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Review Article

Advanced Applications of Computer Aided Drug Design in Pharmaceutical Sciences

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Abstract

The field of research known as computer-aided drug design (CADD) is expanding and has numerous facets. It includes a variety of practical and fundamental research facets. Both basic and applied research converge, enhancing each other's potential in the process. Quantum mechanics and molecular modelling research, including structure-based drug design, ligand-based drug design, database searching, and binding affinity based on knowledge of a biological target, are the theoretical underpinnings of CADD. Additionally, it offers alternatives for comprehending chemical systems in various ways, providing data that is difficult to collect through laboratory examination. The fact that CADD requires less time and money than laboratory studies is one of its main benefits. Therefore, the development of potential medications for treating a variety of diseases has become much more effective because to computer-aided drug design, or CADD. Drug discovery applications using the CADD methodology are advancing daily. Designing strong treatments with multiple targeted effects, more efficacies, and fewer side effects particularly hazardous one is the current trend in drug development. In this review we talk about the various applications of CADD in the field of pharmacy and healthcare system.

Keywords: Computer Aided Drug Design; Quantum Mechanics; Pharmacophore; Molecular Modelling Research; Docking

Introduction

The term "computer-aided design" describes the application of computer software to the design process in order to generate, alter, analyse, and improve a design. CADD is a widely utilised technology that makes use of tools for the management, analysis, and modelling of compounds in addition to computational approaches for the discovery, production, and evaluation of medicines and other physiologically active chemicals. It is essentially a software programme from which we obtain the activity of the structure, lead compound, or target we are searching for. Here, we can create a new molecule, dock it to the target protein, evaluate the molecule's interaction, infer the strength of the binding, and last, identify the drug candidate by inferring the molecule's drug-like features. The cost of drug research and development is decreased because to computer-aided drug design (CADD), which offers a variety of tools and approaches to help at different phases of drug design. There is no process like it in the business sector for finding new drugs, which is a lengthy, expensive, and highly dangerous process. As a result, the pharmaceutical industry frequently employs computer-aided drug design (CADD) techniques to expedite the procedure [1].

Using computational methods at the lead optimization stage of drug development has a major economic advantage. Pharmacological research laboratories invest a lot of money and time in the different stages of drug discovery, from therapeutic target setting candidate drug discovery to assessing the efficacy and safety of recently developed drugs, to drug optimization

through preclinical and extensive clinical trials. The ultra-high throughput screening (uHTS) of numerous drug-like compounds is a common practise that major pharmaceutical corporations have substantially engaged in Simultaneously, virtual screening is being used more and more in medication design and optimization [2].

History of CADD

A Summary of CADD's History P. Enrich (1909) and E. Fisher introduced the receiver and lock-key concept in 1900. The theory of quantitative structure relationships (QS-AR) was developed in the 1970s, although it had some drawbacks. The period of molecular modelling began in the 1980s with the introduction of 2-Dimensional, retrospective analysis, X-ray crystallography, multidimensional NMR, and computer graphics. Together and with chemical synthesis and throughput screening, additional inspection and maintenance like complete genomic bioinformatics were brought to the reducing field of medical science in the 1990s.

CADD process

CADD can be combined with wet laboratory techniques to elucidate and accelerate the drug discovery process to design new drugs (e. g antibiotics) for both known and novel targets. CADD simplifies the drug design process by minimizing time and cost targets. Figure 1 depicted the typical process of computer aided drug design.

Figure 1: Steps involved in computer Aided drug design (CADD).

Advantages of CADD

It is a Cost-effective Process, Time saving process, Fast and automated process, it gives an idea about the pattern of drug -receptor interaction, minimize synthetic and biological testing efforts, minimize synthetic and biological testing efforts and minimize the possibility of final stage Failure [2,3].

Stages of drug design

There are various stages i.e., used in the designing of drug some of these are best illustrated in figure 2 i.e., first one is disease selection then, selection of target drug then, define a bioassay which is followed by a finding of precursor compound with the determination of the structure of lead compound and finally define a SAR (structure activity relationship) [4].

