



International Journal of Innovative Research in Science Engineering and Technology (IJIRSET)

(A Monthly, Peer Reviewed, Refereed, Scholarly Indexed, Open Access Journal)



Impact Factor: 8.699

Volume 15, Special Issue 1, January 2026

Computer Aided Drug Design

Gayatri Khedekar, Aditya Suryawansi, Vignesh Pawar, Mr. Shivaji Giram

Department of Organic Chemistry, Indala Institute of Pharmacy, Bapsai, Kalyan, India

ABSTRACT: The term drug design can be defined as search of novel compounds with biological activity on a systemic basis. The silico approach is playing a great role in drugs designing for identifying active scaffolds and guiding subsequent optimisation process also denovo design is also possible and one such promising area is computer aided drug design. Briefly it includes finding, designing, developing in medicines. It predicts to understand Understanding the disease, Target identification and validation, lead identification and optimization.

CADD method can help to save time and cost by predicting complementing traditional experimental techniques. By help of the computational tools such as molecular modeling, structure activity relationship, virtual screening research can predict the behavior of drug candidates access their interaction with biological targets and optimistic pharmacokinetics properties.

The Impressive progress of machine learning and artificial intelligence in the past decades is reshaping the field of rational drug design. Even though CADD greatly helps drug discovery it is still constrained by experimental validation to solve its drawback and optimize its foretelling. CADD includes two method ligand-based design, which studies known active molecules, and structure-based design, which uses the 3D structure of the target protein. Techniques such as molecular docking, QSAR, pharmacophore modeling, virtual screening, and ADMET prediction allow researchers to select the best possible compounds early in the process. Although experimental studies are still required, CADD improves accuracy, increases success rates, and supports faster development of safer and more effective medicines. Overall, CADD has become an essential part of modern drug discovery and continues to grow with advancements in computer technology and artificial intelligence.

The Future of Drug Design: The significant advancements in Machine Learning (ML) and Artificial Intelligence (AI) over the past few decades are fundamentally transforming the field of rational drug design. While Computer-Aided Drug Design (CADD) is already a major aid in drug discovery, its potential is still limited by the need for experimental validation. Overcoming this constraint is key to improving its predictive power and effectiveness. In essence, CADD combines computational methods with cutting-edge structural biotechnology. This synergy is vital for accelerating the drug discovery process and enhancing the personalization and effectiveness of treatments.

Recently, the entire approach to drug development has been revolutionized by tools such as Virtual Screening, rational drug design, chemoinformatics, and AI. Looking ahead, emerging immersive technologies and quantum computing hold the promise of further boosting the capabilities and precision of CADD.

KEYWORDS: QSAR, PHARMACOPHORE, MACHINE LEARNING, ADMET.

I. INTRODUCTION

The Evolution of Drug Discovery: From Trial-and-Error to Digital Design

Creating a new medicine is a marathon. It is a high-stakes, 15-year journey that often ends in failure because a potential drug either doesn't work as expected or proves toxic to the human body. Historically, this process was built on "trial and error"—testing thousands of molecules in a lab to see what sticks. This empirical approach is not only slow and expensive but often leads to late-stage disappointments. To solve this, the pharmaceutical world has turned to Computer-Aided Drug Design (CADD). By blending chemistry and biology with massive computational power, CADD allows scientists to "test" drug candidates in a virtual environment before they ever touch a petri dish.

How CADD Transforms the Process:

The rise of CADD was made possible by our ability to map the 3D structures of biological targets, like proteins and DNA. Using these "blueprints," researchers can use molecular modeling and simulations to predict how a drug will bind to a target and how the body might process it.

There are two primary ways this is done:

(a) Structure-Based Drug Design (SBDD): Using the 3D shape of a protein “lock” to design a specific molecular “key.”
(b) Drug Design (LBDD): Looking at existing drugs that already work and using their properties as a template to find even better versions.

(c) The Modern Frontie :

The development of CADD was driven by significant progress in structural biology, which provided detailed three-dimensional structures of biomolecular targets such as proteins and nucleic acids. Combined with advances in molecular modeling, quantum mechanics, molecular mechanics, and statistical methods, CADD enables the simulation of ligand–target interactions, binding affinity estimation, and optimization of lead compounds. These techniques help reduce the dependence on large-scale experimental screening and allow researchers to focus on promising candidates with improved efficacy and safety profiles.

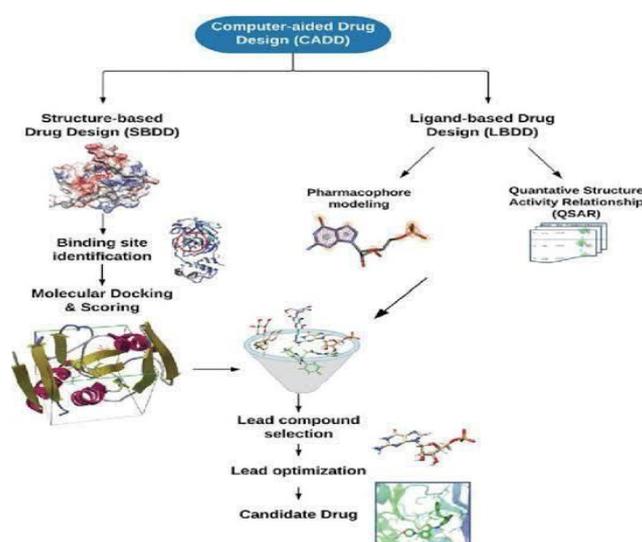


Figure 1: General Principle for Drug designing through CADD

Today, CADD is more powerful than ever. By integrating Artificial Intelligence (AI) and Machine Learning, we can now screen millions of compounds in seconds. This isn't just about efficiency; it's about accuracy. By predicting ADME/Tox (how a drug is absorbed, metabolized, and its toxicity levels) early on, we can weed out dangerous or ineffective candidates years before they reach clinical trial. In an era of rapid global health threats, CADD has moved from being a luxury to an absolute necessity—turning a slow, expensive gamble into a streamlined, rational science.

