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1,5 BENZODIAZEPINE AS A ANTIEPILEPTIC ACTIVITY

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ABSTRACT

Epilepsy is characterized by the presence of recurrent seizures. A seizure can be defined as “an episodic disturbance of movement, feeling, or consciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex”. One in every three patients with epilepsy is probable to be severely disabled. It is continuing this scenario as an attempt to develop potent and nontoxic anti-convulsant agents. Recently discovery of benzothiazepine derivatives as an anticonvulsant agent is significant area for research in medicinal chemistry as it is free from all side effects which is shown by a developed as an anticonvulsant agent. In these we have presented result of 2D and 3D docking poses of molecule containing 1,5 benzodiazepine pharmacophore as anticonvulsant agents Docking analysis was utilized to predict the mechanisms of action of the designed derivatives for anticonvulsant potential. All the molecule exhibited binding score in the range of 7.5 to 8.5. It was noted that the docking score of 2BXF was almost same as that of selected standard range i.e 7.5 as potent anti-epileptic agent.

KEYWORDS: Molecular docking, auto dock pyrx.

1. INTRODUCTION

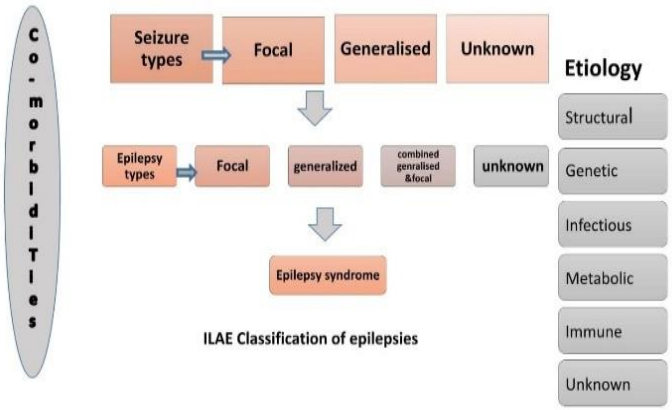
Epilepsy is a condition that affects approximately 70 million individuals worldwide. In India, there are approximately 10 million cases of epilepsy. Although there are only a few incidence studies from India, the most recent one reports an age-standardized incidence rate of 27.3/100,000 per year. Despite the increasing number of anti-epileptic drugs (AEDs) available since the discovery of phenytoin in 1930, nearly one-third of individuals with epilepsy experience persistent seizures. Drug-resistant epilepsy (DRE) is characterized by “the failure of adequate trials of two tolerated appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".

According to a recent meta-analysis of 38 studies, the incidence proportion of DRE ranges from 0.06 to 0.51, and the prevalence ranges from 0.11 to 0.58. Drug-resistant epilepsy (DRE) poses a significant global challenge, impacting the well-being of patients.[1]

Many antiepileptic drugs (AEDs) have been developed and are the treatment of choice for seizures. A seizure results from disruption in brain electrical activity that can be transient or recurrent. According to the Institute of Medicine, epilepsy is defined as or more unprovoked seizures at least 24 hours apart. Epilepsy is one of the most common neurologic disorders in the United States, affecting approximately 2.2 million people. Infrequent febrile seizures are not considered epilepsy. According to a recent report by the World Health Organization, 50 million people have epilepsy worldwide. In 40% of cases, epilepsy has an underlying prenatal or postnatal central nervous system origin, and in 60% there is no identifiable cause. All patients with epilepsy require AEDs, and approximately one-third require more than AED. AEDs are being increasingly used for prophylaxis in patients with seizure tendency.