Figure 2: Different Stages of drug design.

Commonly used methods in drug design

Computer-Aided Drug Design (CADD) has become a successful method for locating prospective lead compounds and assisting in the development of potential medications for a variety of ailments. Today, a variety of computational methods are being employed to pick out possible lead molecules from vast chemical libraries [5,6]. Drug Design can basically be divided into two types i.e., Structure based drug design or indirect drug design and Ligand based drug design or direct drug design. Figure 3 compiles basic components of computer aided drug design.

Figure 3: Classification of Computer Aided drug Design (CADD).

Structure based drug design

A possible drug binding site's 3D structure is defined using a process called structure-based design, which means that the target's known 3D structure when it is attached to a natural ligand or drug is identified by X-ray crystallography or NMR. This strategy of structure-based design of a known target leads to lead discovery. By understanding the ligand binding 3D structure, such as ZINC, virtual screening of a vast variety compounds can be carried out. By running docking tests on this molecular collection, such screening can find possible novel drugs. For the purpose of determining strength, clusters of molecules with comparable properties are frequently utilised to promote bound and hence improve binding affinity/specificity. High-throughput screening is being used (HTS). Structure-based drug design (SBDD) is based on the accessibility of the therapeutic target proteins' three-dimensional structures and examination of the binding site cavity. This method is precise and quick in the identification of lead molecules and their optimization, which has aided in the molecular understanding of disease. Structure-based virtual screening (SBVS), molecular docking, and molecular dynamics (MD) simulations are a few of the frequently used techniques in SBDD. These techniques have a wide range of uses, including the evaluation of binding energetics, protein-ligand interactions, and conformational changes in the receptor upon ligand binding. SBDD is a computational technique that is widely utilised in the pharmaceutical industry and by medicinal chemists. It has significantly aided in the discovery of many medications that are currently on the market. Examples include the identification of topoisomerase II and IV inhibitors for the antibiotic norfloxacin, which is frequently used to treat urinary tract infections, using SBVS, the discovery of dorzolamide, a carbonic anhydrase inhibitor used to treat glaucoma, and the discovery of amprenavir as a potential inhibitor of the human immunodeficiency virus (HIV) protease using protein modelling and MD simulations.

Target structure preparation, ligand binding site identification, compound library creation, molecular docking and scoring functions, molecular dynamic simulation, and binding free energy calculation are the fundamental procedures in SBDD [7,8]. Figure 4 portrays process of structure-based drug design. Table 1 outlines drugs discovered via structure-based drug design approach.

Figure 4: Typical Steps of Structure Based Drug Design.

Drug	Drug target	Target disease	Technique
Raltitrexed	Thymidylate synthase	Human immuno deficiency virus (HIV)	SBDD
Amprenavir	Anti retroviral protease	HIV	Protein modelling and molecular dynamics (md)
Isoniazid	Long chain enoyl-acyl carrier protein reductase (LNHA)	Tuberculosis	SBVS and pharmacophore modelling
Pim-1 kinase inhibitors	Pim-1 kinase	Cancer	Hierarchical multistage virtual screening (VS)
Flurbiprofen	Cyclo-oxygenase 2	Rheumatoid arthritis, Osteoarthritis	Molecular docking
Norfloxacin	Topoisomerase Ⅱ, Ⅳ	Urinary tract infection	SBVS
Dorzolamide	Carbonic anhydrase	Glaucoma, cystoid macular edema	Fragment based screening
Epalrestat[2]	Aldose reductase	Diabetic neuropathy	MD and SBVS

Table 1: Successful cases of drug discovery by structure based drug design methods.

