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Comparative Docking Study of Gamma-Aminobutyric Acid Receptor Subunit Alpha-1 Interactions with Approved and Emerging Antiepileptic Drugs

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Abstract
Epilepsy is a prevalent neurological disorder characterized by recurrent seizures resulting from abnormal brain activity, affecting around 1% of the global population. The GABA-A receptor, a critical mediator of inhibitory neurotransmission, is a key target for antiepileptic drugs (AEDs) aimed at restoring the excitation-inhibition balance in the brain. This study utilized molecular docking to investigate interactions between ten antiepileptic drugs—five approved (Gaboxadol, Allopregnanolone, Cenobamate, Topiramate, Clobazam) and five emerging (Zolpidem, Eszopiclone, Suvorexant, Lemborexant, Bretazenil)—with the GABA-A receptor α1 subunit. Docking simulations were performed using AutoDock Vina, with results analyzed to assess binding affinities, hydrogen bonds, and other molecular interactions. Findings reveal that emerging drugs such as Zolpidem, Suvorexant, and Lemborexant exhibit strong binding affinities comparable to approved AEDs, suggesting their potential to enhance seizure management. The study highlights diverse interaction profiles, including significant hydrogen bonding and hydrophobic interactions, which contribute to the stabilization of drug-receptor complexes. Insights gained from this study could guide the development of more selective and effective treatments for epilepsy, addressing the limitations of current therapies.

Keywords: GABA-A receptor α1 subunit, Antiepileptic drugs, Molecular Docking, AutoDock Vina

1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal electrical activity in the brain. It affects approximately 1% of the global population, making it one of the most common neurological conditions[1]. The impact of epilepsy on patients is profound, often leading to significant physical, psychological, and social challenges. Seizures can cause cognitive impairments, interfere with daily activities, and contribute to a decreased quality of life[2]. Neurotransmitters and their receptors play a crucial role in the pathophysiology of epilepsy. Abnormalities in neurotransmitter systems, particularly the balance between excitatory neurotransmitters like glutamate and inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA), are central to seizure generation. Receptor dysfunction, especially in GABA-A receptors, can exacerbate excitatory signaling and contribute to the development and persistence of seizures[3].

The GABA-A receptor is a pivotal component in the central nervous system, responsible for mediating inhibitory neurotransmission. As a ligand-gated ion channel, it primarily responds to the neurotransmitter GABA, allowing chloride ions to flow into neurons and resulting in hyperpolarization, which reduces the likelihood of neuronal firing[4]. This inhibitory effect is crucial for maintaining the balance between excitation and inhibition in the brain. Dysfunction or reduced activity of the GABA-A receptor can lead to excessive neuronal excitability, which is a hallmark of seizure activity in epilepsy[5]. Consequently, the GABA-A receptor is a key target in the development of antiepileptic drugs (AEDs). Medications that enhance the function of this receptor, such as benzodiazepines and barbiturates, increase inhibitory signaling and help to prevent or control seizures by restoring the excitation-inhibition balance[6]. Targeting the GABA-A receptor remains a critical strategy in the ongoing development of AEDs, aiming to provide better control over seizures with fewer side effects.

Current AEDs target various mechanisms to control seizures in epilepsy patients. Gaboxadol, a selective GABA-A receptor agonist, enhances inhibitory neurotransmission by directly activating GABA-A receptors, but its clinical development was discontinued due to adverse effects despite its potential[7]. Allopregnanolone, a neurosteroid, positively modulates GABA-A receptors and is used to treat seizures associated with specific conditions like epilepsy and postpartum depression, demonstrating strong

efficacy in enhancing inhibition[8]. Cenobamate, a novel AED, reduces neuronal excitability by inhibiting sodium channels and enhancing GABAergic signaling, showing promise in managing drug-resistant epilepsy[9]. Topiramate, a broad-spectrum AED, works by blocking sodium channels, enhancing GABA-A receptor activity, and antagonizing AMPA/kainate receptors, making it highly effective for various seizure types; however, cognitive side effects and weight loss are common limitations[6]. Clobazam, a benzodiazepine, enhances GABA-A receptor-mediated inhibition and is primarily used as an adjunct therapy for Lennox-Gastaut syndrome, though tolerance and sedation limit long-term use[10]. While these AEDs offer significant benefits in managing epilepsy, their efficacy can vary, and side effects remain a major challenge, underscoring the need for continued drug development.

Emerging AEDs, such as Zolpidem, Eszopiclone, Suvorexant, Lemborexant, and Bretazenil, offer novel mechanisms of action that could enhance seizure management in epilepsy. Zolpidem and Eszopiclone, typically used as hypnotics, are selective GABA-A receptor modulators with unique receptor subunit specificity, offering potential in targeting specific seizure subtypes with fewer side effects related to sedation[11]. Suvorexant and Lemborexant, dual orexin receptor antagonists, are designed to regulate the sleep-wake cycle, but their influence on neuronal excitability and network synchronization suggests they may help manage seizures, especially in patients with comorbid sleep disorders[12]. Bretazenil, a partial agonist of GABA-A receptors, offers a more selective effect on the GABAergic system compared to traditional benzodiazepines, potentially reducing tolerance and dependence risks[13]. These drugs are noteworthy for their novel approaches, targeting both neurotransmitter systems and unconventional pathways. They offer potential benefits in personalizing treatment, improving efficacy for refractory epilepsy, and reducing side effects associated with traditional AEDs.