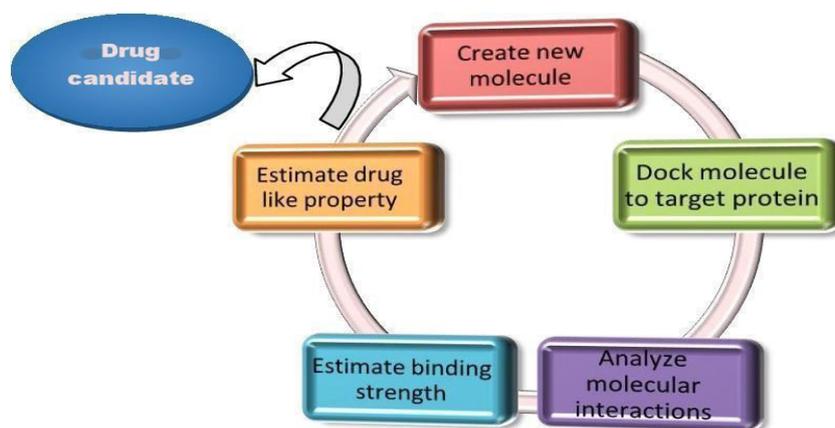


Figure 2: General Representation of workflow for CADD

1.1 MAJOR TYPES OF APPROCHES IN CADD

Their are mainly two types of approaches for drug design through CADD is the following:

1. Structure based drug design/ direct approach
2. Ligand Based drug design / indirect approach

1.2 STRUCTURE BASED DRUG DESIGN

Structure-based drug design (SBDD) is a knowledge-driven strategy in modern drug discovery that utilizes the three-dimensional architecture of a therapeutic target to guide the identification and optimization of bioactive molecules. Understanding the spatial arrangement of amino acids within the binding pocket allows researchers to design ligands that fit precisely into the target site, thereby enhancing selectivity and biological activity. This rational approach has transformed drug discovery by enabling the interpretation of disease mechanisms at the molecular level.

SBDD integrates several computational techniques such as structure-based virtual screening, molecular docking, and molecular dynamics simulations. These tools enable detailed evaluation of protein–ligand interactions, estimation of binding affinity, and assessment of conformational flexibility of the receptor upon ligand binding. Molecular dynamics simulations further provide insights into the stability and dynamic behavior of protein–ligand complexes over time, making SBDD a powerful predictive platform in medicinal chemistry.

The impact of SBDD is reflected in the successful development of numerous clinically approved drugs. For instance, amprenavir was designed as an HIV protease inhibitor using protein modeling and dynamic simulation studies.

Raltitrexed, a thymidylate synthase inhibitor, was developed through structure-guided optimization strategies. Norfloxacin, an antibacterial agent targeting topoisomerase II and IV, was identified through virtual screening approaches. Similarly, dorzolamide, a carbonic anhydrase inhibitor used in glaucoma management, emerged from fragment-based structure-guided studies. Antitubercular drug isoniazid was optimized by targeting enoyl-ACP reductase (InhA) using structure-based screening and pharmacophore modeling, while flurbiprofen, a COX-2 inhibiting NSAID, was refined through docking-based approaches.

The SBDD workflow is inherently iterative and progresses through multiple refinement cycles before a compound reaches clinical evaluation. Initially, the target protein is isolated, purified, and structurally characterized using experimental methods such as X-ray crystallography or NMR spectroscopy, or through computational homology modeling when experimental data are unavailable. Once the target structure is prepared, the ligand binding region is identified, and large chemical libraries are computationally screened against this site.

Docked molecules are evaluated using scoring functions that account for steric compatibility, hydrophobic interactions, electrostatic forces, and hydrogen bonding. The most promising candidates are then validated through biochemical and in-vitro assays. In subsequent optimization cycles, the structure of the protein bound to the lead compound is analyzed to identify regions amenable to chemical modification. Continuous rounds of synthesis, docking, molecular dynamics simulation, and binding free energy calculations lead to progressive improvement in potency, specificity, and pharmacological performance. Through this systematic refinement process, SBDD enables the rational design of optimized drug candidates with a higher probability of clinical success.

