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Modern Strategies for Cns Drug Discovery: Integrating Cadd And Deep Learning For Therapeutic Advances

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ABSTRACT
Developing long-term therapies for diseases of the brain and nervous system (central nervous system), such as neurological and psychiatric disorders, is challenging due to high medication rates for failure and high expenses. Computer-Aided medication Design (CADD) provides a crucial strategy to address these issues, enabling more targeted and cost-effective drug development. The two CADD approaches of Ligand-Based Drug Design (the LBDD method) and Structure-Based Drugs Design (the SBDD method) focus on identifying key ligand physical and chemical and structural properties without requiring knowledge of the target structure. Drug design has been significantly improved in recent years by the combination of CADD with bioinformatics, including proteomics, metabolomics, and genomics. Potential treatment candidates for conditions like Alzheimer's, Parkinson's, neuropathic pain, and Virtual high-throughput drug screening as well as deep machine learning techniques such as convolutional networks of neurons (CNNs), networks of recurrent neurons (RNNs), as well as long short-term memories (LSTM) networks have played a significant role in the discovery of schizophrenia. More than 90% of compounds with desired CNS pharmacological properties are produced using the CNSMolGen model, a unique molecular generation system that makes use of bidirectional recurrent neural networks (BiRNNs). This integrated strategy has the potential to improve treatment results, speed up CNS drug discovery, and cut down on the time and expense of medication development.

Keywords- Ligand-Based Drug Design (LBDD), Structure-Based Drug Design (the SBDD method), and Computer-Aided Drug Design (CADD), Deep Learning (CNNs, RNNs, LSTM), CNSMolGen model

INTRODUCTION

The medical field of mental illnesses, which includes neurological and psychiatric problems, has a significant unmet demand for novel and more sophisticated therapies. The only treatments available for conditions like cognitive impairment and Parkinson's disease are those that reduce symptoms [1,2]. The effectiveness of existing treatments wanes when these illnesses worsen, and they can no longer control them. There are several ways to treat mental diseases like schizophrenia, However, due to cardiometabolic disorder, they are associated with several adverse drug reactions that can significantly impair the physical condition of a patient [3]. There is no known treatment or cure for other neurological conditions such brain injuries. Therefore, it is imperative and important to develop medications that prevent or stop neuronal death and the ensuing impairments. Since 85% of drugs fail phase 2 and 3 tests in clinical trials, creating new drugs is a challenging task that target mental diseases one of the most unsuccessful drug discovery processes [4]. Due to their propensity to fail in later stage trials [5], it is exceedingly expensive to create drugs for the Nervous System (Central nervous system); it is projected that bringing a treatment to market in 2019 would cost up to $2 billion [6]. To ensure that new discovery initiatives get off to the greatest possible start, Methodologies for computer-aided drug design (CADD, which stands) are essential. In contrast to conventional laboratory testing and design of drugs, these procedures are less time-consuming and labour-intensive, making them a mainstay in the early stages of drug development and a popular place to start new studies. Therefore, CADD can reduce the high related expenses and decrease the period from fundamental study before launching a medication. Structure-based and ligand-based techniques are the two primary types of CADD (Figure 1). Complexing agent-based techniques operate based on the idea that a medication's biological action is correlated with its chemical structure. To forecast new and improved compounds, structural activity relationships (SARs) can be calculated using a set of known active and inactive ligands. The primary obstacle in the creation of ligand-based drugs is describing chemical structure. This may be accomplished using 2D or 3D descriptions, depending on the amount of complexity. The 3-D structure form of the biological target must be understood to use structure-based pharmaceutical design strategies. Understanding the design of the binding sites can help one assess if a ligand would make a suitable lead molecule by

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looking at how the binding sites interact. To choose compounds that would be most appropriate for additional study, For tiny compounds, both structure-based and ligand-based methods depend on goodness of fit. Molecules are rated based on characteristics like binding energy, similarity, or correlations to molecular properties, which makes them perfect for the first phases of the drug development process. Although each of these techniques will be discussed independently, it is important to keep in mind that they are often used in combination to reduce the computing burden and generate more accurate results when screening large chemical libraries. A complementary process leading to new chemical entities is the end consequence.