Ligand based drug design

In this technique, it's essential to have a target detection approach that gives biological networks accurate information about the target candidates and position data. By comparing human functional genomes to the corresponding genetics of the pathogen, diseases brought on by exogenous pathogens like bacteria and viruses may uncover pathogen-specific targets. The *Helicobacter pylori* (*H. pylori*) genome was completely sequenced using the subtractive genome approach, which also revealed a collection of genes that are crucial for pathogen survival but are absent in humans. The term "indirect drug design" also applies to LBDD. When the three-dimensional structure of the protein target is unavailable, other methods, such as pharmacophore models, quantitative structure-activity relationships (QSAR), molecular shape-based superposition, and others, are used to build a structure-activity relationship or pharmacophore model. Depending on the amount of information provided, a suitable research methodology must be chosen. Results will be more dependable if the information is more correct. A strategy known as "ligand-based drug design" depends on understanding the compounds that bind to the desired biological target when 3D information about the receptor is lacking. In ligand-based drug design, pharmacophore modelling and 3D quantitative structure activity relationships (3D QSAR) are the most significant and often utilised technologies. For the discovery and optimization of leads, they can offer suitable prediction models. Therefore, some steps are involved in ligand-based drug design which is illustrated in figure 5 [9-12].

Figure 5: Steps involved in Ligand Based drug design.

Virtual screening

Virtual screening is a computer-aided technique which aids in the identification or search of the closest substance or molecule that is likely binding to the target molecule. Virtual screening refers to the in-silico screening of a large number of chemical compounds from component libraries against biological targets.

Protein-ligand complexes are evaluated using molecular docking-based virtual screening methods, and their scores are correlated with the expected binding affinities, which can be determined using a physics-based, empirical, or knowledge-based potential function. Virtual screening tools that are frequently used include Auto Dock, Auto Dock Vina, MOE, GLIDE, Discovery Studio, etc. The pan assay interference chemicals (PAINS) are removed from screening libraries and excluded from biology tests using the internet service PAINS-Remover, which is designed and built for this purpose. According to the Swiss ADME website, online physicochemical descriptions of substances, including their absorption, distribution, metabolism, elimination, and toxicity, are predicted. To increase the success rate of medication research and lessen the issue of money being lost in the later stages of drug development, these virtual screening and compound optimization filtering tools are required [13-15]. Virtual screening is done with different softwares that is represented in figure 6.

Figure 6: Virtual Screening with different softwares.

Biological assay

In CADD applications, a follow-up biological assay is essential to assist calibrate theoretical results with experimental results. Experiments at the molecular, cellular, and animal levels as well as pharmacokinetics are all included in the evaluation and validation of experimental results. The compounds that perform well in each experiment are examined, and those that are chosen as medication candidates [16,17]. There are some processes that are involved in the biological assay Which is illustrated in figure 7.

Figure 7: Steps Involved in Biological Assay.

Prediction and analysis of protein structure

It is based on two significant findings to predict and analyse protein structure using CADD: Homology modelling. A protein's 3D structure is largely influenced by the amino acid sequence that makes up the protein. Second, in comparison to the sequencing, the protein structure is more conserved and evolves at a far slower rate [18]. The following points are considered while designing protein structure.

- Finding a similar protein structure that may be used as template.
- Alignment of target and template protein
- Model validation and assessment

Multi-target searching and designing through CADD

Utilizing the CADD approach, it is possible to find hits for each target while simultaneously searching for medications against a range of targets. The true-hits rates should be higher than the false-hits rates against the targets when doing multi-target searches for enrichment in 60, 61, and 62 [19].

Quantitative structure activity relationship (QSAR) studies through CADD

The link between chemical structure and biological activity is explained by QSAR using a mathematical formula. The QSAR method's main advantages are the features of novel chemical compounds that can be discovered without the need for their production or testing. Furthermore, investigations connect each of them to physiological traits, biological activities, and substance structure descriptors. Through QSAR models, we can relate a variety of characteristics, such as binding sites, rate constants, ligand affinities, inhibition constants, and other biological activities, to either specific structural characteristics or to atomic, molecular, or group characteristics like lipophilicity, electronic, steric, and polarizability among congeneric series of compounds [20]. Types of QSAR is best described in figure 8.

Figure 8: Types of QSAR.