AEDs are classified by generation. The older (or first) generation includes phenobarbital, which was first available in 1912. (23) It was followed by many others, including phenytoin, primidone, ethosuximide, carbamazepine, valproate, and benzodiazepines. This group is primarily metabolized by the liver via cytochrome P450 and associated isotypes, with potential adverse effects on liver function.[24] The second-generation medications have been available for more than 20 years and have fewer adverse effects. This group includes felbamate, lamotrigine, levetiracetam, gabapentin, pregabalin, tiagabine, topiramate, vigabatrin, and zonisamide. They are mostly eliminated by the kidney and have decreased risk of interaction with other medications metabolized by the liver. The newest or third-generation group includes rufinamide, stiripentol, lacosamide, eslicarbazepine, retigabine, and perampanel. Because of their relatively recent availability, the data on their adverse effects are limited. Certain AEDs, across the 3 generations, are metabolized by aromatic hydroxylation (eg, phenytoin, primidone, zonisamide, carbamazepine, lamotrigine, phenobarbital, felbamate, and oxcarbazepine) and, hence, are called aromatic AEDs. In a small percentage of individuals, the metabolism of these compounds leads to the accumulation of toxic metabolites known as arene oxides. In a small number of individuals (16 of 100,000), aromatic AEDs have the potential to cause severe immune-mediated hepatotoxicity. They are also more implicated in causing drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, which is also called antiepileptic hypersensitivity syndrome or drug-induced hypersensitivity syndrome.[2]

Types of epilepsy



The epilepsy types are as follows: (1) focal, (2) generalized, (3) combination of focal and generalized, and (4) unknown. To determine which of these a patient has, all seizure types a patient has must be defined, and then the data must be combined to determine the epilepsy type. If a patient has focal aware cognitive to bilateral tonic clonic seizures which arise from the left and right temporal lobes, they have focal epilepsy. If they have both focal as well as generalized seizures (as in Lennox–Gastaut syndrome, for example), they have combined focal and generalized epilepsy. Once the epilepsy type has been defined, then the etiology should be determined. The categories defined for epilepsy etiologies aspart of the epilepsy classification are (1) structural, (2) genetic, (3) infectious, (4) metabolic, (5) immune, and (6) unknown. A patient may have more than one etiology, and these are not hierarchical.(25) Describing epilepsy as having a structural etiology requires identification of a structural finding that is the likely cause of their epilepsy.(26) A patient with a glioblastoma in the left frontal lobe and seizures emanating from the left frontal lobe would be classified as having epilepsy due to a structural etiology. In contrast, a patient with seizures coming from the right temporal lobe who has a small calcified meningioma in the occipital lobe would not, as the meningioma is likely irrelevant to the epilepsy. However, if it was later found that this patient had seizures originating in the region of the meningioma and propagating to the hippocampus, this epilepsy would be structural.[8]

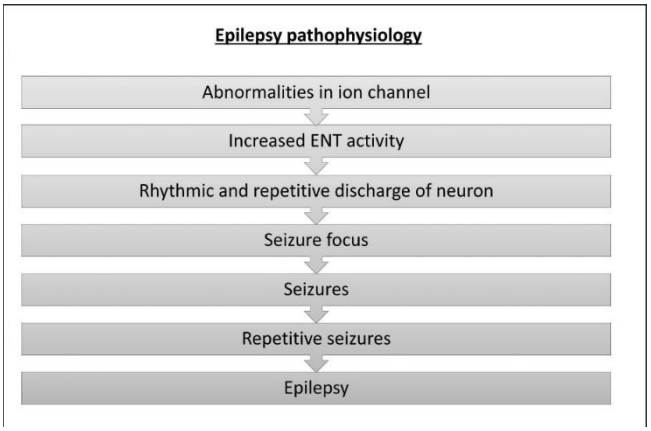
Pathogenesis

Stroke is the most common cause of acquired epilepsy. The pathogenesis of epilepsy after stroke has been studied in depth, with some mechanisms confirmed while others being new hypotheses that awaits confirmation. Currently, it is widely accepted that epilepsy occurs after stroke due to the imbalance of excitatory and inhibitory transmission in the CNS. Some mechanisms have also been proposed, including metabolic abnormalities, synaptic reorganization, proliferation of astrocytes, destruction of BBB, genetic susceptibility and changes in brain network structure. In particular, the changes of brain network structure in patients with epilepsy after stroke are receiving more and more attention, and further studies are needed to determine the independent predictors of post-stroke seizures and different types of seizures, in order to guide clinical prediction of stroke patients who may develop some type of epilepsy. It is important to investigate the new brain network structure in patients with epilepsy after stroke to determine whether there is a new fxed epileptogenic network. This will provide insight into targeted drug intervention strategies in patients with specific brain network structure to prevent the onset of epilepsy and ameliorate aggravation of disability in patients with stroke.[9]

