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CURRENT TRENDS IN COMPUTER - AIDED DRUG DESIGN; A COMPREHENSIVE REVIEW

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ABSTRACT

The process of discovering and developing a new medication is often seen as a lengthy and expensive endeavors. As a result, computer-aided drug design methods are now frequently utilized to improve the efficiency of the drug discovery and development process. Various CADD approaches are regarded as potential techniques based on their needs; nevertheless, structure-based drug design and ligand-based drug design approaches are well-known as highly efficient and powerful strategies in drug discovery and development. Both of these approaches may be used in conjunction with molecular docking to conduct virtual screening for the purpose of identifying and optimizing leads. In recent years, computational tools have become increasingly popular in the pharmaceutical industry and academic fields as a means of improving the efficiency and effectiveness of the drug discovery and development pipeline. In this post, we'll go over computational methods, which are a creative way of discovering new leads and assisting in drug discovery and development research.

KEYWORDS: Computer Aided Drug Design (CADD); Structure-Based Drug Design; Ligand-Based Drug Design; Virtual Screening and Molecular Docking.

INTRODUCTION

The Computer Aided Drug Design (CADD) represents the role in the modern strategy of the biomedical arena hat is emerging way to discovery and design of the new effective therapeutic agents with the help of computer in the drug design process.[1] A drug target is a key molecule involved in particular metabolic pathway which is associated with a specific disease, pathology, survival of microbial pathogen. A drug havea specific to target and it is very vast process or complex process. This process started when a chemist identifies the drug candidate, which shows the biological profile and completed the both optimized chemical synthesis and activity profile of the novel chemical entity.[2] Discovery and development of successful drug is generally known as very complex process, which takes about billion dollars and it also required minimum 12 years for fulfil high cost, insufficient long period of time the risk of the failure is increased to nearly 90% and almost 70%funds are costed on failure due to lack of efficiency or adverse side effects through clinical trials, So to come these problems CADD is used.[3,4]

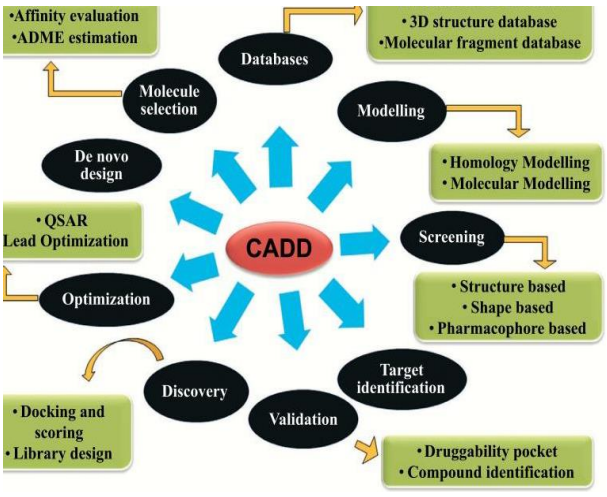


Figure 1: CADD.

NOTE: - In today's the fast growth in the field of pharmaceutical drugs and these drugs was discovered to use or variety of disease. For the reduction in the time and cost the computational approaches emerged in 1960's by Hansch and Fujita, used to mechanistic pathways of the disease, and analyze the drug.[9,10] Computer- aided drug design (CADD) is very useful tool in rational drug design. It is utilized to facilitate the target identification, validation, optimization of the

ADMET(absorption, distribution, metabolism, excretion and toxicity) profile of safe drug. The large amount of the selected molecules are synthesized compound are tested through biological assay and screens, takes lot of time and capital, but CADD has ability to reduce time duration and cost and also verify the period and biological activity of huge quantity of compounds with the help of CADD is possible to explain the molecular therapeutic activity.[5,11] There are so many antibiotic drugs are used in daily routine by the Human to kill the bacteria, which is responsible for bacterial infection. Some bacterial life resist to these antibiotics are called antibiotics drug resistance. So, it is needed to design and invent new antibiotics.[12,13] The identification of new antibiotic target is solution of the antibiotics resistance that represent novel mechanism essential for bacteria survival.