Pharmacophore development through CADD (computer aided drug design)

A pharmacophore is a three-dimensional arrangement of chemical functional groups that is in charge of biological action. Pharmacophore models are now created as part of drug research, design, optimization, and development. With enough diverse

ligands, a pharmacophore model of the receptor site can be produced. Pharmacophore modelling has produced successful results for smaller, non-peptide compounds that may be more stable and bioavailable than their peptide counterparts [21-24].

Figure 9: Pharmacophore development Process Through CADD.

S. no.	Tools	Description
1.	Pharmer	This tool uses compound for virtual screening
2.	Pharmapper	It provides knowledge of more than 7000 target based pharmacophore models and gives the best input match as a ligand against pharmacophore based models
3.	Pharmacist	This tool searches from a set of ligands in the absence of a target
4.	Pharmit tool	This depends on drug monitoring on pharmacokinetics
5.	Discovery studio	This is used for drug monitoring
6.	Ligand scout	It models 3d pharmacophores from structural data either as test set of molecules

Table 2: Tools used for pharmacophore modelling and its applications.

CADD for EGFR protein controlling lung cancer

The receptor tyrosine kinase epidermal growth factor receptor (EGFR) is crucial for the survival of tumour cells. Following activation, phosphorylated EGFR triggers the phosphorylation of downstream proteins, which alters cell proliferation, invasion, metastasis, and the prevention of apoptosis. Commercially accessible medications including Gemzar, gefitinib, and tarceva were used as ligands while human EGFR was taken as a protein. Gefitinib and tarceva were selected based on their energy levels when these medications were bound to this receptor. Modifications to the likely functional groups that were interacting with the receptor molecules were made in order to increase the binding effectiveness and steric compatibility of these two medicines. Analogs were created using ACD chem sketch in MOL Format, and a 3D modelling tool called Weblab viewer light was used to transform them into 3D structures. Then, docking software called Vega ZZ was used to dock it. Tarceva Analog 7 and Gefitinib Analog 2(281) were shown to be superior than commercially available conventional medications due to their much lower energy values [25]. Some structures of Gefitinib analog and Tarceva analog is best depicted in figure.

Figure 10: Structures of Gefitinib Analog 2 and Tarceva Analog 7 with their standard ligands for EGFR.

Structure based virtual screening (SBVS) for the identification of new chemotypes for FLT3 inhibition

Hematopoietic stem and progenitor cells have high levels of the type III tyrosine kinase receptor known as FMS-like tyrosine kinase 3 (FLT3). When FLT3 binds to an external domain, cytoplasmic tyrosine kinase activity is activated, which in turn triggers downstream cell signalling that is necessary for proliferation. The inhibitors are classified as Type I or Type II inhibitors depending on where the Phe residue is located in the DFG motif. The Phe residue is orientated inside the ATP BINDING SITE in a DFG-out conformation as opposed to outside the ATP BINDING SITE in a DFG-in conformation. Type II inhibitors are those that bind to the DFG-out conformation, while type I inhibitors attach to the DFG-in conformation. Acute myeloid leukaemia can be treated more successfully with type inhibitors because they bind FLT3-ITD-mutated kinase tightly.

Docking experiments using known DFG-in (SU11248, CEP-701, AND PKC-412) and DFG-out (SORAFENIB, ABT-869, and AC220) FLT3 INHIBITORS are identified by homology modelling (HM) of the DFG-in-FLT3 structure [26-28].

Fragment based drug design to target the EphA4 kinase domain

The first licenced medication created using a fragment-based strategy is VEMURAFENIB, a kinase inhibitor of the oncogenic B-Raf V600E mutation. An unselective 7-AZAINDOLE fragment was obtained as a hit fragment from high content screening (HCS), a type of phenotypic screening, and then it was optimised by 2 into the selective B-Raf inhibitor PLX472077 to produce vemurafenib PLX4032 [18,20]. Process for the formation of Vemurafenib (PLC4032) from 7 - Azaindole is illustrated in figure 10.