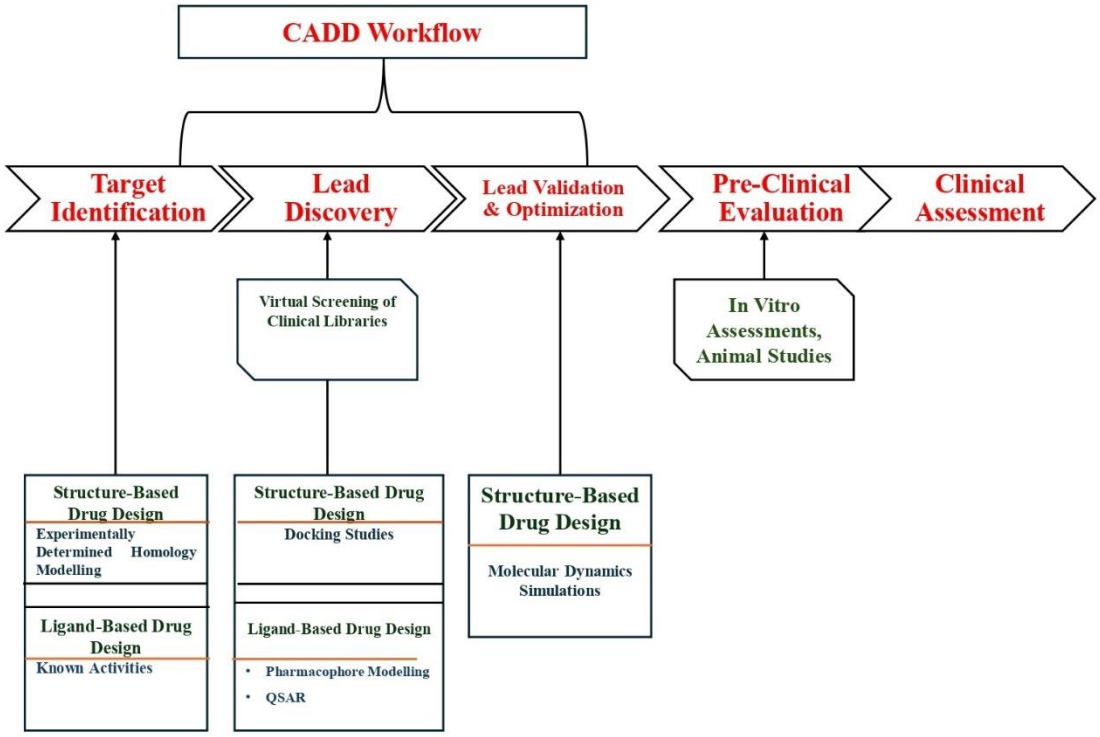

Figure. 1: - A drug design process that incorporates the CADD phases. Applications based on ligands and structures are described. Highlighted are a few examples of software programs and chemical libraries utilized at various phases of the operation. It should be mentioned that these lists are not all-inclusive and that more software programs and libraries are accessible [7].

Molecular modeling and other contemporary medicinal chemistry techniques have become more popular in Structure-activity correlations (SAR) may be effectively studied using based on research pharmaceutical companies [8]. These approaches have also been used to study pharmacokinetic features with pharmacodynamic information (e.g., strength, affinities efficacy, and selective) (ADMET, which is: intake, dispersion, metabolism, excretion, and toxicity) [9]. Alongside the field's advancements have been NMR (nuclear magnetic resonance) and X-ray crystallography are examples of biomolecular spectroscopic methods that have enabled incredible advancements in molecular and structure-based biology. With the use of these methods, more than 100,000 protein structures in three dimensions have been determined, yielding crucial structural data on important macromolecular therapeutic targets [10]. Initiatives to store, organize, along with study such data have led to an increased need for powerful and sophisticated computational tools. Consequently, the accurate combination of in silico & experimental approaches has enabled our present understanding of the intricate features of intermolecular recognition [11]. One important component of modern medicinal chemistry is structure-based drug development (SBDD) methods, which make use of three-dimensional structural information gleaned from biological targets [12]. Because of their numerous applications in the study of the recognition of molecules events, such as binding energetics, interaction between molecules, and induced conformational changes, docking of molecules, structure-based virtual screening (the SBVS), and molecular dynamics (MD) are the most widely used SBDD approaches [13]. Using libraries of bioactive small molecules is a novel approach to medication development. The unique chemical diversity observed in these libraries represents the space occupied by ligands known for their interaction with a certain target. This type of data is used in ligand-based drug development (LBDD) methods [10]. Among the most successful LBDD methods are ligand-based virtual screening (LBVS), pharmacophore development, QSAR modeling, and similarity finding [14]. Both academia and industry have found SBDD and LBDD approaches to be effective drug discovery methods due to their

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versatility and synergistic nature [15]. Several structural, chemical, and biological data have effectively used the integration of various methodologies [16, 17].

DRUG DESIGN BASED ON STRUCTURE (SBDD):

SBDD is a cyclical process that includes the slow collection of data. Potential ligands are found through in silico investigations, which start with a target structure that is known. The most promising compounds are created after these molecular modeling procedures [18]. Biological parameters, including potency, affinity, and effectiveness, are then evaluated utilizing a variety of experimental platforms [19]. If active molecules are identified, the three-dimensional structure of the ligand-receptor complex may be solved. Several intermolecular features that facilitate molecular identification may be seen thanks to the accessible structure. The structural descriptions of complexes between ligand and receptor can be useful for mechanistic research, studies of binding conformations, characterization of significant interactions between molecules, characterization of unknown binding sites, and the elucidation of ligand-induced conformational changes [20]. The structural information is linked with biological activity data after the identification of a ligand-receptor complex [21]. In this manner, new steps of the SBDD process incorporate molecular modifications that might increase the affinity of new ligands for their binding site. Since ligand binding may cause a substantial conformational change, the aim of the receptor's flexibility is an important consideration during the modeling stage. To overcome the flexibility issue, methods like MD and flexible docking are helpful [22,23].