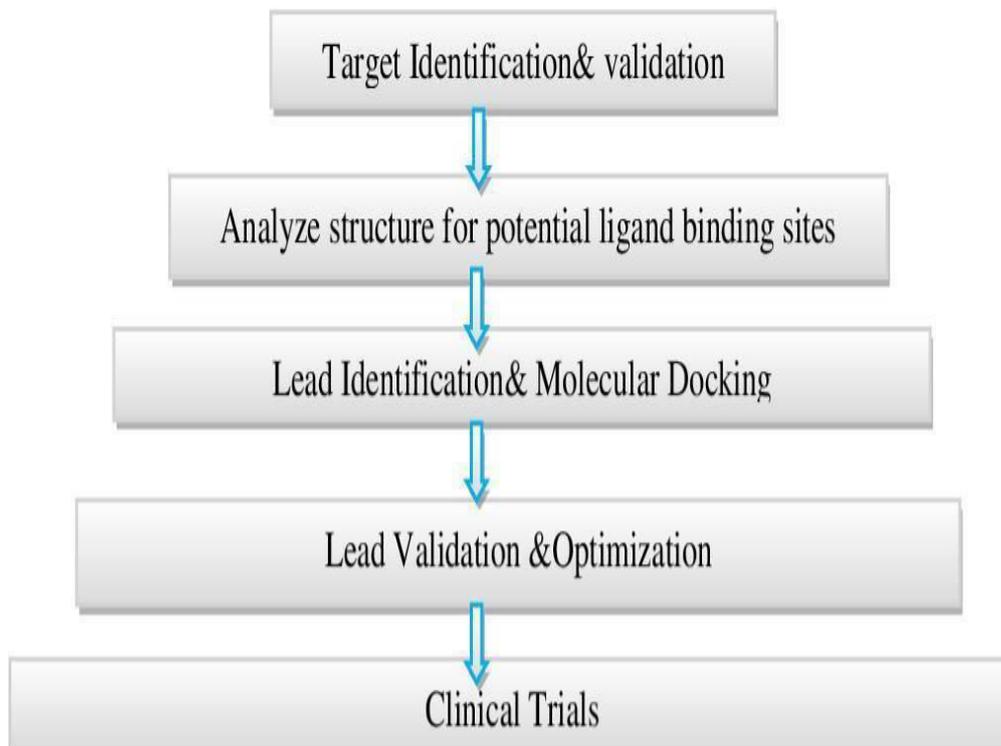


FIGURE 3 Steps Involved In SBDD

1.3 LIGAND BASED DRUG DESIGN

- Ligand-based drug design (LBDD) is a key strategy in computer-aided drug discovery, particularly applied when the three-dimensional structure of the target receptor is unknown. This approach relies on analyzing a collection of compounds that exhibit known biological activity against a specific target. By examining these active molecules, essential physicochemical and structural features responsible for their activity can be identified. LBDD is based on the principle that compounds with similar chemical structures tend to produce comparable biological effects. Commonly employed ligand-based virtual screening techniques include pharmacophore modeling, quantitative structure– activity relationship (QSAR) analysis, and artificial intelligence-driven methods.

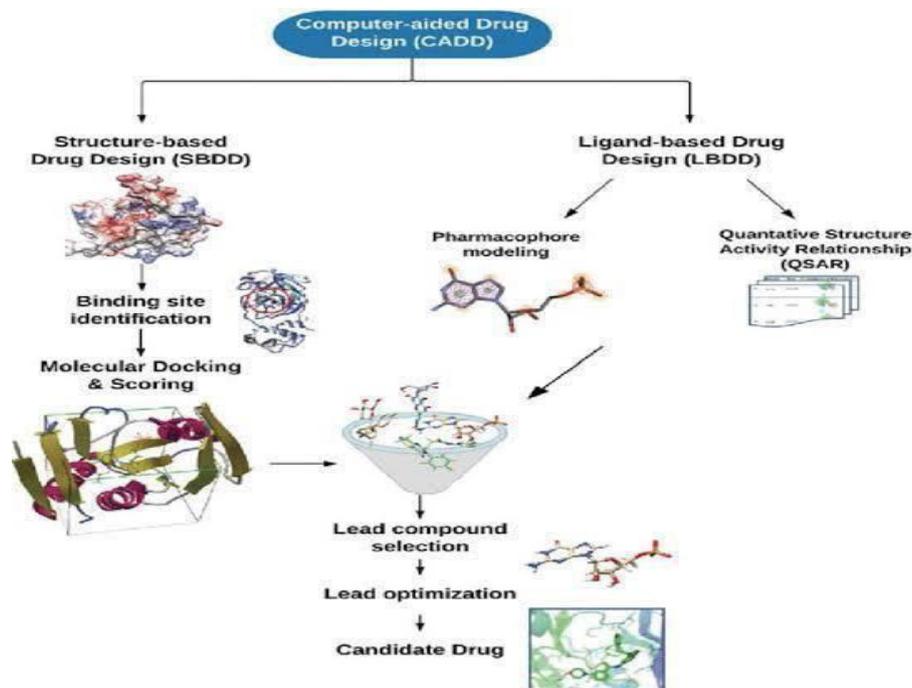


FIGURE 4 Schematic diagram Of VS process of SBDD and LBDD

II. ARTIFICIAL INTELLIGENCE IN DRUG DISCOVERY

Artificial intelligence (AI) refers to computer-based systems capable of learning patterns from existing datasets and using this knowledge to make predictions or decisions. In drug discovery research, AI has emerged as a powerful computational approach for estimating biological activity, toxicity, and pharmacological behavior of potential drug molecules [97]. Its integration into pharmaceutical research has expanded rapidly, with applications ranging from protein structure prediction and protein–protein interaction analysis to virtual screening, quantitative structure–activity relationship (QSAR) modeling, ADMET assessment, and de novo molecular design [103].

Among AI-driven approaches, machine learning (ML) and deep learning (DL) represent the two most influential strategies in modern rational drug design [104]. Traditional ML techniques such as support vector machines (SVM) [105], random forest (RF) algorithms [106], and naïve Bayes (NB) classifiers [107] have been extensively employed to model structure–property and structure–activity relationships. In contrast, deep learning methods—including convolutional neural networks (CNNs), deep neural networks (DNNs), recurrent neural networks (RNNs), autoencoders, and restricted Boltzmann machines (RBMs)—are capable of extracting complex, non-linear features directly from large and diverse datasets [4].

Conventional QSAR approaches have demonstrated success in predicting relatively straightforward physicochemical parameters such as lipophilicity (logP) and aqueous solubility. However, their performance often declines when applied to more complex biological outcomes, including therapeutic efficacy and adverse effects. This limitation is largely attributed to the use of small training datasets [108] and restricted representation of chemical diversity [109]. Furthermore, the exponential growth of data generated through high-throughput screening (HTS) technologies poses significant challenges to classical QSAR and standard ML techniques, which struggle to efficiently process high-dimensional and large-scale datasets [40].

To address these challenges, advanced AI-based models—particularly deep learning—have been developed to handle the volume, variety, and complexity of modern drug discovery data. A landmark demonstration of deep learning in this field occurred during the 2012 Merck-sponsored QSAR machine learning challenge, where DL models showed superior

performance in predicting ADMET properties compared to conventional ML approaches [110]. These findings highlighted the potential of deep learning to improve predictive accuracy in pharmacokinetic and toxicity assessments.

Despite its advantages in accelerating and optimizing the identification of preclinical drug candidates, AI-driven drug discovery is not without limitations. One of the major challenges lies in accurately predicting binding affinities between ligands and their biological targets. The effectiveness of AI models is strongly dependent on the quantity, consistency, and reliability of available training data [4,111]. Variations in experimental conditions across different biological assays, along with the limited availability of high-quality, standardized data in public databases, significantly hinder robust model training and generalization.

2.1 GENETIC ALGORITHMS IN MOLECULAR DOCKING

Genetic algorithms mimic natural evolutionary principles to efficiently explore the vast conformational space of ligand–protein interactions. In this approach, molecular diversity is generated by combining structural features from existing ligand conformations to produce new offspring structures. During successive iterations, only those conformations with superior binding performance are selected to participate in further optimization cycles. As a result, favorable structural traits are preserved and refined across generations, gradually converging toward optimal binding solutions.