Pathophysiology

Epilepsy is the process by which structural and molecular changes occur in the brain and predispose towards epileptic seizures.[27] The epileptogenic process can be initiated by multiple underlying causes such as tumors, infections, stroke, and brain injuries. Epileptogenesis occurs prior to an unprovoked seizure and continues beyond the event. It is a dynamic process that can occur very quickly, after brain injury or stroke, or over an extended period of time (up to months in animal models, and years in humans.[27,28] This window presents a temporal opportunity for treatment approaches, but also provides challenges for studying the process. Understanding the pathophysiological changes that occur during epileptogenesis is a pivotal part of developing new therapies. Changes during epileptogenesis occur in both neuronal and glial cells, all of which contribute to the dysfunction of neuronal circuits. The mechanisms underlying epileptogenesis suggest that the pathophysiological and compensatory changes are connected. Animal models of epileptogenesis have displayed histologically-detectable changes, such as sprouting along the mossy fiber

pathway, neurogenesis, and gliosis alterations, all of which can contribute to the potential for hyperexcitability.[29] The condition most frequently associated with mossy fiber sprouting is temporal lobe epilepsy (TLE), the most common type of epilepsy in adults (30), but can occur in epilepsy patients without TLE.[22] Sprouting occurs when granule cell axons in the inner molecular layer (mossy fibers) project into the hilus of the dentate gyrus and CA3 region of the hippocampal formation, creating their own dendritic field. Mossy fibers synapse onto hilar mossy cells, CA3 pyramidal cells, and interneurons.[23] to create de novo recurrent excitatory circuits. Aberrant sprouting in a model of TLE was reported to contribute to excitatory feedback loops of normal and ectopic granule cells.[24] Another study described aberrant mossy fibers that drive inhibitory basket



cells to reduce neuronal excitability.[25] Mossy fiber sprouting is increased through the activation of several granule cell factors, such as neuromodulin and brain-derived neurotrophic factor (BDNF).[26] and involves the secretion and deposition of molecules of the extracellular matrix that facilitate aberrant growth.[27–29] The number of granule cells also affects mossy fiber sprouting. Hippocampal neurogenesis, which leads to the formation of new granule cells, is increased shortly after an epileptic seizure, but the increase is transient. The development of new granule cells, and their ectopic integration into neuronal networks contribute to aberrant mossy fiber sprouting that is evident post-seizure.

Benzodiazepine : BDZ also has wide pharmacological applications outside the central nervous system (CNS) such as anticancer, anti trypanosomal, non-nucleoside inhibitors of HIV-1 reverse transcriptase, antimicrobial agent, antimalarial, antitumor agent, inhibitors of cholesterol absorption, inhibitors of the respiratory syncytial virus, and inhibitors of HCV NS5B polymerase. Due to the broad biological applications of this class of compound, knowledge of structural parameters, electronic proprieties, and chemical reactivity of basic rings is certainly of great interest and can help in understanding the affinity of those drugs for the specific receptors. Thus the contribution in the systematization of their main therapeutic activities by modifying the old molecules or generating new substance. Literature revealed that there are many previous studies discussing the synthesis of different benzodiazepine derivatives with various biological activities based on modifications and substitutions to these six basic rings. However, to our knowledge, these chemical structures have not been the subject of a theoretical study.[3]

Benzodiazepines (BZDs) represent a diverse class of bicyclic heterocyclic molecules. In the last few years, benzodiazepines have emerged as potential therapeutic agents. As a result, several mild, efficient and high yielding protocols have been developed that offer access to various functionalized benzodiazepines (BZDs). They are known to

possess a wide array of biological activities such as anxiolytic, anticancer, anticonvulsant, antipsychotics, muscle relaxant, antituberculosis, and antimicrobial activities. The fascinating spectrum of biological activities exhibited by BZDs in various fields has prompted the medicinal chemist to design and discover novel benzodiazepine-based analoges as potential therapeutic candidates with the desired biological profile. In this review, an attempt has been made by to summarize.