MOLECULAR DOCKING:

The docking of molecules among the most widely used methods in SBDD, is highly accurate when predicting the shape of small-molecule ligand inside the right target binding site [24]. Drug discovery relied heavily on molecular docking when the 1980s saw the development of the first algorithms [25]. Investigating key molecular procedures, like as ligands binding methodologies and the accompanying intermolecular in connections that stabilize the ligand-receptor complicated, is one example of how this may be done easily [26]. Additionally, Molecular docking techniques, which provide quantitative estimations of binding energetics, rank docked molecules based on the attachment affinity of ligand-receptor complexes [26, 27]. A key component of virtual screening is accurately evaluating and assessing the binding of docked molecules. Three categories include commonly used scoring functions, as documented in many articles [28, 29]: (a) Binding affinity determined by Force field-based functions are used to calculate the target-ligand complex's physical atomic interactions. Solvation & entropy terms can also be evaluated. (b) Empirical-based functions employ simpler energy terms, such as those for hydrogen bonding and hydrophobic interactions, determined by experimental binding affinity data. (c) Knowledge-based functions obtain binding energy using statistical analyses generated from an initial group of protein–ligand atom pairs frequencies. Various docking systems and their score functions have been evaluated in numerous research to assess how well they can rank and score ligands that attach to a protein target. Despite significant advancements in present scoring mechanisms, further work is required to improve hit rating accuracy. The target (ranking or score), as well as the ligands series and families of proteins under consideration affect how well scoring functions perform [30–33]. When it comes to scoring and ranking compounds, it has been shown to be more advantageous to combine the outcomes of two or more scoring systems and create a consensus. Due to its higher accuracy, consensus scoring increases the likelihood of finding real possible hits [34, 35].

DRUG DESIGN BASED ON LIGANDS (LBDD):

Essential structural and physicochemical characteristics (molecular indicators) that oversee the watched biological activity can be found using data from a group of ligands active against a pertinent target (enzyme or receptor) in situations where the intended the protein's 3-dimensional structure is unavailable. In this case, it is hypothesized that molecules with comparable structures interact with the target and show comparable biological reactions [36], and to create a reliable ligand-based screening model, the chemical set should span a broad range of levels (a minimum of four orders of magnitude) [37]. Pharmacophore-based approaches and connections between quantitative structure and activity (QSARs) are common ligand-based design strategies. The structure of the therapeutic target is unknown when employing the ligand-based pharmaceutical design technique, and the receptor's homology modeling is used to anticipate the structure. After choosing the best-generated model, additional adjustments, including QSAR, were made to identify the best compounds exhibiting the greatest potential drug-receptor interactions. However, the biochemical reaction of the target receptor depends on a thorough understanding and knowledge of drug metabolism, ADME research, and model stereochemistry. Bioisosterism aids in process optimization by improving the lead compounds' pharmacodynamic and pharmacokinetic characteristics. Moreover, the safety and improved therapeutic profile of a medicine are greatly dependent on the use of retro metabolism-based drug design (RMDD) techniques [38].

1. **Freely Available:** 3 tools (AutoDock, Dock, FRED)
2. **Paid:** 7 tools (Gold, Glide, FlexX, LigandFit, ICM, eHiTS, Surflex-Dock)

Search Method Breakdown

- **Genetic Algorithm: -** AutoDock, Gold
- **Monte Carlo: -**Glide, LigandFit, ICM

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- **Incremental Construction: -**FlexX, eHiTS, Surflex-Dock
- **Shape Fitting: -**Dock (sphere sets), FRED (Gaussian)

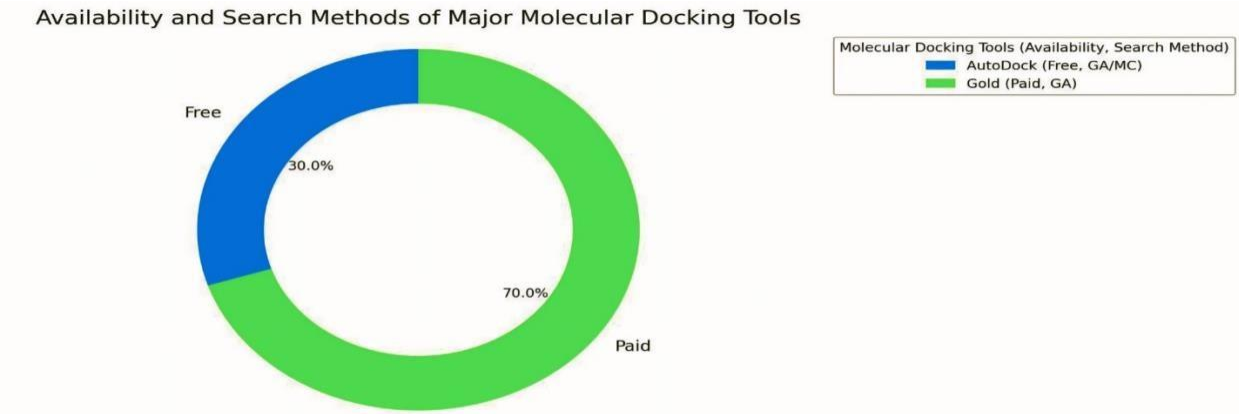

Figure. 2: - Molecular Docking Tools and their Availability and Search methods [38].