Within the context of molecular docking, ligand poses are represented by a set of adjustable parameters known as state variables. These variables describe key features such as ligand translation, spatial orientation, internal flexibility, and interaction characteristics including hydrogen bonding. The numerical encoding of these parameters forms the genotype, while the corresponding three-dimensional ligand–protein complex represents the phenotype. The quality of each phenotype is evaluated using a fitness function, typically based on binding energy or scoring functions.

Genetic operations such as crossover and mutation introduce variability by recombining large segments of parental parameter sets or by randomly altering specific ligand attributes. These operations enable efficient sampling of diverse conformations and prevent premature convergence. A prominent example of this strategy is the Genetic Optimization for Ligand Docking (GOLD) algorithm, which employs a genetic algorithm to allow full ligand flexibility while incorporating limited flexibility in the protein binding site.

III. CHALLENGES AND LIMITATIONS IN COMPUTER AIDED DRUG DESIGN (CADD)

Computer-Aided Drug Design (CADD) has made drug discovery faster and more efficient, but it also has several limitations that must be understood to use it correctly.

Need for Skilled Experts:

CADD requires knowledge of biology, chemistry, and computer science. However, there are limited professionals who are trained in all these areas together. Because of this, the proper use of advanced tools like artificial intelligence and molecular modeling becomes difficult. More training and skill development are needed to overcome this challenge.

Difficulty in Mimicking Real Biological Systems:

Living systems are very complex, but computer models can only give a simplified picture of them. Factors such as protein movement, interaction with water, and changes inside the body are not fully represented. This can affect the accuracy of predictions made by CADD tools.

Limited Accuracy of Predictions:

Most CADD methods depend on theoretical calculations and algorithms. Sometimes these methods may predict that a molecule will work well, but in reality it may fail in experiments. Errors such as false positive or false negative results are common, so experimental testing is always necessary.

Poor Quality and Limited Data:

CADD tools depend heavily on available data. If the data used are incomplete, incorrect, or inconsistent, the predictions will also be unreliable. Many datasets used for drug discovery lack standardization, which reduces the effectiveness of computational models.

Challenges in Handling Molecular Flexibility:

Drug molecules and their targets are flexible and can change shape. Many CADD methods treat them as rigid structures, which can lead to inaccurate binding predictions and poor results.

Difficulty in Understanding AI Predictions:

Modern CADD uses artificial intelligence models that give results without clearly explaining how they were reached. This lack of transparency makes it hard to understand why a compound is predicted to be effective or how it can be improved.

Limited Prediction of Safety and Toxicity:

Although CADD can estimate toxicity and side effects, these predictions are not always accurate. Human biology is complex, and many drugs fail later because safety issues were not correctly predicted by computational models.

IV. CASE STUDY: THE SUCCESS OF COMPUTER AIDED DRUG DESIGN

The true value of any scientific methodology is best demonstrated through its real-world applications. In the field of Computer-Aided Drug Design (CADD), several drug discovery programs have successfully progressed from *in silico* concepts to clinically approved therapies, clearly illustrating the transformative role of computational approaches in modern medicine [94].

One of the earliest and most impactful successes of CADD was observed in the development of HIV protease inhibitors. Drugs such as saquinavir were designed using molecular modeling techniques that enabled researchers to visualize the active site of HIV protease and predict optimal ligand–enzyme interactions. This rational approach significantly accelerated lead identification and optimization, resulting in highly effective antiretroviral agents [95].

Similarly, structure-based drug design played a crucial role in the development of anti-influenza drugs, particularly neuraminidase inhibitors like oseltamivir (Tamiflu). By examining the three-dimensional structures of influenza neuraminidase, computational tools helped identify critical binding regions, leading to the rational design of drugs capable of preventing viral replication [96].

Another landmark achievement of CADD is the development of imatinib (Gleevec) for the treatment of Chronic Myeloid Leukemia (CML). Computational studies enabled precise targeting of the BCR-ABL tyrosine kinase, resulting in a highly selective inhibitor. This example highlights how CADD can facilitate the design of targeted therapies with improved efficacy and reduced toxicity [97].

CADD has also significantly advanced the treatment of Hepatitis C virus (HCV) infections. The discovery of HCV protease inhibitors, such as boceprevir, was supported by molecular docking and molecular dynamics simulations. These techniques allowed researchers to understand enzyme–inhibitor interactions at the atomic level, leading to the development of potent antiviral agents and improved therapeutic outcomes [98].

In the context of Alzheimer's disease, CADD has contributed to the identification of potential disease-modifying therapies by targeting key enzymes such as β -secretase (BACE-1). Several inhibitors designed using computational strategies have entered clinical trials, including donanemab and solanezumab, reflecting the growing importance of *in silico* methods in tackling complex neurodegenerative disorders [99–101].

The global COVID-19 pandemic further underscored the importance of CADD in rapid drug discovery. Computational screening approaches were extensively used to identify potential antiviral candidates against SARS-CoV-2. Studies involving molecular docking of flavonoid glycosides, alkaloids, and vanillin derivatives suggested their possible inhibitory effects on viral proteins. Both ligand-based and structure-based modeling approaches provided valuable insights, demonstrating the versatility and speed of CADD in emergency drug discovery scenarios [102].

Overall, these case studies clearly demonstrate the substantial impact of Computer-Aided Drug Design in accelerating drug discovery and development. By integrating computational chemistry with medicinal and biological sciences, CADD continues to shape the future of rational drug design and personalized medicine.

4.1 Case Study: COVID-19 Drug Discovery Using CADD

During the COVID-19 pandemic, computer-aided drug design (CADD) played a major role in finding possible treatments for SARS-CoV-2. Since developing new drugs takes a long time, most studies focused on drug repurposing and natural compounds using ligand-based and structure-based approaches.

Researchers used homology modeling to build viral protein structures such as the main protease (Mpro), RNA-dependent RNA polymerase (RdRp), nucleocapsid protein, and ACE2 receptor. These models were then explored using molecular docking, pharmacophore modeling, QSAR, virtual screening, and molecular dynamics (MD) simulations.

