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A REVIEW ARTICLE ON COMPUTER AIDED DRUG DESIGN

Ritesh R. Dabhere*, Pratiksha V. Jadhao, Pratik S. Jaiswal, Ashish S. Kanthale, Farheen A. Shah

Asst. Prof, Jagadambha Institute of Pharmacu and Resrarch, Kalamb-445404, Maharashtra, India.

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***Corresponding Author**
Ritesh R. Dabhere
Asst. Prof, Jagadambha Institute of Pharmacu and Resrarch, Kalamb-445404, Maharashtra, India.

ABSTRACT

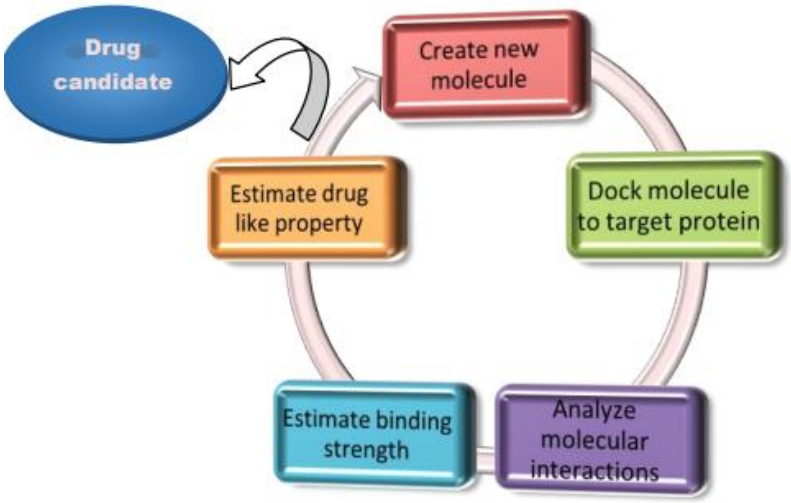
Computer Aided Drug Design (CADD) is an innovative approach that combines computational method and technique to expedite the drug discovery and development process. By utilizing computer algorithms, molecular modelling, and stimulations, CADD helps in identifying potential drug candidates, predicting their interactions with target protein, and optimizing their properties. This abstract explores the various components of CADD, including virtual screening, molecular docking, and quantitative structure activity relationship (QSAR) analysis, highlighting its significant impact on accelerating the drug discovery pipeline and improving the efficiency of pharmaceutical research.

KEYWORDS: *Molecular modelling, molecular docking, molecular dynamics stimulations, QSAR technique, bioinformatics*.

INTRODUCTION

Medicine discovery is a lengthy process that takes around 10- 15 times[4] and costs up to2.558 billion USD for a medicine to reach the request.[5] It's a multistep process that begins with the identification of suitable medicine target, confirmation of medicine target, hit to lead discovery, optimization of lead motes, and preclinical and clinical studies.[6] Despite the high investments and time incurred for the discovery of new medicines, the success rate through clinical trials is only 13 with a fairly high medicine waste rate. CADD correspond use of any software program grounded process for establishing a standard to relate exertion to structure. This review composition provides useful perceptivity into some of the common in silico

styles used in CADD and how these styles have been presently used and can be of help in the medicine discovery process of COVID- 19.[7]