RELATIONSHIP BETWEEN QUANTITATIVE STRUCTURE AND ACTIVITY (QSAR):

The cornerstone of QSAR research is the idea that structural or molecular differences in a group of chemicals are linked to changes in bioactivity [39, 40]. This association is used to create novel chemicals and predict their biological characteristics theoretically through the creation of a statistical model [41]. The following criteria must be fulfilled in order to generate a reliable QSAR model: (a) the biological activity data has to come from a standard the experimental protocol and be sufficiently large (at least 20 current compounds) in order for the potency values to be similar as well (b) compounds must be appropriately selected for the purpose of training and validation groups; (c) The ligand molecular descriptions must not autocorrelate in order to avoid overloading; and (d) the model's predictions must be validated externally and/or internally to determine its usefulness and predictivity [42]. When compared the molecular field investigation (CoMFA) [43] is still one of the most employed 3D-QSAR methods more than thirty decades after it was first developed. Field adaptation for molecular comparison, or AFMoC [46], and the link between spectral structure and activity (S-SAR) [45], Topomer CoMFA [44], and analysis of comparative residue interactions (CoRIA) [47] are more modern 3D-QSAR techniques. Despite its noteworthy achievements in the field of drug devlopment, 3D-QSAR continues to have several drawbacks that may handle by more advanced multidimensional QSAR methods, such as 4D, 5D, and 6D-QA. The development of 4D-QSAR focused on ligand orientation and conformation at the target interaction site, while 5D-QSAR considers issues such receptor flexibility and induced fit effects. Finally, 6D-QSAR considers the solvation effects, especially its vital role in receptor-ligand interaction [48]. Improvements in QSAR model construction and validation have Additionally, improvements in software speed have made it conceivable & processing Strength, such as Discovery Bus [49] and AutoQSAR [50]. Both approaches include continually adding new artificial intelligence agents and system descriptions, allowing for the objective discovery, updating, and validation of Several hundred statistical models with great prediction power.

PHARMACOPHORE MODELING:

Finding drugs with distinct scaffolds; however, a comparable Pharmacophore screening aims to determine the three-dimensional arrangement of significant interacting functional groups [51]. The pharmacophore model may incorporate binding site information by using the biologically active conformation of possible medications. Furthermore, the molecular alignment stage of QSAR modeling studies is when pharmacophore modeling is commonly conducted [52]. Programs like Discovery Studio, PHASE [53,54], Ligand Scout [55], and MOE are frequently used for automated pharmacophore creation. There has previously been a thorough study of these programs and other methods [56]. Therefore, to reduce the number of false positives and false negatives, respectively, it is crucial to develop a framework that has a well-rounded sensitivity and specificity. The model may be made less restricted by refining the spatial restrictions in regions that are inhabited by inactive molecules. Additionally, characteristics that are inconsistent with active chemicals must be eliminated from the model or made optional. Validation tests must be conducted after model refining to assess a model's sensitivity and specificity in comparison to an external test set [56]. Sequence-derived 3D pharmacophore modelling may be produced without both a set of active ligands and receptor 3D data. Based on the idea that comparable receptors can bind with similar ligands, Pharma3D can generate a database of single-feature pharmacophores and determine a similar sequence pattern for ligands biomolecular identification in protein families utilizing homologous models and 3D crystal structures [57]. This technique has been successfully applied to virtual screening for GPCR (family A). According to theory, sequences with similar motifs might distinguish the exact same ligand functionality in a same geographic area. The fact that is used to identify the sequence motifs associated with single-feature pharmacophores and

create the 3D pharmacophore model. For therapeutic targets with little to no accessible receptor and ligand information, this method is appealing despite its drawbacks [57,58].

"ADMET" STANDS FOR "ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION, AND TOXICITY":

The need of identifying leads' ADMET properties early in the drug screening process arose from high attrition rates brought on by subpar pharmacokinetic profiles. However, it is not feasible to spend time and money experimentally evaluating the pharmacokinetic characteristics of millions of substances. Virtual screening may therefore be used to exclude compounds with undesired characteristics and filter hits to quickly assess a lead chemical's drug-likeness prior to additional clinical testing [59]. The ADMET filters in silico are used to forecast a compound's drug-like properties and are obtained from chemical or molecular descriptors, just like QSAR. The most basic and well-known models are the Veber rules [62], The Five Lipinski Rules [60], and for fragments, the rules of Three [61]. We may filter a huge chemical database or a list of possible leads using publicly accessible web servers such as ChemBioServer [63] and Free ADMET Filtering-Drugs2 (FAF-Drugs2) [64,65]. In addition to displaying compounds and graphing molecular attributes, ChemBioServer can also filter compounds according to toxicity, steric clashes, and other chemical characteristics, search for substructures, categorize chemicals and recommend a spokesperson for every group [66]. However, FAF-Drugs2 offers several pre-defined filters, including the ones listed above, as well as others like the reactive group filter and the central nervous system (CNS) filter [67]. The identification of compounds with unfavorable moieties may also be done using pharmacophore models made from toxicity-causing inhibitors [68]. Drug metabolism can be addressed with the use of reactivity models like those found in SMARTCyp. An application called SMARTCyp, which can be downloaded for free, predicts where Phase I CYP450-mediated decomposition is most likely to occur in 2D chemical structures. It uses quantum chemical simulations to evaluate the responsiveness of ligand segments and the availability of atom in the molecular structure to identify possible sites of metabolism [69]. A similar approach is also used by MetaSite [70] to find possible metabolic reactivity sites, but the query input is the compound's 3D configuration. We should bear in mind that the in silico ADMET models are more useful for qualitative examination of hits or complex sets as opposed to for precise quantitative value prediction. The above techniques have useful for ranking a class of drugs that have been identified for evaluation of a certain descriptor and SAR in vitro or in vivo [71].