1. Recent advances in the synthetic chemistry of benzodiazepines which enable their synthesis with desired substitution pattern;
2. Medicinal chemistry of BZDs as therapeutic candidates with promising biological profile including insight of mechanistic studies;
3. The correlation of biological data with the structure i.e. structure-activity relationship studies were also included to provide an insight into the rational design of more active agents.[4]

Benzodiazepines modulate the γ-aminobutyric acid (GABA) A receptor, and produce sedative, anxiolytic, and anticonvulsive effects, with potential dose-related effects on respiratory and hemodynamic parameters. Cardiorespiratory adverse effects have been reported in the treatment of status epilepticus with intravenous anticonvulsants and such effects have been observed in some studies of treatment for seizure clusters but were not observed in other studies.[5]

Benzodiazepines have been the mainstay of rescue therapy, with rectal diazepam (Diastat), in particular, considered the standard of care in an outpatient setting, as it is appropriate for administration by non–health care professionals. However, rectal administration is associated with several limitations, including that it may be difficult to administer during active seizure particularly in larger patients, has wide pharmacokinetic variability for reasons including that the gel can be expelled during seizure-associated incontinence, and may result in embarrassment to patients and caregivers. Consequently, there remains a need for easier, more consistent, and more socially acceptable routes of administration.[6]

Benzodiazepines (BZDs), such as lorazepam (LZP), midazolam (MDZ), diazepam (DZP) and clonazepam (CZP), are established first-line drugs for the acute treatment of seizures. BZDs are a family of drugs that exert their effects by allosterically modulating the activity of the ionotropic gamma-aminobutyric acid (GABA)-A receptor in the central nervous system (CNS). These drugs increase the probability that GABA binding to the receptor will open the associated Cl^- channel. Thus, these drugs generally decrease neuronal excitation and exhibit antiseizure, sedative-hypnotic, anxiolytic, muscle relaxant and amnesic properties. As a side effect, BZDs can cause drug dependence, mostly due to recreational misuse or long-term intake against medical advice, cognitive impairment and—when administered in higher doses—can cause respiratory depression.[7]

1,5 benzodiazepine derivative

1.N-desmethylclobazam

Clobazam (CLB) is approved as adjunctive treatment for seizures associated with Lennox–Gastaut syndrome in patients aged 2 years and older. It is converted to an active metabolite N-desmethylclobazam (NCLB) by CYP3A4, which is then broken down to an inactive metabolite by CYP2C19. This study characterizes the impact of CYP3A4 and CYP2C19 drug interactions on CLB and NCLB serum concentrations (Cp) and concentration/dose (Cp/D) ratios in pediatric patients with epilepsy.[10]

The authors monitored the plasma levels of clobazam (CLO) and its principal metabolite, N-desmethylclobazam (NCLO) during chronic treatment of more than 400 epileptic patients receiving different co-medications, such as phenytoin (PH), carbamazepine (CBZ), sodium valproate (VPA) and phenobarbital (PB). This study investigated the influence of age and antiepileptic drugs on plasma levels of CLO and NCLO.[11]

2. (2S)-6-(2-chlorophenyl)-2,3,4,5-tetrahydro-1-methyl-1H-benzodiazepin-2-ol

Loprazolam works much the same as most other benzodiazepines, which means its main mechanism of action is through its interaction with GABA receptors along the brain and central nervous system (CNS). GABA — or gamma-aminobutyric acid — receptors are the chief inhibitory neurotransmitters in the body, and what benzodiazepines do is potentiate their natural function in order to produce a generalized depressive state in the CNS. This effect then, in turn, is responsible for the anxiolytic, hypnotic, and muscle relaxant properties of benzodiazepines.[12]

3. 7-Nitro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one

Maximal Electroshock method was adopted to explore anticonvulsant effect. Swiss albino mice weighing around 25g were selected on approved from Institutional Animal Ethical Committee. Animals were exposed to an alternating current of 50 mA for 0.2 s through a pair of electrode to each ear. Animal were grouped in six numbers for standard, test and control group. Each group were treated with each selected test drugs (20mg/kg), diazepam (2mg/kg) and normal saline with1% tween 80 respectively, in a single volume of 2ml/kg. Duration of seizure in each animal was noted and percentage inhibition of seizure with each selected tested drugs and standard were with control.[13]

4. 7-chloro-5-(cyclohex-2-en-1-ylmethyl)-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one

