unique chemical compounds).

**Molecular Dynamic (MD) Simulation:-**

The MD simulation of a protein was first performed in the late 1970s .This powerful physical technique is used to predict the positions of Each atom in a molecular system with respect to time which is based On Newton's laws of motions governing interatomic interactions . The Forces between interacting atoms are estimated using a suitable force Field which is used to determine the overall energy of the system., MD simulations have been widely used for several reasons. The position and motion of every atom of the system are captured at every point in time, which is quite tough using any experimental technique. The simulation conditions are exactly known and can be carefully modulated.

**2. Ligand-Based Drug Design:-**

Ligand-based drug design is another widely used approach used in computer-aided drug design and is employed when the three-dimensional structure of the target receptor is not available. The information derived from a set of active compounds against a specific target receptor can be used in the identification of physicochemical and structural properties responsible for the given biological activity which is based on the fact that structural similarities correspond to similar biological functions . Some of the common techniques used in the ligand-based virtual screening approach include pharmacophore modelling, quantitative structure-activity relationships (QSARs), and artificial intelligence (AI).

**Pharmacophore Modelling:-**

A pharmacophore model elucidates the spatial arrangement of chemical features in ligands that are required for interaction with the target receptor . Some of the chemical features used in pharmacophore modelling include hydrogen bond donors, hydrogen bond acceptors, aromatic ring systems, hydrophobic areas, positively charged ionizable groups, and negatively charged ionizable groups. Ligands having different scaffolds but the similar spatial arrangement of key interacting functional moieties can be identified using pharmacophore-based virtual screening. The bioactive conformation of the molecules within the target binding site can be incorporated into the pharmacophore model. The pharmacophore model is also often used in QSAR studies in the molecular alignment stage. Some frequently used programs which allow automatic construction of the pharmacophore model include Catalyst, PHASE, Ligand

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Scout, GALAHAD, and Pharm Mapper .A good pharmacophore model also incorporates spatial constraints in regions occupied by inactive molecules and often optimized further to make the model less restrictive. All the pharmacophoric features which are not consistently detected in active molecules are either made optional or removed from the final model. The pharmacophore model generated should have optimum sensitivity and specificity to minimize the chances of false negative and false positive results and must be validated using an independent external test set . If the information about the 3D structure of a receptor and a set of known active compounds are lacking, then a sequence-derived 3D pharmacophore model is quite useful.[14]

**DRUG DISCOVERY AND DEVELOPMENT PROCESS:-**

Drug discovery can be defined as the process of identifying chemical entities that have the potential to be therapeutic agents. An important role of drug discovery campaigns is the recognition of new molecular entities that may be valuable in the treatment of diseases characterized as unmet medical needs. The development of a drug is a very complex process that can take about 5-10 years from the first idea to hitting the market and cost USD 1.7 billion. A new development idea, current requirements of the market, emerging diseases, academic and clinical research, commercial sector, etc. It can come from a variety of sources, including Once a target has been selected for discovery, the pharmaceutical industries or related academic centres work on early processes to identify chemical molecules with suitable properties to make targeted drugs.