COMPUTER-AIDED DRUG DESIGN USING BIOINFORMATICS:

The National Institutes of Health, also known as NIH, created the Biomedical Information Technology and Science Initiative (BISTI) to evaluate the current state of bioinformatics in the United States. According to BISTI, bioinformatics has uses in biomedical studies, namely in pharmaceutical development and discovery projects. It was believed that bioinformatics will revolutionize the way medications are discovered, developed, tested, and finally sold [72]. The specialist field of Using computational methods, computer-assisted drug design (CADD) models drug-receptor interactions with one another. Bioinformatics tools and applications are essential to CADD approaches. On the hub's support side, Databases, software programs, information management, computer resources, and information technology all contribute to bioinformatics infrastructure. Molecular biology, genomics, proteomics, other developing fields (such as transcriptomics and metabolomics), and CADD research all heavily rely on bioinformatics techniques [73].

VIRTUAL HIGH-THROUGHPUT SCREENING (vHTS):

To create novel therapeutic molecules, pharmaceutical firms are always looking for fresh leads. Virtual high-throughput screening is one search technique. If a chemical has a substantial affinity for a protein target, it will be compared to database of small molecules compounds in vHTS. A chemical can be taken out of the database for additional testing if there is a "hit" with it. On sufficiently big, clustered computers, it is possible to screen several million chemicals in a few days using today's processing capabilities. Researchers can save a significant amount of time and money by pursuing a small number of good leads for additional development. One excellent illustration of a vHTS compound library is ZINC [74].

LIGAND-BASED vHTS:

The observed activities of some known drugs can be utilized to build a pharmacophore model in situations when the target's structure is unknown. The latter encapsulates the arrangement of essential characteristics that potential ligands should match, such as hydrophobic groups and hydrogen bonds. The most promising applicants from the library can be chosen using this approach as a template [75,76]. This approach may also be employed as a filter prior to applying a structure-based vHTS, resulting in a final docking of just 1–10% of the original database [77].

STRUCTURE-BASED vHTS:

Docking methods are most likely to be applied most simply in structure-based vHTS. It involves utilizing a molecular docking tool to identify the protein target's binding mechanism for a comprehensive library of real or hypothetical substances [78–80]. Approximations of the binding free energy or associated affinity of the drug are made using the bound conformations. The most promising molecules are then kept for additional experimental examination. Docking applications for vHTS that are most frequently used include DOCK, FlexX, Glide, GOLD, and AutoDock. A few minutes

or less is the maximum amount of time that can be spent on each docking because the libraries employed in this method range in size from hundreds of thousands to a few million compounds. The size of the database is determined by a trade-off among the total amount of compounds that can be analysed in a reasonable amount of time and the required coverage of its chemical space. Conformational sampling is consequently relatively restricted, and vHTS suffers from many false negatives despite the continuous advancements in computer technology. Although a great deal of money has been spent on HTS and vHTS, and there have been several successful trials [81–84], the results in terms of novel compounds entering the clinic may be viewed as relatively unsatisfactory [85,86].

DEEP LEARNING'S GROWTH IN COMPUTER-ASSISTED DRUG DISCOVERY:

Even though DL, which is, or deep learning is not a novel approach— The situation became used for decades in language and image processing—its use in drug development initiatives has only just been apparent [87]. To manage the computationally costly computations involved in deep learning, this has been expedited using GPUs [88]. By employing several processing layers, or neurons, to generate predictions from enormous sets of multi-dimensional data, DL goes beyond conventional machine learning techniques [89]. DL models may be trained using biological data for various CNS targets from open-source datasets like ChEMBL [90], PubChem [91], and MolData [92]. Pharmaceutical companies also frequently employ internal databases from experimental research [93]. While there are many other kinds of deep learning architectures, multi-tasking learning (MTL), long-short-term memories (LSTM), recurring neural networks (RNNs), and convolutional neural network networks (CNNs) are the most often used in drug design and discovery. Therefore, this will be the review's focus. Schmidhuber et al. [94] and Le Cun et al. [89] offer thorough analyses of all forms of deep learning and the underlying theories behind them. Due to their architecture's resemblance to the visual cortex, CNNs are most frequently utilized in image recognition [95]. CNNs use a feature map that is produced from convolutional layers to gather information about whether features are present or absent in various picture regions. CNNs have an awareness of space advantage compared to alternative designs for DL because of these feature maps. The model's nonlinearities and variable interactions are then taken into consideration by using A linear activation function that has been corrected (ReLU). To avoid model overfitting, the data collected in the layers will be compiled by a pooling layer. To link the output to the hidden layers, these procedures will be carried out several times using at least one completely linked layer [96]. With a greater accuracy over other forms of Deep neural network technology and learning from machines (DNN) techniques that rely on molecular fingerprints, CNNs are utilized in drug design to take characteristics out of molecular graphs in two or three dimensions [97]. The molecular graphs' features may be utilized to determine the optimal binding positions and affinities of ligand-protein complexes [98,99] or to forecast pharmacokinetic characteristics [97]. To find novel the disease of Alzheimer's therapy with inhibitors of AChE, graphic CNNs were used, using pictures of molecular fingerprints as the input. Three distinct machine learning methods: XGBoost, random forest, and linear regression—were surpassed by the deep learning model. Out of two million tiny molecules in the library, two hit compounds were found. The resultant leads showed promise as possible medications as they could pass across the blood-brain barrier (BBB) And performed better in vitro than galantamine [100].