Structure based drug design

The structure of the target protein is known in structure based drug design (SBDD), and following docking, the interaction or bio-affinity for all tested compounds is calculated, allowing a new therapeutic molecule to be designed that has a better interaction with the target protein. These methods are very efficient and alternative approach to the discovery and development of drug design course. The three-dimensional (3D) structure of proteins (more than 100,000) are provided in SBDD.

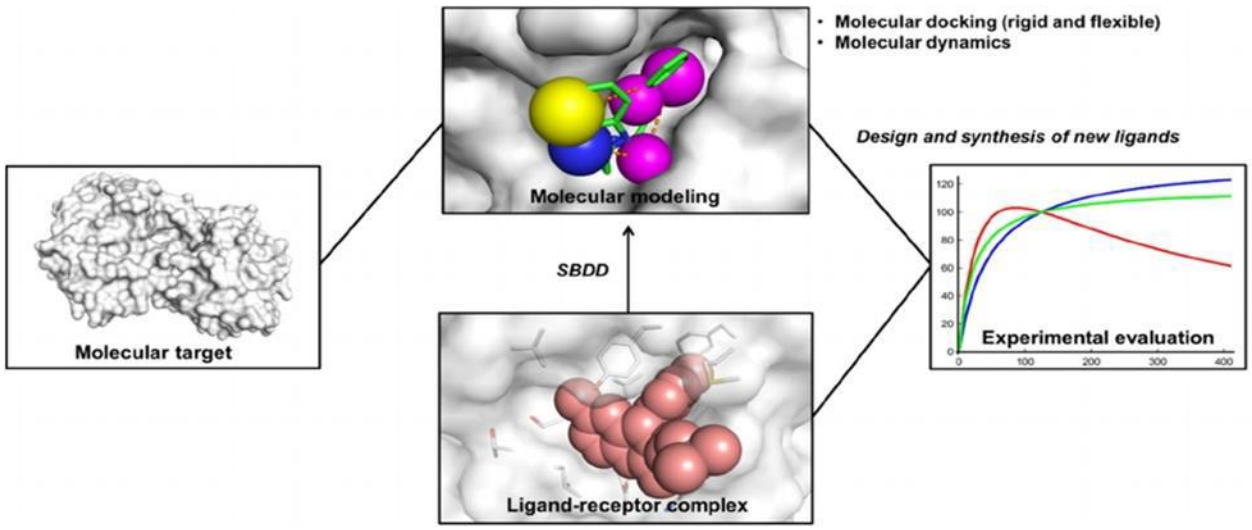


Figure 2: Layout of SBDD.

Ligand based drug design

The 3D structure of the target protein is unknown in ligand based drug design (LBDD), but the ligands that bind to the intended target location are. These ligands can be utilized to create a pharmacophore model or molecule that has all of the structural characteristics needed to bind to a target active site.