Molecular docking is a computational technique used in drug discovery to predict the interaction between a small molecule (such as a drug) and a target protein or receptor. It involves simulating how a drug fits into the binding site of a receptor and calculating the strength of the interaction, which helps in determining the binding affinity and orientation of the drug[14]. This method is crucial in drug discovery as it allows researchers to screen vast libraries of compounds and prioritize those with the best potential for binding efficacy. Docking studies provide detailed insights into drug-receptor interactions, enabling the identification of key molecular

features responsible for binding, such as hydrogen bonds, hydrophobic interactions, and electrostatic forces. Understanding these interactions helps in optimizing drug candidates by modifying specific functional groups to enhance binding affinity and selectivity[15].

Molecular docking has been widely employed in the study of GABA-A receptors to investigate how various ligands, including antiepileptic drugs and sedatives, interact with this receptor's binding sites. By simulating these interactions, researchers can predict the binding affinity and optimal orientation of ligands within the receptor's specific subunits[16]. This approach is particularly valuable in studying the GABA-A receptor, a complex heteromeric ion channel, because it allows for the identification of subunit-specific binding sites that influence the receptor's response to different ligands. For example, docking studies have been used to explore how benzodiazepines, neurosteroids, and novel compounds interact with GABA-A receptor subunits to enhance inhibitory signaling[17]. Understanding these receptor-ligand interactions is crucial for improving drug efficacy and specificity. By identifying key molecular interactions that stabilize the binding of a ligand, researchers can design more selective drugs that target specific receptor subunits, potentially reducing side effects and increasing therapeutic benefits[18].

Previous molecular docking studies involving the GABA-A receptor have provided valuable insights into the receptor's interaction with various ligands, including benzodiazepines, barbiturates, neurosteroids, and novel antiepileptic drugs. These studies have revealed the importance of specific subunits, such as the α1, β2, and γ2 subunits, in determining ligand affinity and receptor activation. For instance, docking simulations have shown how benzodiazepines selectively bind to the α1 and γ2 subunit interface, enhancing inhibitory signaling by stabilizing the open conformation of the chloride ion channel[19]. Similarly, neurosteroid docking studies have identified key binding pockets within the transmembrane domain that potentiate GABA-A receptor activity[20]. However, despite these advances, there are significant gaps in the research. One major limitation is the incomplete understanding of how receptor subunit composition influences ligand binding in vivo, as many studies rely on static models that do not fully capture the dynamic nature of receptor-ligand interactions[21]. Additionally, docking studies often focus on well-known ligands, leaving less-explored compounds and their potential therapeutic roles under-researched. To enhance drug discovery efforts, further studies incorporating

advanced techniques like molecular dynamics simulations and considering allosteric modulation are necessary to refine our understanding of GABA-A receptor pharmacology.

Several studies have compared the interactions of various AEDs with the GABA-A receptor, revealing differences in their mechanisms and efficacy. For example, benzodiazepines like Clobazam and Diazepam bind to the GABA-A receptor at the benzodiazepine site, enhancing the receptor's response to GABA by increasing chloride ion influx and thus hyperpolarizing neurons[22]. In contrast, newer drugs like Cenobamate, though primarily a sodium channel inhibitor, also exhibit positive modulation of GABA-A receptors, increasing their inhibitory effects, which makes them highly effective in drug-resistant epilepsy[9]. Bretazenil, a partial agonist of the GABA-A receptor, demonstrates reduced sedative effects compared to full agonists like Clobazam, which could make it a better candidate for long-term use[13]. Studies comparing these drugs emphasize the importance of understanding the nuances of GABA-A receptor modulation, as different drugs affect the receptor subunits in varied ways, influencing therapeutic efficacy and side effect profiles.

Comparing approved and emerging AEDs through molecular docking is crucial for advancing epilepsy treatment by optimizing drug efficacy and specificity. Molecular docking predicts how different AEDs interact with specific receptor subunits, such as the GABA-A receptor α1 subunit, which is pivotal in inhibitory neurotransmission. While current research often focuses on well-established drugs, less-explored AEDs, particularly their interactions with important receptor subunits, remain understudied. This study addresses this gap by evaluating both approved drugs (Gaboxadol, Allopregnanolone, Cenobamate, Topiramate, and Clobazam) and emerging drugs (Zolpidem, Eszopiclone, Suvorexant, Lemborexant, and Bretazenil) using AutoDock Vina. By comparing these drugs, the study aims to uncover their binding affinities and interaction profiles with the GABA-A receptor α1 subunit. This approach not only benchmarks existing treatments but also investigates novel interactions with less-studied drugs, potentially identifying new therapeutic candidates and optimizing current therapies. Insights gained could lead to more selective drug development, enhancing treatment efficacy for epilepsy while minimizing side effects.