APPLICATIONS TO NEUROLOGICAL AND PSYCHIATRIC CONDITIONS:

Drug design now requires the use of computational approaches. Recent instances have shown how these methods may speed up the drug development process and cut down on the time and cost of clinical trials and laboratory testing. Additional examples are included in the text below. It offers an overview of how CADD approaches are being used to produce medications that target neurological and mental diseases. The most common disease target identified by our literature search was Alzheimer's disease; several CADD trials employing a wide variety of pharmacological targets are detailed below. The search for novel therapies is critical since Over 55 million individuals worldwide suffer from Alzheimer's disease, and the WHO estimates that figure will nearly double in the next 30 years [101]. This requirement is best shown using CADD research in Alzheimer's disease applications. Targets like α7 nAChR were chosen to enhance the therapy choices for individuals with schizophrenia, which was the most prevalent mental illness target in the literature study. It is crucial to remember that, although having identical target proteins, many of the diverse treatment areas covered here have radically different clinical phenotypes. It is outside the purview of this work to discuss the connection between common disease genotypes and different clinical presentations, which can be partially explained by epigenetic variables [102].

ALZHEIMER'S DISEASE:

To discover new Alzheimer's disease therapies, a 3D-QSAR model with multi-target functionality was developed targeting the serotonin transporter (SERT) and acetylcholinesterase (AChE), GSK3β, or glycogen synthase kinase, and beta-secretase 1 (1 BACE1) [103]. The QSAR model was constructed using both A model of a neural network that is artificial (ANN) and multilinear regression utilizing IC50 data from ChEMBL [106]. FQSARModel was used to create molecular descriptors, then the 2D ligand structures were converted to 3D using OpenBabel. ANN models were chosen for use in virtual screening as it was evident during model validation that they performed better. The ZINC (biogenic) database's more than 20,000 chemicals docked against each of the four proteins. 57 substances having favorable a binding agent effectiveness & therapeutic characteristics were evaluated against the QSAR models after docking in both Autodock and

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Glide. According to the models, there was potential for five ligands to target three out of the four proteins, at least. (1, Figure 3A) ZINC4027357. was one drug that showed both AChE and BACE1 inhibition. At the chosen potencies, none of the hits exhibited inhibitory qualities against GSK3β or SERT.