General Principle for Drug design through CADD

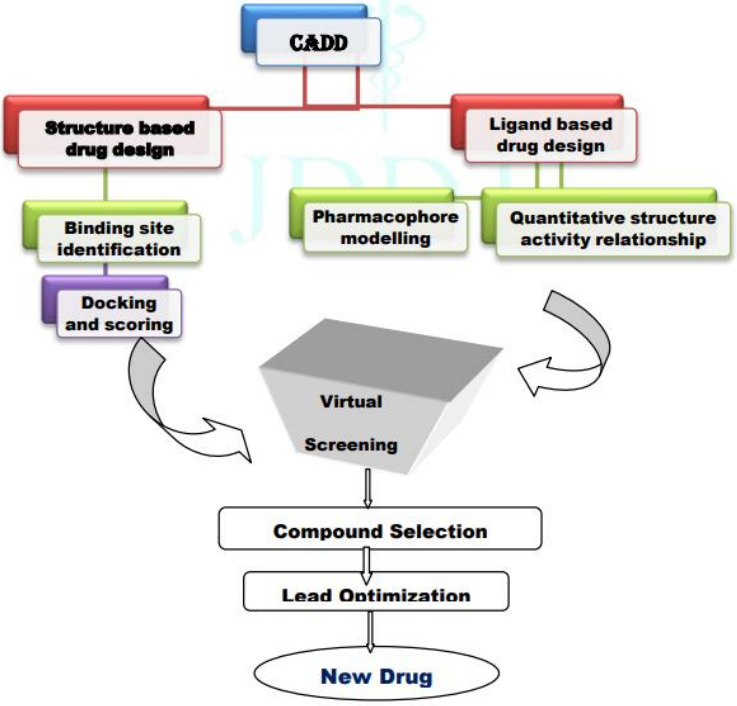
Objective of CADD

1) Random screening against illness assays.
2) Targeted screening against disease assays.
3) Synthetic chemicals vs. natural products.
4) Rational medicine development and testing.
5) Increase the speed of the screening process.
6) Increase the efficiency of the screening.
7) Design from scratch.
8) Testing as part of the design process.
9) Fail medications quickly.

Major types of approaches in CADD

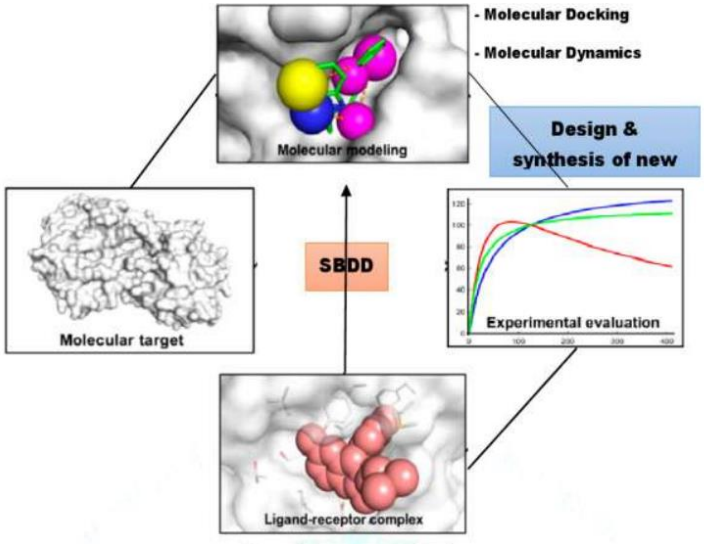
There are substantially two types of approaches for medicine design through CADD is the following

1. Structure grounded medicine design/ direct approach.
2. Ligand grounded medicine design/ circular approach.



STRUCTURE BASED DRUG DESIGN

The vacuity of the three- dimensional structure of the remedial target proteins and disquisition of the list point depression forms the base of structure- grounded medicine design (SBDD).[8] This approach is specific and effectively presto in the identification of lead motes and their optimization which has helped to understand complaint at a molecular position.[9] Some of the common styles employed in SBDD include structure- grounded virtual webbing (SBVS), molecular docking, and molecular dynamics (MD) simulations. These styles find multitudinous operations similar as assessment of binding energetics, protein- ligand relations, and conformational changes in the receptor upon binding with a ligand.[10]



LAYOUT OF SBDD

Ligand Based Drug Design

Ligand- grounded medicine design is another extensively used approach used in computer-backed medicine design and is employed when the three- dimensional structure of the target receptor isn't available. The information deduced from a set of active composites against a specific target receptor can be used in the identification of physicochemical and structural parcels responsible for the given natural exertion which is grounded on the fact that structural parallels correspond to analogous natural functions.[11] Some of the common ways used in the ligand- grounded virtual webbing approach include pharmacophore modelling, quantitative structure- exertion connections (QSARs), and artificial intelligence (AI).