Many FDA-approved antiviral drugs like remdesivir, lopinavir, ritonavir, saquinavir, ribavirin, favipiravir, and atazanavir showed strong binding with key viral enzymes, especially Mpro and RdRp, suggesting their potential to block virus replication. Several studies also highlighted natural compounds and phytochemicals such as hesperidin, rutin, resveratrol, piceatannol, myricitrin, flavonoids, coumarins, and compounds from Indian spices and medicinal plants as promising inhibitors.

Advanced AI and deep-learning models helped predict drug–target interactions quickly, while pharmacophore and QSAR models were used to design and screen new molecules. MD simulations further confirmed the stability of drug–protein complexes.

Overall, CADD significantly accelerated COVID-19 drug discovery, helped identify potential lead molecules, and guided experimental and clinical research. These studies proved that computational methods are powerful tools for rapid response during global health emergencies.

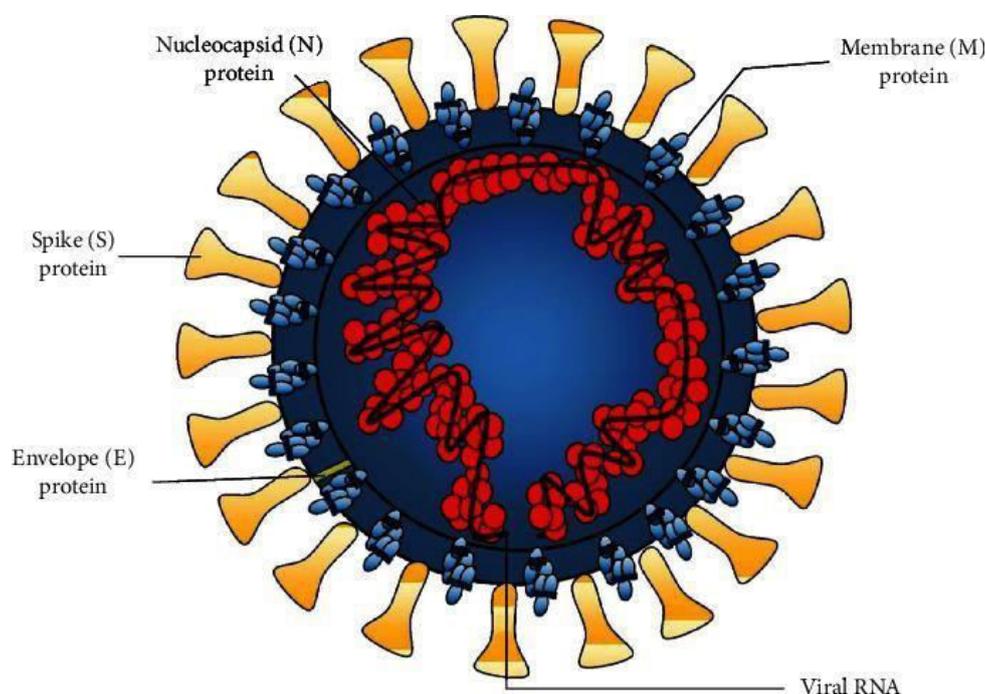


Figure5 : The structural proteins of SARS-CoV-2.

V. SOFTWARE FOR GENERAL PURPOSE MOLECULAR MODELING

For workstations, minicomputers, and supercomputers (SGI, Sun, Cray, etc.)

1. AMBER—Peter Kollman and coworkers, UCSF. Computer assisted model building, energy minimization, molecular dynamics, and free energy perturbation calculations.
2. Midas Plus—UCSF Computer Graphics Laboratory.
3. CHARMM—Martin Karplus and coworkers, Harvard.

4. QUANTA/CHARMm—Molecular Simulations Inc. (MSI) molecular/drug design, QSAR, quantum chemistry.
5. X-ray & NMR data analysis Insight/DISCOVER— Biosym, Inc. Now MSI became Accelrys .SYBYL—Tripos, Inc. For personal computers (Apple, Compaq, IBM, etc.
6. Alchemy III—Tripos, Inc.
- 7.Desktop Molecular Modeller—Oxford Elec. Publish- ing Molecular Modeling ProWindowchem Software Energy minimization, QSAR (surface area, volume, logP), etc.
- 8.PC MODEL—Serena Software..

VI. CURRENT CHALLENGES IN CADD AND OVERCOMING BARRIERS

Although Computer-Aided Drug Design has greatly improved the drug discovery process, it still faces several important challenges. One major problem is the quality and availability of data. If the chemical structures or biological activity data are incorrect or incomplete, computer predictions can become unreliable. In addition, much useful data is kept private by organizations, which limits data sharing and slows progress.

Another challenge is the limited accuracy of prediction models. Sometimes, these models identify compounds that later fail in experiments or miss good drug candidates. Improving the reliability of drug–target interaction predictions remains a key need.

Biological molecules such as proteins are not rigid structures; they constantly change shape. Capturing this flexibility accurately in computer simulations, especially for long time periods, requires high computational power and remains difficult.

As databases grow larger and models become more complex, scaling up computations efficiently is another hurdle. This demands faster algorithms and better computing resources. Moreover, combining different types of biological data, such as genomic and proteomic information, into a single meaningful analysis is still challenging.

Finally, the use of patient-related data in CADD raises ethical and privacy concerns, especially in personalized medicine. Protecting sensitive data while enabling scientific research is essential.

Overall, while CADD is a powerful tool, overcoming these challenges is necessary to make drug discovery faster, more accurate, and more reliable in the future.

VII. FUTURE PERSPECTIVES OF COMPUTER-AIDED DRUG DESIGN (CADD)

7.1. Emerging Technologies Shaping the Future of CADD

Drug Design has already transformed modern drug discovery, but its future promises even greater advancements. New technologies are expected to overcome current limitations and make drug development faster, more accurate, and more patient-focused. Conventional computing struggles with highly complex molecular systems; however, quantum computing offers the potential to process massive molecular data at unprecedented speeds, enabling rapid exploration of chemical space.