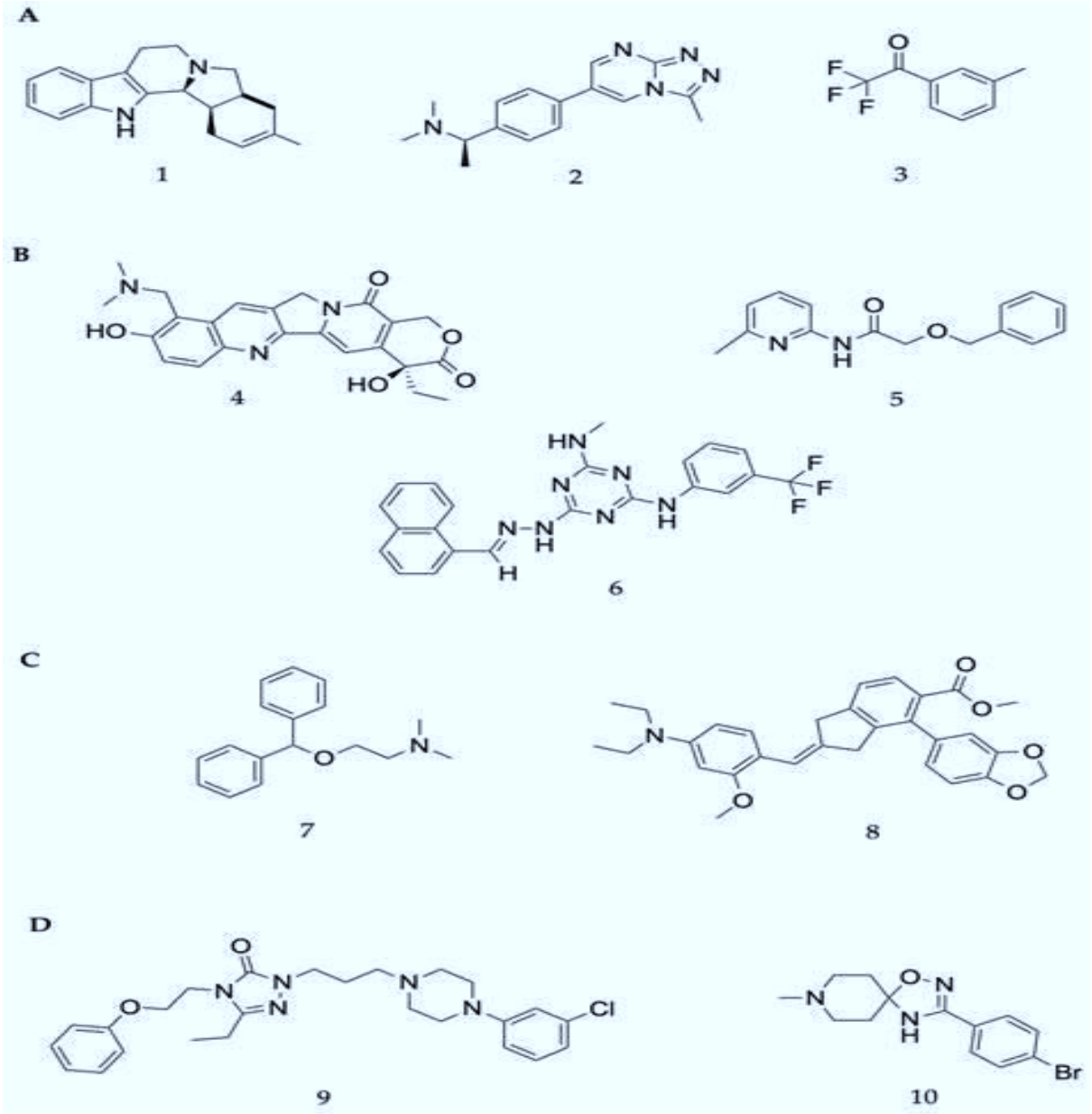

Figure. 3: - The molecular makeup of lead compounds with the highest reported activity in vitro from representative papers are covered in the following section. It is suggested that the molecules might be used in treatments for schizophrenia (D), neuropathic pain (C), Alzheimer's syndrome (A) and Parkinson's disease (B) [7].

THE DISEASE PARKINSON'S:

Examining links among licensed drugs and Parkinson's disease-related proteins, drug repurposing research sought to develop novel therapies for the condition. The accuracy of the CNN model was 91.57%, which was better than other benchmark techniques (such as DTINet and deepDTnet). The CNN model also fared better than conventional machine learning methods. Using molecular docking, to ascertain if these ligands and the desired proteins interacted favorably, the top ten compounds from the unidentified specimens were evaluated against the target protein 5-hydroxytryptamine receptor 2A (5HTR2A). Three of the 10 ligands exhibited comparable binding energies when pimvanserin was used as a positive control; This most promising of these was topotecan (3, Figure 3B), an inhibitor of topoisomerase [104]. To find chemicals that resemble piperine and medications that target these targets, a different deep learning method was developed employing a deep neural network design. The accuracy of the model was 87.5%. To uncover comparable structures, 57,423 compounds from the PubChem database and the databases ZINC databases were subjected to a similarity search based on

piperine. Five of the 101 compounds that were chosen for additional study via bonding in auto-docking 4.0 were suitable for AMBER platform MD simulations. According to the MD and docking investigations, the additional ring present in the best-performing molecules (5, Figure 3B) likely helps create the bonds of hydrogen in the active site, enhancing their ability to inhibit Monoamine-oxidase A as well as B (the MAO-A and MAO-B) [105]. Schrodinger's Maestro software's Glide and Prime modules were used to do a Over 1.6 million of small molecules were docked against a homologous model of LRRK2. A total of twenty-eight high-performing compounds were acquired for biological analysis. LY2019-005 and LY2019-006, two small compounds with unique characteristics, were discovered to be able to pass through the blood-brain barrier. That binding mechanism of these ligands was examined using MD simulations. The most effective ligand was LY2019-005 (6, Figure 3B), It showed the two the wild-type strain and G2019S mutant enzymes' nanomolar IC50 values. Given the neurotoxic potential associated with the G2019S variant of LRRK2, nanomolar IC50 is particularly important [106].

NEUROPATHIC PAIN:

To prevent bias, the biological data of 180 sigma-1 receptors (S1R) inhibitors were chosen from the scientific literature and split into 4:1 training and test sets. After then, the randomization process was carried out fifty times. MOE software was utilized to generate 206 molecular descriptors, and principal component analysis (PCA) was utilized to reduce their dimensionality. Using the partial least squares approach, A 3D-QSAR model based on atoms was produced. Its final model had an R2 of 0.92 and an RMSE of 0.29, both of which are indicative of a model with strong predictive capabilities. To provide structural details of the binding location to the 3D-QSAR model, an energy-based pharmacophore was also created. This was employed in the Schrödinger's Glide-developed virtual screening trials to make sure the ligands were oriented correctly for the binding site. Following pre-filtering procedures, 1935 FDA-approved drugs were selected from the Drug Bank dataset using the pharmacophore model. Next, each ligand's best-fitting conformer was screened using the 3D-QSAR model. Using a radio–ligand binding experiment, twelve of the best-performing ligands that lacked biological affinity data for S1R were subjected to further in vitro testing. Phenyltoloxamine and diphenhydramine, two drugs, demonstrated 66 and 70% inhibition at 1 μM, respectively. Additionally, diphenhydramine (7, Figure 3C) has been reported in the literature to be an adjective analgesic [107]. To find novel binding sites and potential therapies for neuropathic pain, A highlight on the target sequence (HoTS) model developed using deep learning was used to scan the purinergic P2X3 sequence of proteins [108]. Following the identification of possible binding sites using the DL model, to verify their feasibility, the volume of these binding sites was assessed using simulations using MD in the CDOCKER programming package. Utilizing the BIOVIA program's known antagonist's binding mechanism and its variations, a pharmacophore model was created for each of the four newly discovered binding areas. The pharmacophore model was used to screen more than 97,000 chemicals. After that, 2346 ligands in all were docked to help prioritize them for in vitro evaluation; 500 of them were chosen for experimental confirmation. Sixteen compounds with low micromolar IC50 values and unique structures were found. The most effective lead chemical was compound 8 (Figure 3C).