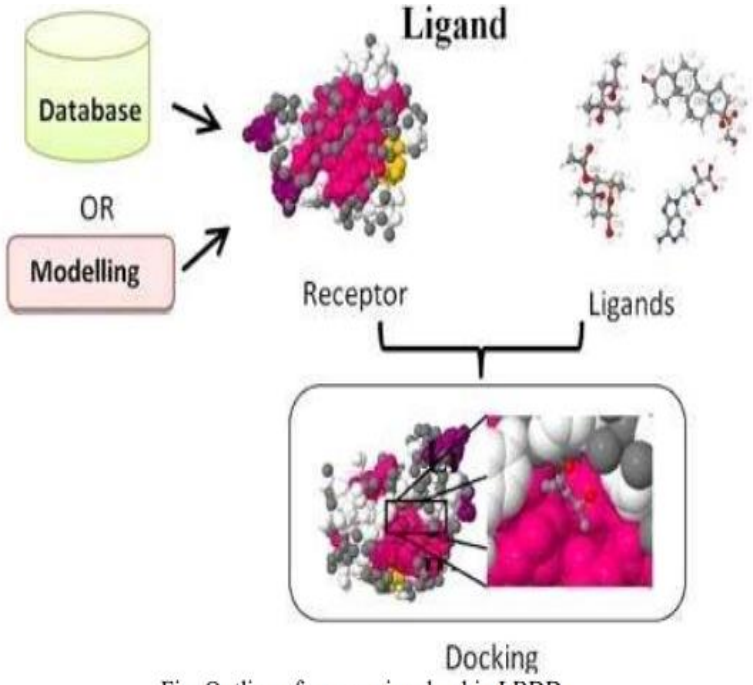


Fig: Outline of process involved in LBDD

WORKING OF CADD

Computer backed medicine designing process consists of 3 stages

Stage 1 Involves identification of remedial target and erecting a heterogenous small patch library to be tested against it. There's development of virtual webbing protocol initialised by docking of small motes.

Stage 2 The named successes are checked for particularity by docking at binding spots of other known medicine targets.

Stage 3 The named successes are subordinated to computational ADMET profiling studies and those who pass these studies are called leads.[12]

- **Target Identification**

It's the first crucial stage in the medicine discovery channel. Identification of correct targets from thousands of seeker macromolecules is a tedious process, which can be achieved by literature pertaining, Genomic analysis, pathway analysis.[12]

- **Target Validation**

After target identification, a rigorous evaluation is needed to demonstrate that modulation of target will have desired therapeutic effect. Target validation process determines whether modulation of target will have desired therapeutic effect.[13]

- **Lead**

Leads can be linked with the help of ways like Structure grounded design. At this point, the structure of the target protein in complex with the lead patch can be extremely useful in suggesting ways to ameliorate the affinity of the lead for the target. Leads which are used in this case may be far from perfect, therefore they should be optimised in order to increase their affinity for the target spots. Optimisation may be attained by altering their structural features.[14]

- **IN SILICO ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity)**

Prediction Techniques like molecular modelling, data modelling are used to study the interaction of proteins involved in ADMET process.[15]

- **Parameters considered for drug design**

Whole Genome Sequence Analysis

Medicine design is deficient without mortal genome design. With the help of inheritable law, the complete Genome has been utilised to find the nature and structure of the receptors. Once the structure of receptor is known it becomes easy to design a patch (medicine) which can bind to it.[16]

- **Structure activity relationship determination**

This is done with the help of tool 3DQSAR (Quantitative Structure Activity Relationship). It is used to help guide chemical synthesis. It is responsible for quantifying relationship between structure and biological data and is useful for optimizing the groups that modulate the potency of the molecule.[17]

- **ADME (Absorption, Distribution, Metabolism, Excretion)**

The description of drug distribution and elimination are often called drug disposition. Characterisation of drug disposition is important for determination of dosing intervals.[18]

Advantages

a) Cost savings.

b) Time- to- request, as CADD's prophetic power aids in the identification of prospective supereminent campaigners, reducing time spent on dead ends.

c) Assists scientists in reducing the quantum of time and plutocrat spent on synthetic and natural testing by fastening solely on the most promising substance.

Disadvantages

a) Targeted systems are cleared quickly.

b) Immune reactivity to carrier systems given intravenously.

c) Inadequate targeting of targeted systems within tumor cells.

d) Drug release diffusion and redistribution

e) Formulation necessitates exceedingly advanced technologies.

e) Manufacturing, storage, and administration skills are required.

f) Toxicity symptoms may result from drug accumulation at the target site.

g) It's difficult to keep the dosage form stable.[19]