Fourier transform-Raman and IR spectra of four compounds that are closely related to diazepam (Valium)1 have been recorded. The compounds, delorazepam, fludiazepam, flurazepam, and 7-chloro-1,3-dihydro-[2W]-1,4-benzodiazepln-2-ones and differ from diazepam by the substituents at positions 1 and 5 of the diazepine ring. The spectra show characteristic features associated with both the diazepine ring and substituents. A strong line near 1610 cm-1 in the Raman spectra is assigned to the C=N stretch of the diazepine ring, and very strong IR absorption near 1690 cm-1 is attributed to the C=0 stretching mode. Various IR and Raman vibrational features serve to characterize and differentiate these molecules. Evidence for intermolecular hydrogen bonding in one of the compounds (delorazepam) is presented.[14]

MATERIAL AND METHOD

Auto dock 2.0 was used to estimate molecular docking with sketch module-built ligand structures. The water molecules having their innate ligands were removed, polar H-atoms were restored to each molecule, and energy was then conserved. Pymol was used for three-dimensional depiction of binding interactions.[15]

Molecular docking analysis was applied to determine the interactions between the active ingredients determined according to their high potential on ion channels for the treatment of epilepsy and the protein targeting their mechanisms and to calculate the binding energy. In the study carried out with this method, firstly, the structures previously studied were extracted from the receptor structure in the Discovery Studio 2020 Client and the ligand structures were recorded in pdb format. In the second step, the structures saved in pdb format were converted to pdbqt format by following the necessary steps in the Autodock Vina program, which is the Autodock Tools interface. Then,

the conformational structure with the best binding affinity was sent into the receptor and the interactions were examined.[16]

Ligand Preparation

AutoDock accepts PDB or mol2 files as an input. In the novel compound, the first three-dimensional (3D) structure of the compound is prepared. The two-dimensional (2D) structure of the proposed compound can be prepared with the help of Chem Draw or Chem Doodle and saved as a SMILES file. The SMILES file is pasted into the online CORINA Classic service to prepare meals or.pdb files, but it needs further structural optimization through a suitable method such as Merck Molecular Force Field. On the other hand, for simple preparation to optimize 3D structures, the online molsoft is recommended. It can prepare 2D as well as 3D structures in a single place. During the conversion of a 2D structure into 3D, it automatically optimizes the structure through MMFF. It has been found that the most accurate, optimized structure can be offered by DFT, but MMFF is still useful for an organic molecule. If the proposed compound has a known structure, then its crystalline 3D structure can be obtained from PubChem and Chem Spider etc. The coordinate setting of proposed compounds needs the addition of hydrogen atoms that are included in the 3D structure. The proposed compound's open 3D structure is selected as a ligand in ADT, and the 'edit' button is clicked to add polar hydrogens, Gasteiger charge, number of torsions, and detect root. At this moment, the ligand will be visible on the screen in which aromatic carbons appear green and another fragment looks red. Now click 'ok' and save it as a ligand pdbqt file.[17]

Protein preparation

BZD compounds were reported to possess kinase enzyme inhibitory properties. The 3D structures of the proteins were retrieved from the RCSB PDB database as complexes bound with their respective co-crystallized inhibitors. The ligand and water molecules were removed from the protein and later assigned with polar hydrogens and Kollman charges. The designed molecules were minimized and the docking analysis was performed on the prepared proteins. The ligand-binding interactions with the respective proteins were compared with the co-crystalized ligands using a standard docked method, the same one used for the calculation of the RMSD of the docked molecules.[18]

The docking workflow encompassed three steps: protein preparation, ligand preparation and the docking operation. This process entailed the designation of bond orders, addition of hydrogen atoms, retention of waters beyond 5Å distance with ligands, and the construction of missing side chains and loops. Subsequently, H-bond assignments were optimized based on PROPKA-predicted pKa values, followed by a restrained energy minimization using the default force field. Protein grid files were generated by Receptor Grid Generation panel.[19]

CO-CRYSTAL LIGAND

Cocrystal structure of DENV-2 C protein in complex with an inhibitor. ST148 was added to the DENV-2 C protein to form a cocrystal differing by 1.5 Å. The cocrystal belongs to the P2 space group and has a symmetric C dimer, which forms a tetramer from the P2 crystallographic symmetry. Both inhibitors bind to the pocket formed by the C tetramer by kissing between dimers. The pocket has P22 symmetry due to the amorphous two-fold symmetry of the dimer and the crystalline two-fold symmetry of the tetramer. Therefore, inhibitor dimers can bind the pocket in both directions. Seven residues of each tetrameric protein (Thr30, Phe33, Leu35, Met37, Leu38, Leu50, and Phe53) are assembled in the inhibitor pocket. This model demonstrates the following inhibitor-protein interactions:

1. The two amine groups of the ST148 dimer form H bonds with one pair of Phe33 carboxylates, while the other

Phe33 carboxylate pair is absent in the C tetramer Binding;

2. A pair of Leu38 side chain groups into the triple ring of ST148;
3. The residue of ST148 binds via hydrophobic interactions.