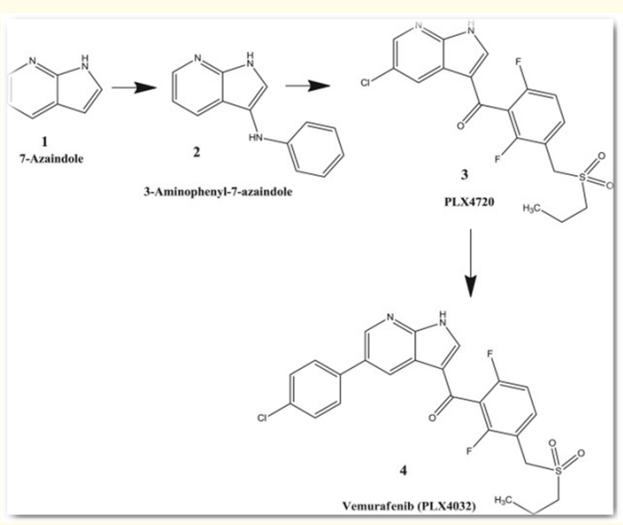

Figure 11: Process for the formation of Vemurafenib from 7 - Azaindole which is used in the fragment-based drug design.

S. no.	Program	Availability	Search method
1	AutoDock	Freely available	Genetic algorithm
2	Dock	Freely available	Shape fitting
3	LigandFit	paid	Monte Carlo
4	Surflex.docx	paid	Incremental construction
5	FRED	Freely available	Shape fitting
6	FleXX	paid	Incremental construction

Table 3: List of major docking tools.

Drug	Biological action	Year of approval
Captopril	Anti hypertensive	1981
Dorzolamide	Carbonic anhydrase inhibitor	1995
Indinavir	Human immunodeficiency virus	1996
Ritonavir	Human immunodeficiency virus	1996
Saquinavir	Human immunodeficiency virus	1995
Triofiban	Fibrinogen antagonist	1998
Raltegravir	Human immunodeficiency virus	2007
Zanamivir	Neuraminidase inhibitor	1999
Aliskiren	Human renin inhibitor	2007
Boceprevir	Hepatitis c virus (HCV) inhibitor	Phase Ⅲ clinical trials
Nolatrexed	Liver cancer	Phase Ⅲ clinical trials
Tmi-005	Rheumatoid arthritis	Phase Ⅱ clinical trials
Oseltamivir	Active against influenza a and b viruses	1999
Ly-517717	Serine protease inhibitor	Phase Ⅱ clinical trials

Table 4: List of clinically approved drugs discovered by CADD.

Recent trends in drug designing

A specialised field called computer-aided drug design (CADD) employs computational techniques to promote drug receptor interactions. The tools, programmes, and databases used in bioinformatics are strongly reliant on CADD techniques. As a result, CADD research and bioinformatics have a lot in common. Regarding CADD research, there are a number of crucial bioinformatics

fields. The process of drug reprofiling allows researchers to find all possible uses for a given substance that go beyond its current or experimental uses. As new indications of either approved, unsuccessful, or abandoned compounds are found for use in treating various diseases, the idea is known as drug reprofiling.

Conclusion

The development of various novel approaches in molecular biology, biotechnology, genomics, and bioinformatics during the 1990s revolutionised the drug discovery process. High throughput screening (HTS) is an effective method for accelerating the screening process. The advantage of target-oriented development is that receptors like G-protein coupled receptors (GPCRs) have been successfully addressed. Despite this, there aren't many new therapeutics being discovered, making the drug discovery process time-consuming, expensive, challenging, and ineffective. There may have been a decrease in the no. of new drugs as well.