Visualization technologies such as augmented reality (AR) and virtual reality (VR) are also gaining attention in CADD. These tools allow researchers to interact with molecular structures in a more intuitive and visual manner, improving understanding of drug–target interactions and enhancing collaborative research. At the same time, machine learning—especially deep learning—has become a powerful component of CADD. These models can analyze large datasets to predict drug toxicity, binding affinity, and even propose new drug candidates.

With the growing availability of genomic data, CADD is moving toward personalized medicine. Future drug design strategies may focus on tailoring therapies based on an individual’s genetic profile. Additionally, open-source platforms and global collaborations are expected to play a crucial role by allowing scientists worldwide to share data, tools, and expertise. Incorporating green chemistry concepts into CADD will further support environmentally sustainable drug development.

7.2. Role of Collaboration and Open-Source Platforms in CADD

In today's interconnected scientific ecosystem, collaboration has become essential for progress in CADD. Open-source platforms enable researchers from diverse backgrounds to access advanced computational tools, reducing dependency on expensive infrastructure. This democratization of drug discovery allows meaningful contributions from academia, small laboratories, and researchers in developing regions.

Global initiatives, such as open-source drug discovery projects, demonstrate how collective efforts can address complex diseases. Crowdsourcing approaches invite innovative solutions from a broad scientific community, often leading to unconventional yet effective outcomes. Community-driven platforms also benefit from continuous improvement, as tools are refined through shared feedback and regular updates. Overall, collaborative networks promote faster innovation and reinforce the idea that shared knowledge can accelerate healthcare advancements.

7.3. Ethical and Regulatory Challenges in CADD

Despite its advantages, CADD raises important ethical and regulatory concerns that must be addressed responsibly. The use of patient data in personalized drug design requires strict protection of privacy and compliance with data protection laws. Ensuring secure handling of sensitive information is critical for maintaining public trust.

Intellectual property issues also become complex in collaborative and open-source environments. Clear policies are needed to balance openness with fair recognition of contributors. Moreover, artificial intelligence models may reflect biases present in their training data, making transparency and interpretability essential. Reproducibility of computational results remains another challenge, particularly as algorithms become more complex.

While CADD reduces experimental burden, animal testing remains necessary at later stages, raising ethical concerns. Regulatory guidelines emphasize minimizing animal use and ensuring humane practices. Furthermore, for CADD-based discoveries to be accepted clinically, regulatory agencies must recognize and validate these computational approaches. Active communication between researchers and regulators is therefore essential.

7.4. Future Outlook of Computer-Aided Drug Design

The future of CADD lies at the intersection of innovation and responsibility. Advances in quantum computing and artificial intelligence are expected to significantly improve the accuracy and efficiency of drug discovery. AI-based models capable of predicting protein structures and drug interactions will further refine lead identification.

Integrating data from genomics, proteomics, and metabolomics will allow CADD to capture the complexity of biological systems more effectively. However, managing and standardizing large-scale biomedical data will remain a major challenge. Sustainability will also become a priority, with future models considering environmental impact alongside therapeutic effectiveness.

As AI continues to influence drug discovery, ethical issues such as algorithmic transparency and bias must be carefully managed. In summary, the next phase of CADD will be shaped by technological progress, ethical awareness, and global collaboration. By addressing these challenges proactively, CADD can continue to play a vital role in delivering safer and more effective medicines.

VIII. USE OF COMPUTER AIDED DRUG DESIGN IN ALZHEIMER DISEASE

Lack of association in mouse models or in human cohorts :

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by memory loss, cognitive decline, and structural damage to neurons. At the molecular level, the disease is mainly associated with two pathological features: extracellular amyloid- β plaque deposition and intracellular accumulation of abnormal tau protein. Amyloid pathology is generally considered an early event, while tau-related changes are more closely linked to neuronal dysfunction and disease severity. Understanding how these two processes interact remains a major focus of AD research.

Transgenic animal models have been widely used to study AD mechanisms. Mouse models expressing human amyloid precursor protein (APP) reliably develop amyloid plaques as they age, making them useful tools for studying amyloid-driven pathology. However, most APP-only models do not spontaneously develop robust tau aggregation or neurofibrillary tangles similar to those observed in human AD. This limitation has encouraged researchers to generate

compound transgenic models that combine amyloid-related genes with tau or other neuronal regulatory genes to better mimic disease complexity.

The p73 protein, encoded by the Trp73 gene, belongs to the p53 family and plays a crucial role in brain development, neuronal differentiation, and cell survival. Given its importance in maintaining neuronal integrity, p73 has been investigated as a possible contributor to neurodegeneration. Experimental studies using Trp73-deficient mice have shown subtle neuronal abnormalities, raising the question of whether reduced p73 activity could influence amyloid or tau pathology in Alzheimer’s disease.

To explore this possibility, researchers examined compound mouse models combining APP overexpression with partial or complete loss of Trp73. Biochemical and histological analyses across different ages revealed that amyloid deposition progressed as expected in APP transgenic mice, but tau pathology remained minimal in Trp73-modified animals. Importantly, no consistent increase in insoluble or phosphorylated tau species was observed, even in older animals or when both genetic modifications were present together.

Overall, these findings suggest that p73 does not play a direct or dominant role in driving amyloid- or tau-mediated pathology in Alzheimer’s disease. Instead, AD appears to result from a complex interplay of multiple genetic, molecular, and age-related factors. This highlights the limitations of single-gene models and supports the need for advanced experimental