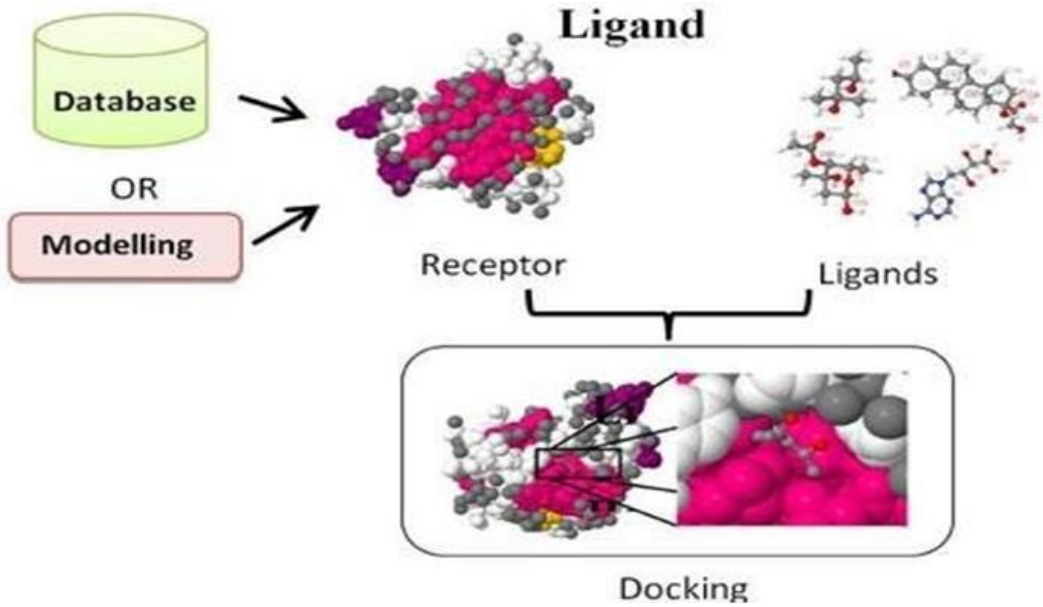


Figure 3: Outline of process involved in LBDD.

The pharmacophore-based method and quantitative-structure activity connections are two common ligand-based approaches (QSARs). In LBDD, substances with comparable structural similarities are considered to have similar biological actions and interactions with the target protein.

Virtual screening

Virtual screening is a computational method used in drug design. In this method the large libraries of compounds are bind with specific site on the target molecules such as- proteins and well-compounds tested. Virtual screening is also helping to find or identify those structures which are most likely to bind to a drug target (protein receptors or enzyme). Virtual screening has become an integral part ofdrug target (typically, protein receptor or enzyme) and drug discovery process. Although filtering chemical universe may be more practical virtual screening scenarios focus on optimizing targeted combinational libraries of available compounds from in-house compound repositories. Virtual screening is less expensive, less time consuming, scanning the larger number of potential drugs and also very faster than conventional screening.[14]

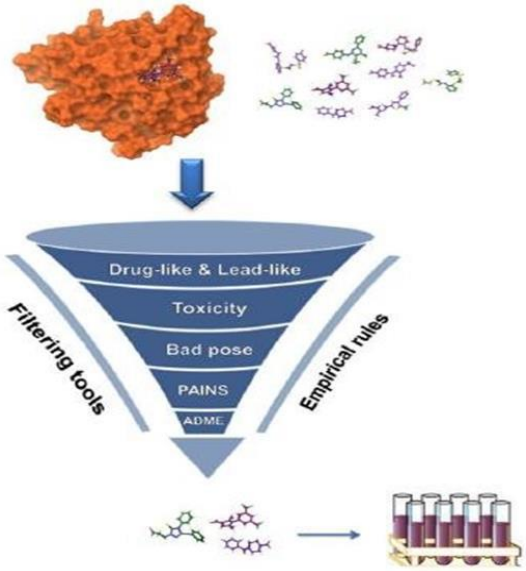


Figure 4: Virtual screening.

Molecular docking

Molecular docking is an in-silico approach for predicting the location of tiny molecules or ligands within their target protein's active region (receptor). It is primarily utilized to accurately estimate the most favorable binding modes and bio-affinities of ligands with their receptors, and it is now widely employed in virtual screening for lead compound optimization.

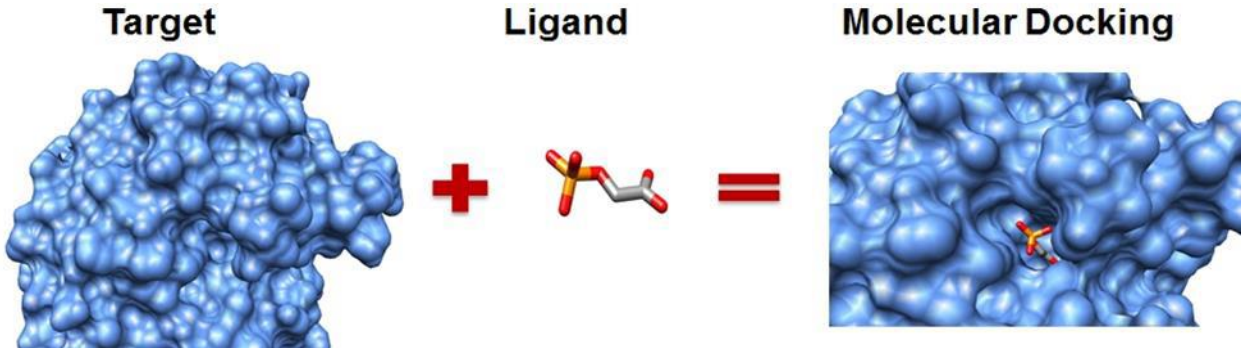


Figure 5: Molecular docking process.