Bibliography

1. Savant B., *et al*. "A review on computer aided drug design and its implications in drug discovery and development process". (2019).
2. Song CM., *et al*. "Recent advance in computer aided drug design". *Brief in Bio Information* (2009).
3. Hughes JP. "Principles of early drug discovery." *British Journal of Pharmacology* 162.6 (2011): 1239-1249.
4. Crasto AM. "All About Drugs. Mumbai, India".
5. Lionta G., *et al*. "Structure-based virtual screening for drug discovery: Principles, applications and recent advances". *Current Topics in Medicinal Chemistry* 14 (2014): 1923-1938.
6. Kalyaanamoorthy S and Chen YP. "Structure-based drug design to augment hit discovery". *Drug Discovery Today* 16 (2011): 831-839.
7. Anderson AC. "The process of structure-based drug design". *Chemistry and Biology* 10 (2003): 787-797.
8. Wlodawer A and Vondrasek J. " Inhibitors of HIV-1 protease: A major success of structure-assisted drug design". *Annual Review of Biophysics and Biomolecular Structure* 27 (1998): 249-284.
9. Clark DE. "What has computer-aided molecular design ever done for drug discovery". *Expert Opinion Drug Discovery* 1 (2006): 103-110.
10. Rutenber EE., *et al*. "Binding of the anticancer drug zd1694 to E. Coli thymidylate synthase: Assessing specificity and affinity". *Structure* 4 (1996): 1317-1324.
11. Laurie AT., *et al*. "Q-SiteFinder: An energy-based method for the prediction of protein-ligand binding sites". *Bioinformatics* 21 (2005): 1908-1916.
12. Maria Garcia-larrosa and Maria Baer R. "FLT3 inhibitors in acute myeloid leukemia: current status and future directions". (2017): 991-1001.
13. Zhang Y., *et al*. "Identification of covalent binding sites targeting cryteines based on computational approaches". *Molecular Pharmaceutics* 13.9 (2016): 3106-3118.
14. Grant MA. "Protein structure prediction in structure-based ligand design and virtual screening". *Combinatorial Chemistry and High Throughput Screening* 12 (2009): 940-960.
15. Pau L., *et al*. "Teleonomic acid binding pocket in prb from liberibacterasiaticus". *Frontiers in Microbiology* 8 (2017): 1591.
16. Ajjarapu Suchitra. Computer-Aided Drug Design (CADD)-Definition, Types, Uses, Examples, Softwares (2022).
17. Tardif JC., *et al*. "Treatment With 5-Lipoxygenase Inhibitor VIA-2291 (Atreleuton) In Patients with Recent Acute Coronary Syndrome". *Circulation: Cardiovascular Imaging* 3.3 (2010): 298-307.
18. Gajipara Janvi and Georrge John J. "TOOLS FOR LIGAND BASED DRUG DISCOVERY". *Recent Trends in Science and Technology* (2018).
19. Ramen Kalita, Ali Amir, chapter-3 applications of computer aided drug design in drug discovery, Akinik publications 43-53.
20. Sliwoski Gregory., *et al*. "Computational Methods in Drug Discovery". *Pharmacology Review* 66.1 (2014): 334-395.
21. Abrams CF and Vanden-Eijnden E. "Large-scale conformational sampling of proteins using temperature-accelerated molecular dynamics". *Proceedings of the National Academy of Sciences of the United States of America* 107 (2010): 4961-4966.

22. Salman M., *et al*. "Advances in applying computer-aided drug design for neurodegenerative diseases". *International Journal of Molecular Sciences* 22.9 (2021): 4688.

23. Surabhi S and Singh BK. "Computer aided drug design: an overview". *Journal of Drug delivery and Therapeutics* 8.5 (2018): 504-509.

24. Macalino SJ., *et al*. "Role of computer-aided drug design in modern drug discovery". *Archives of Pharmacal Research* 38.9 (2015): 1686-1701.

25. Xiang M., *et al*. "Computer-aided drug design: lead discovery and optimization". *Combinatorial Chemistry and High Throughput Screening* 15.4 (2012): 328-337.

26. Mei Wu., *et al*. "FLT3 inhibitors in acute myeloid leukemia". *Journal of Hematology and Oncology* (2020): 682-696.

27. Dohner H. "Acute myeloid leukaemia". *The New England Journal of Medicine* 373 (2015): 1136-1152.

28. Baig H M., *et al*. "Computer aided drug design: success and limitations". *Current Pharmaceutical Designs* 22.5 (2016).