Auto dock

Molecular docking was previously accomplished using AutoDock. When compared to AutoDock, the new AutoDock Vina can accelerate the rate by around two orders of magnitude thanks to its more precise binding algorithm. Furthermore, according to the training experiments used in AutoDock, binding mode predictions have greatly improved. Using multithreading on multicore computers allows parallelism to be processed more quickly. AutoDock Vina computes the grid maps automatically and groups the results transparently for the user.[20]

Pyrx

PyRx is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. PyRx enables Medicinal Chemists to run Virtual Screening from any platform and helps users in every step of this process - from data preparation to job submission and analysis of the results. While it is true that there is no magic button in the drug discovery process, PyRx includes docking wizard with an easy-to-use user interface which makes it a valuable tool for Computer-Aided Drug Design. PyRx also includes chemical spreadsheet-like functionality and powerful visualization engine that are essential for structure-based drug design. Please visit Videos page for getting started screencasts**.**

CB DOCK

CB-Dock is a protein-ligand docking method which automatically identifies the binding sites, calculates the center and size, customizes the docking box size according to the query ligands and then perform the molecular docking with AutoDock Vina. Large-scale benchmarks show that the cavity-focused docking can enhance the hit ratio and accuracy of blind docking. Accordingly, CB-Dock can facilitate the docking procedure and improve the accuracy by predicting the binding sites of target proteins using our curvature-based cavity detection approach (CurPocket) and the binding poses of query ligands using AutoDock Vina.

Pharmacokinetic analysis

Docking is a good approach to perform in silico screening on large library of compounds and propose structural hypotheses of how the ligands inhibit the target receptors. This procedure is invaluable in lead optimization.[21]

Molecular docking studies were analyzed for exploring the interaction mechanism between the receptor sites and inhibitors. In the field of drug discovery, the prediction of interactions between molecules and their targets has a great importance. One can easily find out the mechanisms of selectivity by the docking of molecules with protein targets.[22]

Analysis of panel of oral drugs and drug candidates and determine a self-selected threshold value to capture approximately 90% of the four calculation ranges. This analysis resulted in a set of “rules”: Its molecular weight is 500 pounds. Calculate the octanol/water partition coefficient (CLogP) £5. Value of hydrogen bond donor £5 Number of hydrogen bond acceptors £10. These expanded guidelines have been published as the "Rule of 5" (Ro5) and indicate that molecules with properties outside these limits are less likely to be absorbed orally. In practice, Pfizer ingredients

that violate more than two of the above rules are considered problematic. In many cases, Ro5 is misunderstood as the phrase "similar drug"

Molecular Weight (MW): Rule: The molecular weight should be less than 500 daltons.
Significance: Compounds with a molecular weight under 500 daltons are more likely to be efficiently absorbed through the gastrointestinal tract. Larger molecules may have difficulty passing through biological barriers.

Lipophilicity (LogP): Rule: The logarithm of the partition coefficient (LogP) should be less than 5.
Significance: LogP measures the lipophilicity of a compound. A LogP value below 5 suggests that the compound has an optimal balance of hydrophilic and lipophilic properties, making it more likely to be absorbed in the body. Compounds that are too lipophilic may have poor bioavailability.

Hydrogen Bond Acceptors (HBA): Rule: The number of hydrogen bond acceptors should be less than 10.
Significance: Hydrogen bond acceptors are sites on a molecule where it can form hydrogen bonds with surrounding molecules. Fewer acceptors indicate a molecule is less likely to form strong interactions that could hinder absorption.