Methods

- **Molecular docking and its role in CADD**

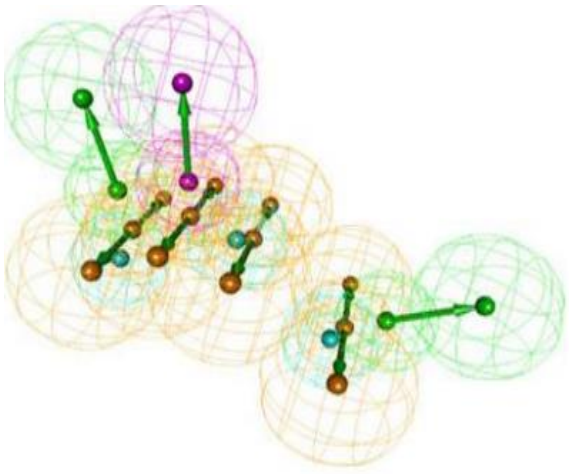
In molecular docking, the three-dimensional structures of both the target protein and the small molecule are used to predict their optimal spatial arrangement and binding orientation. Various algorithms and scoring functions are employed to calculate the binding energy or affinity between the two molecules, which helps in evaluating the likelihood of a successful drug protein interaction. One popular docking algorithm is AutoDock, which uses a combination of genetic algorithms and empirical force fields to explore the conformational space of the ligand (small molecule) within the binding site of the protein. AutoDock can predict the binding poses and affinities of ligands with high accuracy, making it a widely used tool in CADD research.

There are also other docking software available, such as AutoDock Vina, DOCK, and GOLD, each with its own unique algorithms and features. These tools provide a user-friendly interface for setting up docking experiments and analysing the results.[20]

- **Pharmacophore modelling for identifying key features in potential drug candidates**

By analysing the structure of known active compounds and their interactions with the target protein, pharmacophore modelling aims to generate a three-dimensional representation of the common features necessary for activity. These features can include hydrogen bond acceptors/donors, aromatic rings, hydrophobic regions, or specific spatial arrangements of functional groups. The generated pharmacophore model can then be used to screen large compound databases to identify molecules that share similar features and have the potential to interact with the target protein.

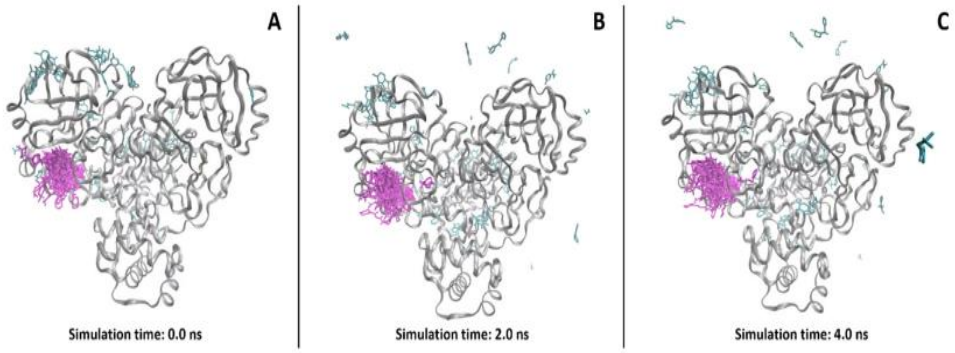
There are several software tools available for pharmacophore modelling, such as Maestro, Discovery Studio, and MOE, which provide user-friendly interfaces for building and validating pharmacophore models. These tools utilize sophisticated algorithms and scoring functions to enhance the accuracy and reliability of the models.[21]



- **Molecular dynamics simulations to study the stability and dynamics of drug-protein interactions**

In MD simulations, a three-dimensional model of the drug-protein complex is built, and the equations of motion are numerically solved for all atoms in the system. The interactions between atoms are described by force fields that capture the potential energy associated with bonded and non-bonded interactions. By iteratively solving these equations, the behaviour and dynamics of the system can be modeled over nanosecond to microsecond timescales.

Through MD simulations, researchers can investigate critical aspects of the drug-protein complex, such as binding stability, conformational changes, and intermolecular interactions. These simulations provide valuable information about the dynamic behaviour of the complex, including insights into binding kinetics, ligand diffusion, and flexibility of both the drug and the protein.[22][23]



Applications

- CADD's contribution to the discovery of novel drugs
- Optimization of existing drugs using CADD
- CADD's role in personalized medicine and drug repurposing.

Strengths and Challenges of CADD in COVID-19 Research

With the steady rise in the number of verified positive and death cases from SARS- CoV- 2 infection, computer- backed medicine design (CADD) emerges as a fast and dependable fashion in medicinal and medicinal exploration since it not only saves time but also helps to cut costs of designing remedial agents.[24] Further, realizing the inflexibility of COVID- 19 and the lack of approved remedial agents clearances the need for chancing potent medicines in lower time, and the CADD system makes this possible by easing the discovery of new medicines or repurposing FDA- approved medicines whose safety 12 BioMed Research International and adverse goods are formerly known.[25] Since the essential insubstantiality of the SARS- CoV- 2 genome may hamper complaint forestallment and treatment, CADD can be used efficiently to prognosticate the goods of mutation on medicine list with the molecular receptors.[26] thus, CADD can greatly help in accelerating the medicine discovery and development process. Still, CADD styles have some limitations similar as lead motes deduced from the virtual webbing process that still need confirmation through preclinical and clinical assessments before request blessing.[27] The fact that the molecular medium studies underpinning the complaint pathogenesis of COVID- 19 are still underway, and the actuality

of bias and imbalance in the limited data available can have a major impact on the vaticination delicacy of CADD styles similar as artificial intelligence.[28]