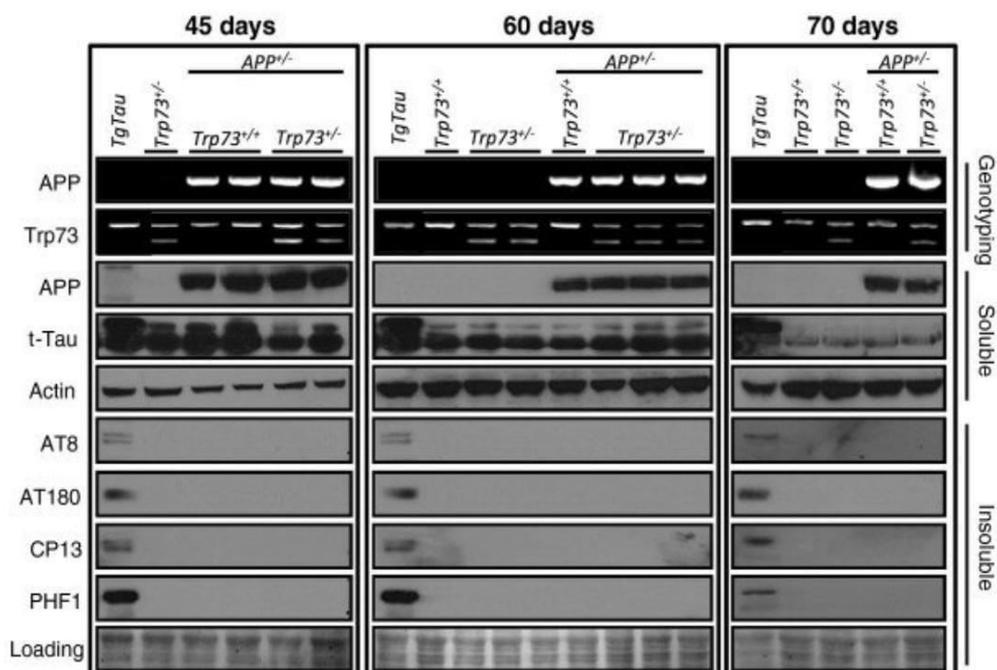


Figure 6: Biochemical analysis of tau species in control and compound mutant young mice

The figure presents a comparative biochemical evaluation of brain tissues from control and compound transgenic mice across different ages (45, 60, and 70 days). Immunoblot analysis was performed to assess the expression of APP, total tau, and multiple phosphorylated tau species using site-specific antibodies. The results demonstrate a gradual, age-related increase in tau phosphorylation, indicating progressive molecular changes associated with neurodegeneration. Consistent loading across samples confirms that the observed differences reflect true biological variation rather than experimental bias.

In contrast, early amyloid presence does not appear to significantly influence tau pathology at these time points, as soluble tau species remain largely comparable between genotypes. This suggests that tau-related biochemical alterations may

evolve independently during early disease stages and become more pronounced with advancing age. Overall, the data highlight the importance of temporal progression in tau pathology and support the view that neurodegenerative mechanisms develop incrementally rather than abruptly in these models.

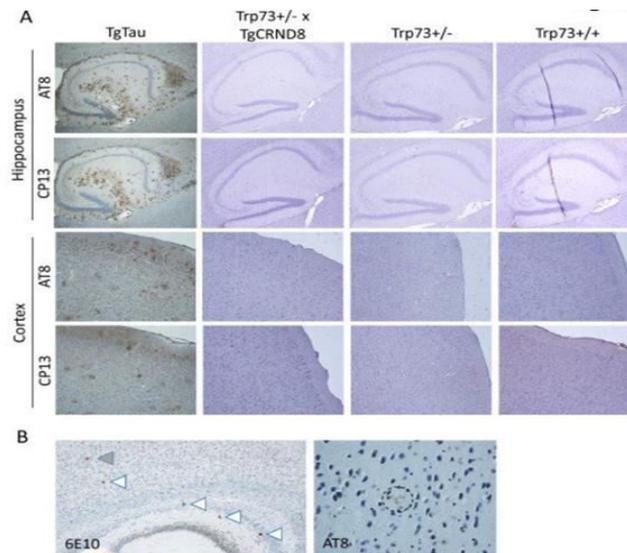


Figure 7: Immunohistochemical analysis of tau species in control and compound mutant young mice

- This figure demonstrates the immunohistochemical evaluation of tau pathology in the hippocampus and cortical regions of control and compound mutant mice. Brain sections were stained with phosphorylation-specific tau antibodies, allowing visualization of tau accumulation at the tissue level. Strong tau immunoreactivity is clearly observed in the positive control model, particularly within the hippocampal formation, whereas compound transgenic and Trp73-modified mice show minimal to no detectable tau staining. These observations indicate an absence of early neurofibrillary-like pathology in the experimental groups.
- In cortical regions, a similar pattern is evident, with tau-positive structures largely restricted to the control samples. Higher-magnification images further confirm the lack of abnormal tau deposition in young compound mutant mice, suggesting that tau pathology does not develop at early stages despite genetic modification. Overall, these findings support the conclusion that early tau-related neurodegenerative changes are limited and region-specific, emphasizing the role of disease progression and aging rather than early genetic interactions alone.

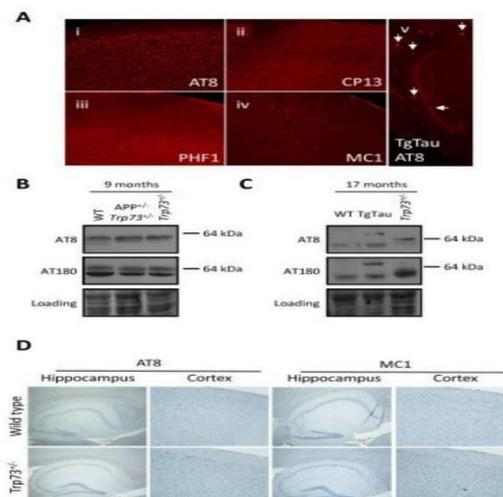


Figure 8: Biochemical and histochemical analysis of tau species in older compound and Trp73 mutant mice.