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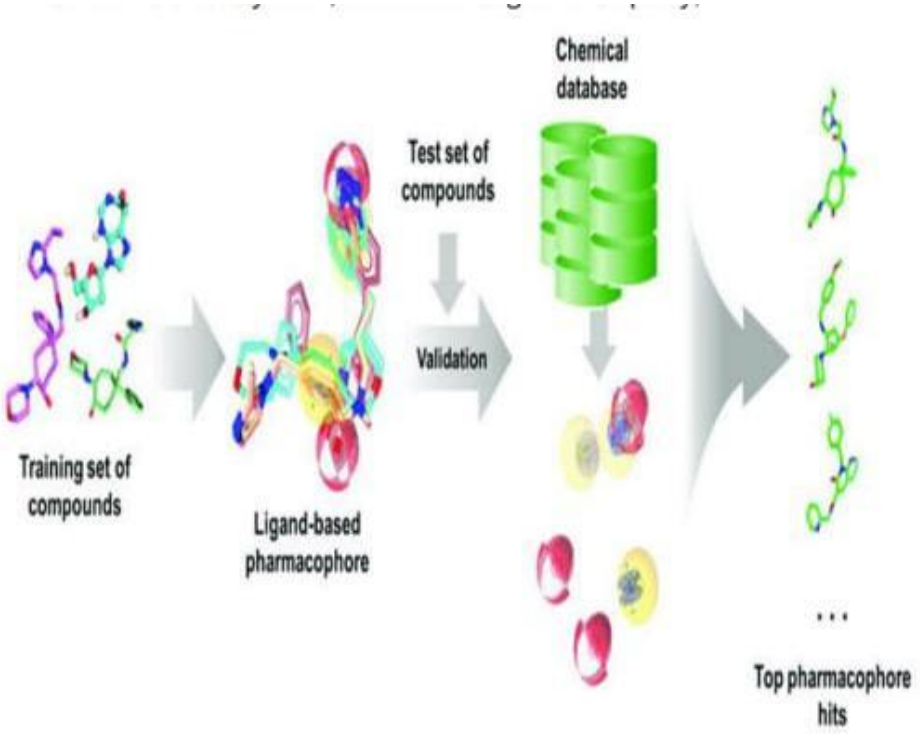
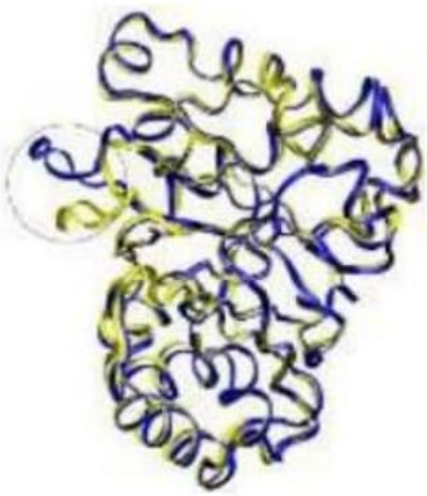



In the last few years, CADD has grown rapidly, reinforcing the perception of multifaceted and difficult biological processes. With the help of these computational tools, it is now possible to find new pharmacologically active agents in a short time.



**Docking:-**

Essentially, molecular docking aims to give a prediction of the ligand-receptor complex structure using computation methods . Docking can be achieved through two interrelated steps: firstime by sampling conformations of the ligand in the active site of the protein; then ranking these conformations via a scoring function. Ideally, sampling algorithms should be able to reproduce the experimental binding mode and the scoring function should also rank it highest among all generated conformations. From these two perspectives, we give a brief overview of basic docking theory.

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Fig. Superimposed apo- (in yellow) and holo- (in blue) crystal structures of triose phosphate isomerase. PDB code 1YPI and 2YPI, respectively.The 11 residue-loop composed of the landing site is the only region that has large motion upon ligand binding (in a circle).

## II. Conclusion:-

Drug design and discovery is a complex and multifaceted process that involves identifying potential drug targets, designing and synthesizing molecules that interact with those targets, and testing their safety and efficacy in preclinical and clinical trials. The process typically begins with target identification, which involves identifying the molecular structures or biological pathways involved in a disease. This information can be obtained through a variety of approaches, including genetic studies, bioinformatics, and high-throughput screening.The advent of new pharmacologic treatments and introduction of novel medications have reduced the serious complications of peptic ulcer disease. Similarly, thanks to many new antiviral medications with which the outlook for HIV-infected patients has improved. It is important that physicians understand the process of drug discovery and development. Structure-based and ligand-based drug design form two branches of the computer-aided drug discovery process which plays a significant role in the design and identification of drug molecules in reduced time and cost. Drug discovery is a high- risk, high-reward business that requires a multidisciplinary approach. Behind every successful drug, there are usually identifiable champions who have been prepared to stand by the drug through the tortuous route. The easiest decision at every stage of drug discovery is to kill the project, and there are usually reasons to consider doing so. Keen scientific judgment is required.The optimal unit for drug discovery integrates the science of the various functions including chemistry, biology, clinical science, and toxicology.[15]

## Acknowledgment

I would want to thanks everyone who helped me in this project. I want thanks my college principal Dr. Megha Salve mam and my mentor Mr. Abhijeet Shete sir, for their support and a lot of guideline in completing our review. His suggestions and remarks were helpful in finishing this review. Finally, I'D want to thank my brother and friends for their insightful criticism and support while I completed this review.

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