Prediction of binding posture, bio affinity, and virtual screening are the three major aims of molecular docking technique, which are all interrelated. The search algorithm and scoring algorithms used in the molecular docking technique are the foundation tools for producing and evaluating ligand conformations.

Pharmacophore

The term "pharmacophore" refers to a schematic depiction of bioactive functional groups and their interatomic distance. During the late 1800s, ‘Paul Ehrlich' created the initial idea of the pharmacophore. At the time, it was thought that a biological impact was caused by certain chemical groups or functions of a molecule, and that compounds with comparable effects had similar functions.

Much later, in his book Chemo-biodynamics and drug design, ‘Suhveler' developed the term ‘pharmacophore,' which was described as a molecular framework that contains (phoros) the key characteristics responsible for a drug's pharmacon biological action. In computer-assisted drug design, the pharmacophore idea plays a critical role (CADD). The characteristics are pharmacophores that have been decreased by certain atoms and molecules. These compounds can be hydrogen bond donors or acceptors, cation, anionic, aromatic, hydrophobic, or any combination of these.

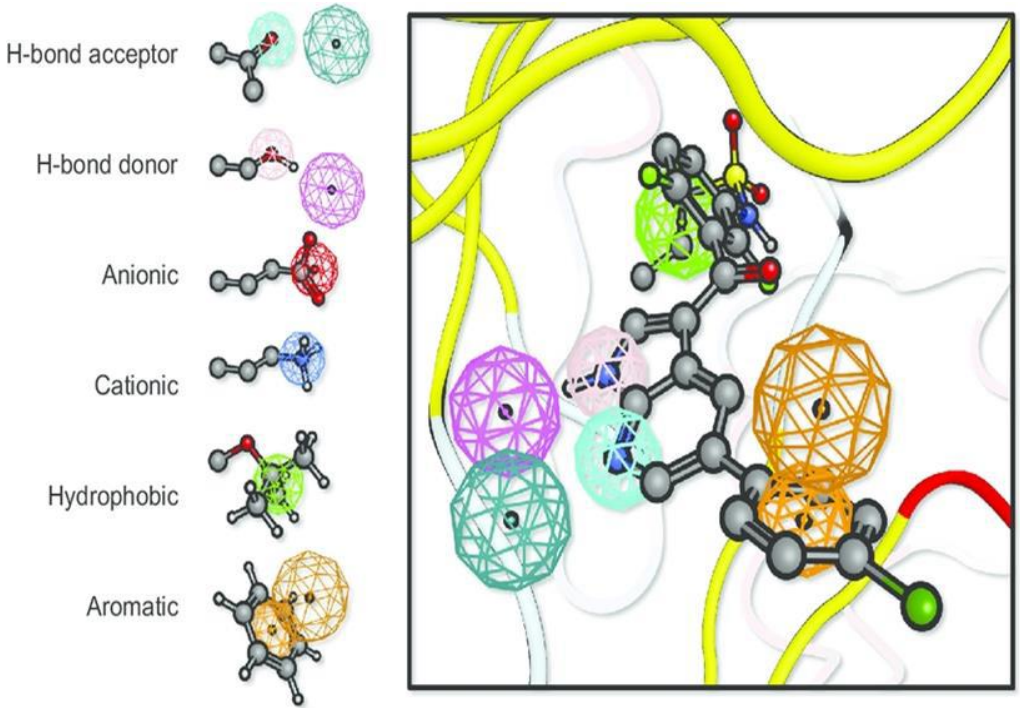


Figure 6: Overview of pharmacophore mapping.

Quantitative structure–activity relationship (QSAR)

The QSAR technique an essential part of drug optimization process. To Quantify the correlation between thechemical structure and biological process of a series of compounds the QSAR method is used.[15,16] The developed QSAR model is used as guiding tool for identification of compound to modification and also optimize the active compound to maximize relevant biological activity.