- This figure illustrates the biochemical and histological assessment of tau pathology in older compound transgenic and Trp73 mutant mice. Fluorescent and immunohistochemical staining were carried out using phosphorylation-specific tau antibodies to detect abnormal tau accumulation in brain regions associated with neurodegeneration. In contrast to the tau transgenic positive controls, which displayed strong somatodendritic tau immunoreactivity and clear neurofibrillary-like structures, the compound mutant and Trp73-modified mice showed little to no detectable tau pathology. These findings suggest that tau aggregation is not prominently induced in these models even at later stages of disease progression.
- Quantitative analysis further supports these observations, as biochemical assays revealed no consistent increase in insoluble phosphorylated tau species in the experimental groups when compared to controls. Any minor variations observed across individual samples fell within the expected range of biological variability and did not reach statistical significance. Importantly, parallel processing of control and experimental tissues ruled out technical bias, confirming that the absence of tau pathology reflects true biological differences rather than methodological limitations.
- Overall, the data indicate that loss or modification of Trp73 does not independently drive tau-mediated neurodegeneration, even in the presence of amyloid-related genetic factors. These results highlight the complexity of molecular interactions underlying neurodegenerative disease and suggest that additional aging-related or environmental factors may be required to trigger full pathological progression. Collectively, this study reinforces the concept that tau pathology develops through multifactorial mechanisms rather than as a direct consequence of single-gene alterations.

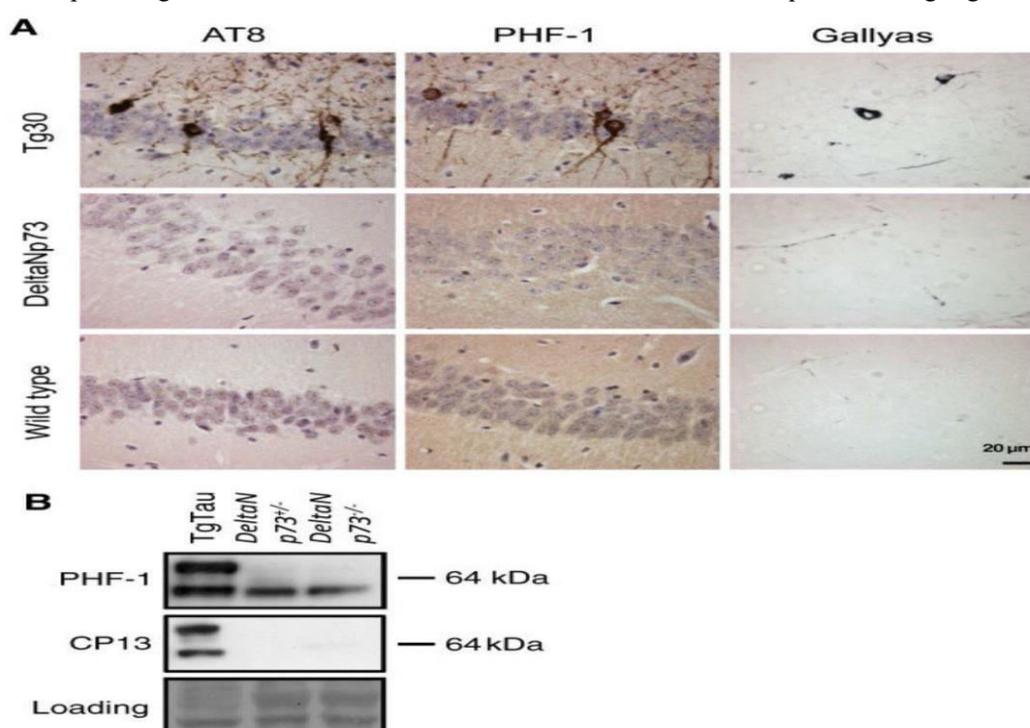


Figure 9: Analysis of tau species in aged delta NP73 null mice.

IX. ROLE OF ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN MODERN DRUG DESIGN

Artificial intelligence (AI) and machine learning (ML) are rapidly influencing many areas of science, including drug discovery. When combined with Computer-Aided Drug Design (CADD), these technologies are changing how new medicines are identified and developed.

Deep learning, a branch of machine learning, is especially useful in drug design. Techniques such as neural networks can study molecular structures and predict important drug properties. AI models can also identify possible drug–drug interactions, helping researchers understand whether medicines will work well together or cause harmful side effects.

By analyzing large databases containing chemical and clinical data, AI can find new uses for already approved drugs, saving time and cost in drug development. Machine learning also improves QSAR models by making better predictions

about how a chemical structure will behave biologically. In addition, AI speeds up virtual screening by quickly scanning millions of compounds and selecting the most promising candidates.

Another important application of AI in CADD is the design of new drug molecules. AI systems can create molecules with desired features, such as strong activity and fewer side effects. However, despite these advantages, challenges still exist. Poor data quality, overly complex models, lack of transparency, and high computational demands can affect the reliability of AI-based predictions.

Overall, AI and ML are playing a major role in shaping the future of drug discovery. When combined with CADD, these technologies offer a powerful approach for developing safer, more effective, and more personalized medicines.

X. CONCLUSION

Computer-Aided Drug Design (CADD) has emerged as a cornerstone of contemporary drug discovery, reshaping the way therapeutic molecules are identified and optimized. By integrating structure-based and ligand-based strategies, CADD enables a rational and systematic exploration of chemical space, significantly accelerating the discovery process while minimizing cost and experimental burden. Its impact has been particularly evident during global health emergencies such as the COVID-19 pandemic, where rapid access to viral target structures facilitated the virtual screening and identification of promising inhibitors, providing valuable starting points for further optimization.

The adaptability of CADD is crucial in addressing challenges posed by rapidly mutating pathogens, such as RNA viruses, where resistance to single-target therapies can arise swiftly. In this context, multi-target drug design and scaffold-based optimization offer robust strategies to enhance therapeutic efficacy and durability. The growing integration of machine learning and artificial intelligence has further strengthened predictive accuracy, enabling better assessment of binding affinities, pharmacokinetics, and toxicity profiles at early stages of drug development.

Despite its transformative potential, CADD continues to face challenges related to data quality, model reliability, and ethical considerations, underscoring the need for continuous refinement and responsible application. The future of CADD lies in the harmonious integration of computational predictions with experimental validation, open collaborative platforms, and interdisciplinary training. As emerging technologies such as quantum computing, personalized medicine, and sustainable chemistry converge with CADD, the field is poised to deliver faster, more precise, and patient-focused therapeutics. Ultimately, CADD represents not just a technological advancement, but a paradigm shift toward a more efficient, collaborative, and innovation-driven drug discovery landscape.

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