Molecular Descriptors

Molecular descriptors can include parcels similar as molecular weight, figure, volume, face areas, ring content, rotatable bonds, interatomic distances, bond distances, snippet types, planar and nonplanar systems, molecular walk counts, electronegativities, polarizabilities, harmony, snippet distribution, topological charge indicators, functional group composition, aromaticity indicators, solvation parcels, and numerous others[29] These descriptors are generated through knowledge- grounded, graph-theoretical styles, molecular mechanical, or amount-mechanical tools[30,31] and are classified according to the dimensionality ‖ of the chemical representation from which they are reckoned[32]

1- Dimensional (1D), scalar physicochemical parcels similar as molecular weight;
2- 2D, molecular constitution- deduced descriptors;2.5 D, molecular configuration- deduced descriptors;
3- 3D, molecular conformation- deduced descriptors. These different situations of complexity, still, are lapping with the more complex descriptors, frequently incorporating information from the simpler ones.

Quantitative Structure Activity Relationship (QSAR) Studies Through CADD

For many cases in which structural based approaches are not applicable because of absence of target macromolecule structure information, in those cases QSAR approach is used.[33,34] QSAR gives information about relationship between chemical structure and biological activity in the form of a mathematical expression. The main advantages of QSAR method is to identification of properties of novel chemical compounds in which there is no need of synthesis and testing of them. Studies also relate all of them like structural descriptor of compounds, physiological properties and biological activities.[35]

Conformation Generation Through CADD

One of the important aspects of medicine design and development is that generation of conformation of small emulsion because it governs the physical and natural parcels. It's necessary that conformer should have reasonable energy and good list property in relation to a particular target. Cyndi is a largely effective system of conformation generation. It's grounded upon MOEA i.e., multi-objective elaboration algorithm. Through using MOEA, Cyndi searches the conformational space in constant time, also controls geometric diversity

as well as energy availability. Another bone is Marco Model integrated in MaestroV7.5 (Schrodingerinc) which is different from Cyndi in terms of slice depth of conformational space and the conformational cost.[36,37]

Clinically Approved Drug Discovered Through CADD Approaches

Some examples of clinically approved drugs with year of approval and therapeutic actions developed through CADD approaches have been shown in Table.

LIST OF SOME CLINICALLY APPROVED DRUG DISCOVEREDTHOUGH CADD APPROACHES

Drug	Year of approval	Therapeutic action
Captopril	1981	Antihypertensive
Saquinavir	1995	Human immunodeficiency Virus (HIV) inhibitor
Dorzolamide	1995	Carbonic anhydrase inhibitor
Indinavir	1996	Human immunodeficiency Virus (HIV) inhibitor
Ritonavir	1996	Human immunodeficiency Virus (HIV) inhibitor
Triofiban	1998	Fibrinogen antagonist
Zanamivir	1999	Neuraminidase inhibitor
Oseltamivir	1999	Active against influenza A and B viruses.
Raltegravir	2007	Human immunodeficiency Virus (HIV) inhibitor
Aliskiren	2007	Human renin inhibitor
TMI-005	Phase II clinical trials	In Rheumatoid arthritis
LY-517717	Phase II clinical trials	Serine protease Inhibitor
Boceprevir	Phase III clinical trials	Hepatitis C virus (HCV) inhibitor
Nolatrexed	Phase III clinical trials	In Liver cancer
NVP-AUY922	Phase I clinical trials	Inhibitor for HSP90

Drug development and drug discovery needs different databases and tools which are the necessary parts in drug design. Different tools and databases which are employed in drug development.