The methods some are used in QSAR

1. Experimentally measure value of desired biological activity and then, identify the ideal ligand
2. Determine molecular descriptors with physic-chemical properties of molecules.
3. The molecular description and biological activity correlation discover.
4. At the last test QSAR model for statistical stability.

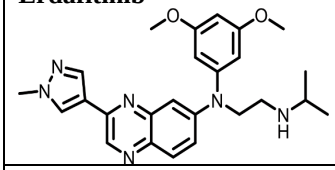
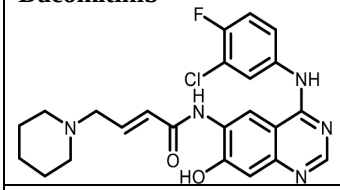
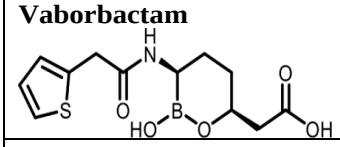
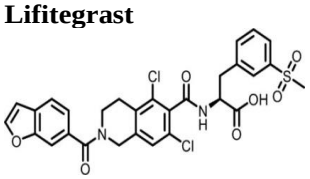
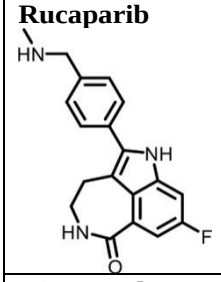
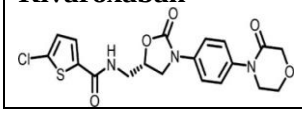
The work-flow of QSAR method

Firstly, identify or select the series of molecules or compounds with experimentally measured values of the desired biological activity. When the molecules are selected then, they are study in the silico-model by using molecular mechanism or quantum mechanical methods.[17,18-19] After identify active ligand, the molecular descriptors are generated for describe chemical features of molecules.[20] The determine suitable molecular descriptors with physico- chemical properties of molecules. Molecular descriptors is used to create a molecular.[21] 'Fingerprint' for each molecules. The knowledge-based, molecular mechanical or quantum chemical tools are used to generate molecular descriptors. Molecular descriptors used to develop a mathematical relation, which is explain about the variability of the biological activity of molecules. The final step is developed models are subject.[22]

Advantages of CADD

- We can save time and money by reducing the amount of synthetic and biological testing we do.
- It identifies the most promising therapeutic candidate by excluding molecules with unfavorable characteristics (low effectiveness, low ADMET, etc.) using in silico filters.
- It is a low-cost, time-saving, rapid, and fully automated procedure.
- We can learn about the drug-receptor interaction pattern from it.
- In compared to traditional high throughput screening, it provides compounds with high success rates by exploring vast libraries of compounds in silico.
- These methods reduce the likelihood of failures in the last phase.

Applications of CADD in drug

DRUG	TARGET	THERAPEUTICUSE	YEAR OF FDA APPROVAL	REFERENCE
Erdafitinib 	Fibroblast growth factor receptors (FGFR)	**Urothelial carcinoma**	2019	(Murray et al., 2019)
Dacomitinib 	**Multi-kinase**	**Non-Small-Cell Lung Cancer (NSCLC**	**2018**	**(Reed and Smaill, 2016)**
Vaborbactam 	beta-lactamase	Bacterial infections	2017	(Hecker etal., 2015)
Lifitegrast 	LFA-1/ICAM-1(leukocyte function-associated antigen-1/Intercellular Adhesion Molecule-1)	Dryeyedisease	2016	(Abidietal.,2016)
Rucaparib 	Poly(ADP-ribose)polymerase (PARP-1)	Prostate Cancer	2016	(Whiteetal., 2000)
Rivaroxaban 	ClottingFactorXa	DeepVenous Thrombosis(DVT)	2011	(Perzbornetal.,2011)

CONCLUSION

Computer-aided drug design (CADD) is a useful tool in the field of drug discovery and development since it allows us to quickly identify the most promising therapeutic candidates at a low cost. It always gives me optimism for progress in the field of drug discovery. Many amazing investigations have been accomplished in recent years thanks to computer assisted drug design, and it will continue to play an essential role in the near future. With present achievements, computer aided drug design has a promising future in aiding drug discovery of many more curatives in the future.

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Disclosure of conflict of interest

All the author approved the contents of the manuscript.

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