Hydrogen Bond Donors (HBD): Rule: The number of hydrogen bond donors should be less than 5.
Significance: Hydrogen bond donors are sites on a molecule capable of donating hydrogen bonds. A lower number of donors suggests fewer potential interactions that could slow down absorption.
Molecular weight: 699.85
Log P: 6.9
Hydrogen bond donor: 4
Hydrogen bond acceptor: 11
Rotational bond: 7

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RESULT AND DISCUSSION

Epilepsy, a complex neurological disorder, presents various challenges in understanding its pathogenesis, identifying effective treatments, and optimizing therapeutic outcomes. This study explored the diverse facets of epilepsy, including its types, underlying mechanisms, pharmacological interventions, and computational approaches for drug discovery. The classification of epilepsy into generalized, focal, and mixed seizures provides a framework for understanding its clinical manifestations and guiding treatment strategies. The pathogenesis of epilepsy is multifactorial, encompassing genetic predisposition, neuronal hyperexcitability, neurotransmitter imbalance, and environmental triggers. Pathophysiological mechanisms involve aberrant neuronal firing, synaptic dysfunction, and network hyperexcitability, leading to seizure generation and propagation. Benzodiazepines and their derivatives, such as diazepam and lorazepam,

are cornerstone antiepileptic drugs that potentiate GABAergic inhibition, thereby suppressing excessive neuronal activity. Understanding their molecular interactions with GABA receptors through docking analysis elucidates their mechanism of action and aids in drug optimization. Molecular docking analysis enables the exploration of ligand-receptor interactions, guiding the design and optimization of benzodiazepine-based antiepileptic drugs. Ligand and protein preparation are critical steps to ensure the accuracy and reliability of docking results. Virtual screening of docking analysis facilitates the identification of novel compounds with improved efficacy and specificity, offering promising avenues for drug discovery. In these we have presented result of 2D and 3D docking poses of molecule containing 1,5 benzodiazepine pharmacophore as anticonvulsant agents. Pharmacokinetic analysis of benzodiazepines and their derivatives is essential for determining drug absorption, distribution, metabolism, and excretion profiles. Understanding the pharmacokinetic properties guides dosing regimens, predicts drug-drug interactions, and ensures therapeutic efficacy while minimizing adverse effects. All the molecule exhibited binding score in the range of 7.5 to 8.5. It was noted that the docking score of 2BXF was almost same as that of selected standard range i.e 7.5 as potent anti-epileptic agent. Overall, this study underscores the importance of interdisciplinary approaches in advancing our understanding of epilepsy and developing more effective therapeutic interventions. By integrating clinical, molecular, and computational insights, there is potential for improved management strategies and better outcomes for individuals living with epilepsy.

CONCLUSION

Epilepsy is a complex neurological disorder characterized by recurrent seizures, affecting millions worldwide. This study comprehensively examined the various aspects of epilepsy, including its types, pathogenesis, pharmacological interventions, and computational approaches for drug discovery and optimization. The classification of epilepsy into generalized, focal, and mixed seizures provides insight into its diverse clinical presentations and guides treatment strategies tailored to individual patients. Epilepsy's pathogenesis involves a complex interplay of genetic predisposition, neuronal hyperexcitability, neurotransmitter imbalance, and environmental triggers. Pathophysiological mechanisms contribute to aberrant neuronal firing, synaptic dysfunction, and network hyperexcitability, culminating in seizure generation and propagation. Benzodiazepines and their derivatives are key components of antiepileptic therapy, acting by potentiating GABAergic inhibition to suppress excessive neuronal activity. Understanding their molecular interactions through docking analysis elucidates their mechanism of action and facilitates drug design and optimization. Molecular docking analysis and virtual screening techniques enable the exploration of ligand-receptor interactions, aiding in the identification of novel compounds with improved efficacy and specificity as potential antiepileptic agents. Rigorous ligand and protein preparation are essential steps in computational drug discovery, ensuring the accuracy and reliability of docking analysis results. Pharmacokinetic analysis of benzodiazepines and their derivatives is crucial for determining drug absorption, distribution, metabolism, and excretion profiles, guiding dosing regimens, predicting drug-drug interactions, and optimizing therapeutic outcomes. In conclusion, this study highlights the interdisciplinary nature of epilepsy research, where clinical insights, molecular understanding, and computational methodologies converge to advance our understanding of the disorder and improve treatment strategies. By integrating these approaches, there is potential for the development of more effective therapies and better management of epilepsy, ultimately enhancing the quality of life for individuals living with this condition.

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