DIFFERENT TOOLS AND DATABASES EMPLOYED IN DRUG DESIGN PROCESS

Tool	Brief description with uses
BLAST	Basic local alignment search tool; used for sequencing of DNA and protein
RasMol	Raster molecule tool; used for molecular visualization of RNA/DNA and protein
Discovery studio	Software; used for modelling and simulation
Pub Med	Free search engine; used for searching matter related to medical and life sciences
PDB	Protein data bank; used to collect information related to macromolecule
Chem Draw	Part of the Chem office programs; used to draw chemical molecule
Marvin Sketch	Advanced chemical editor; used to draw chemical structures and reactions
PubChem	Database; used to collect information about structure and physiochemical properties of chemical compound.
Auto Dock	Software; used for molecular docking

Chemical drawing and visualization software

- **PubChem sketcher**

It's a network- grounded tool for molecular sketching which is incorporated with PubChem. It's a web- grounded information pool for chemical and bioactivity. It's a Web- bas0ed delineation tool for interactive sketching of chemical structures. It's a complete platform for

independent and vindicated work on all major Web cybersurfs, including aged bones without support for Web2.0 JavaScript objects.[38,39]

- **ChemSketch**

ChemSketch is a delineation package that allows drawing chemical structures, including organics, organometallics, polymers, and Markush structures. It also includes computation of molecular parcels like molecular weight, viscosity, molar refractivity, 2D and 3D structure cleaning and viewing, functionality for naming structures (smaller than fifty tittles and three rings), and vaticination of log. The freeware interpretation of ChemSketch doesn't include all of the functionality of the marketable interpretation. Visit ACD/ ChemSketch to learn further about the marketable interpretation.[40,41]

- **Chemdraw**

KingDraw is a free chemical drawing editor that allows druggies to sketch motes, responses, and organic chemistry objects and pathways. druggies can also use it to assay emulsion property, convert chemical structures to IUPAC names and view 3D models. KingDraw will give strong software support for chemical exploration, including further chemical related functions and new structure drawing modes to connect Android & iOS bias and PC, realising rapid-fire transubstantiating from KingDraw to Office, ChemDraw and picture. It has numerous important functions, like AI image identification, intelligent gesture delineation, clean up structure, get 3D model, conversion between name and structure, structural formula searching, chemical property analysis, erected- in group and free sharing.[42,43]

- **MedChem**

Designer It is a tool that combines innovative molecule drawing features with fast and accurate ADMET property predictions from our top ranked ADMET Predictor. Chemists who design new compounds for pharmaceutical, cosmetic, industrial chemical, herbicide, pesticide, and food applications will enjoy the highly intuitive interface with several convenience features and capabilities not available in other molecule drawing software.[44]

- **Vortex**

Vortex is a chemically apprehensive data analysis and spreadsheet tool from Dogmatics. It can import lines from a SQL database and do substructure or structural similarity quests. Calculate numerous physicochemical parcels and perform data analysis and display. It's an interactive data visualisation and analysis result for scientific decision support. structure on

and extending the spreadsheet paradigm, it provides the data manipulation, statistical analysis and sophisticated conniving capabilities needed to explore and understand any complexity and size of data. Whirlpool is also scientifically apprehensive, furnishing native cheminformatics and bioinformatics analysis and visualisations.[45,46]

- **AutoDock**

Autodock is a suite of automated docking tools. It's designed to prognosticate how small motes, similar as substrates or medicine campaigners bind to a known 3D structure receptor. It has been modified and bettered to add new functionalities, and multiple machines have been developed. Now two major generations are there AutoDock 4 and AutoDock Vina. AutoDock- GPU is an accelerated interpretation of AutoDock4 that's hundreds of times faster than the original single- CPU docking law. It can also help to guide organic synthetic druggists to design better binders.[47,48]

FUTURE PROSPECTIVE

The future prospective of computer aided drug design (CADD) are incredibly promising. With advancements in computational power and algorithms, CADD is expected to revolutionize the drug discovery process. It has the potential to significantly reduce time and cost by enabling virtual screening of vast chemical libraries, predicting drug target interactions with higher accuracy, and facilitating the design of personalized medicine. Additionally, the integration of artificial intelligence and machine learning into CADD holds great potential for accelerating drug discovery and optimizing drug efficiency. Overall, the future of CADD looks bright and holds tremendous potential for transforming the field of pharmaceutical research.

CONCLUSION

Computer Aided Drug Design (CADD) offers immense potential in revolutionizing the drug discovery process. By leveraging computational methods and algorithms, CADD enables faster and more efficient screening of potential drug candidate, prediction of drug target interactions, and optimization of drug properties. With ongoing advancement in technology and the integration of artificial intelligence, CADD is poised to further enhance the efficiency and success rate of drug discovery efforts. Embracing CADD as a powerful tool in pharmaceutical research holds great promise for accelerating the development of new and improved medicines for the benefits of patient worldwide.

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