SCHIZOPHRENIA:

Using 159 sigma 2 receptor (S2R) inhibitors that have been documented in the literature, a 2D-QSAR model was created. Each ligand's molecular descriptors were created using MOE software to create a QSAR model. Four methods were produced: the authors' own GreedGene algorithm, Lasso, genetic algorithm (GA), and stepwise regression. GreedGene was chosen for screening because it performed the best, with an R2 of 0.56. Glide was also used to create a pharmacophore model for virtual screening. More than two thousand small compounds were screened through the Drug Bank database using the QSAR model, which has a pKi cut-off of 5.5. In contrast to the pharmacophore approach, shape-based screening was performed on the top 120 ligands after screening. Both siramesine-like ligands and compounds with a scaffold consisting of piperazine, which or tetrahydroisoquinolinyl molecules were kept for in vitro testing. The strong affinity for S2R binding of these scaffolds is well recognized. This scaffold was found in 30 compounds, which were deemed potential leads. Three FDA-approved medications, nefazodone, cinacalcet, and pimozide, were found to have nanomolar binding affinity values after six molecules completed biological testing; nefazodone (9, Figure 3D) was the most powerful of the three [109]. Using eleven α7 nAChR agonists from the literature, a pharmacophore was created. The pharmacophore was made up of one positively ionized group, a hydrophobic center, and a hydrogen bonding area. Additionally, a recursive partitioning model was employed to lower the quantity of false positives. The ChemDiv database was virtually screened against these two models. Ten of the 13 ligands that were chosen for in vitro evaluation after filtering to make sure there were no violations of the Lipinski criterion showed inhibitory effects. T761-0184's strong potency led to its selection for more research. To determine the binding mechanism for structural optimizations, this ligand was made to conform to an α7 nAChR homology model. Out of the 51 optimized structures, B10, which is (10, Figures 3D) was the most subtype specific for α7 nAChR. Additionally, B10 was one of the most interesting ligands with an IC50 threshold of 5.4 μM [110].

CNSMOLGEN: A DE NOVO CNS DRUG DESIGN APPROACH USING DEEP LEARNING:

A revolutionary molecular generation model called CNSMolGen was created to create medications for the central nervous system (CNS) from the ground up. The model creates novel chemical compounds with CNS therapeutic characteristics using a set of bidirectional recurrent neural networks (BiRNNs). More than 90% of novel compounds with CNS

therapeutic characteristics that might be synthesized were produced by the previously taught model. To evaluate the model's capacity for CNS medication optimization, transfer learning was carried out on tiny datasets with biological activities. Particularly when working with minimal datasets, the model showed notable efficacy in producing CNS medications. SSRI was used as an example to validate the use of CNSMolGen in the real production of CNS medication molecules. 129 of the 215 compounds that the model produced had strong molecular docking binding affinities. Future CNS drug development will be given a fresh boost by this model's performance, which shows its promise in CNS drug design and optimization [111,112].

FUTURE PROSPECTIVES

In the field of the CNS, or central nervous system, drug development, changing because of the confluence of deep learning (DL) and computer-aided drug design (CADD). This strategy seeks to address issues including rising prices and high development failure rates. Advanced multi-omics integration for targeted therapies, real-time drug screening and optimization, the development of novel therapeutic targets through deep learning models, cross-disciplinary collaboration, drug repurposing and precision medicine, ethical and regulatory adaptations, global collaborative networks, improved predictive modeling for long-term therapy efficacy, AI-driven drug design for neurodegenerative diseases, and quantum computing for drug discovery are some of the major opportunities for the future. These developments will speed up drug discovery timelines, enhance the precision of molecular docking, predictive modeling, and the design of highly precise CNS-targeted medications, and allow the creation of customized treatments based on each patient's own molecular profile.

CONCLUSION

CNS drug discovery is being revolutionized by the combination of Deep Learning (DL) and Computer-Aided Drug Design (CADD), which is overcoming rising costs and high development failure rates. Therapeutic options for neurological and psychiatric illnesses are being identified and optimized more quickly because to CADD methodologies like LBDD& SBDD. Its capacity of machine learning to produce extremely precise CNS-targeted medications is demonstrated by the CNSMolGen model, which makes use of BiRNNs. Targeted, customized treatments based on the molecular profiles of individual patients will result from the combination of multi-omics data with AI-driven drug development. Real-time drug screening will increase the effectiveness of clinical studies and cut down on the time needed to find viable medication candidates. Advances in precision medicine, medication repurposing, and emerging novel therapeutic targets will open new treatment options for illnesses for which there are now no viable treatments. Quantum computation has the potential to revolutionize the process of creating drugs since it allows for the simulation of chemical interactions at the atomic level.

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