Rationale for Focusing on the α1 Subunit and Study Scope:

The α1 subunit was selected as the primary target for this comparative docking study due to its predominant role in mediating the sedative-hypnotic effects of many GABA-A receptor modulators (e.g., Zolpidem)

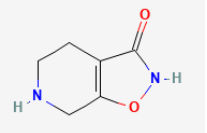
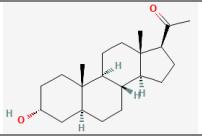
and its ubiquitous presence in receptor isoforms. This focus allows for a direct comparison of binding modalities within a well-characterized context. However, it is critically acknowledged that the antiepileptic and anxiolytic effects of many AEDs and benzodiazepines are primarily mediated through α2, α3, and α5-containing receptors. Therefore, the findings presented herein offer a partial, subunit-specific perspective and should not be interpreted as representing the complete pharmacological profile of these drugs, which arises from interactions with heteromeric receptor complexes.

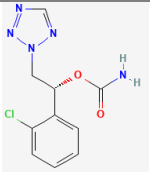
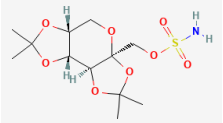
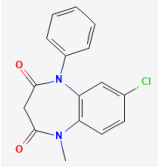
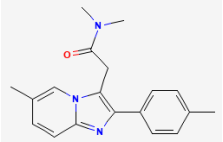
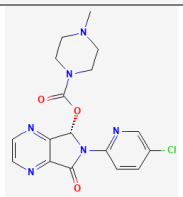
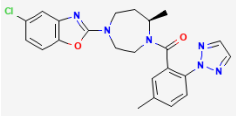
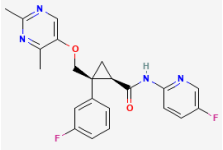
2. Materials and Methods

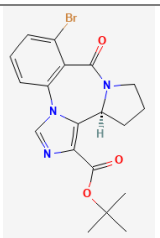
2-1. General Principles of Study

In this study, molecular docking was conducted using AutoDock Vina (version 1.1.2)[23]. The software was installed on a 5-core Windows-based computer. The interactions between the GABA-A receptor α1 subunit and ten antiepileptic drugs—five approved (Gaboxadol (THIP), Allopregnanolone, Cenobamate, Topiramate, and Clobazam) and five emerging (Zolpidem, Eszopiclone, Suvorexant, Lemborexant, and Bretazenil)—were investigated. Three-dimensional structures of the drugs in SDF format were obtained from the PubChem database (http://pubchem.ncbi.nlm.nih.gov)[24]. Table 1 illustrates the general and detailed chemical structures of these ten compounds. For the receptor, the crystallographic structure of the human GABA-A receptor (PDB ID: 6X3T), with a resolution of 2.55 Å, was retrieved from the Protein Data Bank (http://www.rcsb.org)[25]. This structure consists of nine chains and a total of 1,967 residues. The docking results were further analyzed using UCSF Chimera, LigPlot+, and the PLIP (Protein-Ligand Interaction Profiler) online tool.

Table 1. Chemical structures of the ten investigated drugs.

Compound Number	Drug Name	Structure	IUPAC Name
1	Gaboxadol (THIP)		4,5,6,7-tetrahydro-[1,2]oxazolo[5,4-c]pyridin-3-one
2	Allopregnanolone		1-[(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-hydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-

Compound Number	Drug Name	Structure	IUPAC Name
			tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl]ethanone
3	Cenobamate		[(1*R*)-1-(2-chlorophenyl)-2-(tetrazol-2-yl)ethyl] carbamate
4	Topiramate		[(1*R*,2*S*,6*S*,9*R*)-4,4,11,11-tetramethyl-3,5,7,10,12-pentaoxatricyclo[7.3.0.0^{2,6}]dodecan-6-yl]methyl sulfamate
5	Clobazam		7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione
6	Zolpidem		*N*,*N*-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide
7	Eszopiclone		[(7*S*)-6-(5-chloropyridin-2-yl)-5-oxo-7*H*-pyrrolo[3,4-b]pyrazin-7-yl] 4-methylpiperazine-1-carboxylate
8	Suvorexant		[(7*R*)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl]-[5-methyl-2-(triazol-2-yl)phenyl]methanone
9	Lemborexant		(1*R*,2*S*)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-*N*-(5-fluoropyridin-2-yl)cyclopropane-1-carboxamide

Compound Number	Drug Name	Structure	IUPAC Name
10	Bretazenil		*tert*-butyl (7*S*)-14-bromo-12-oxo-2,4,11-triazatetracyclo[11.4.0.0^{2,6}.0^{7,11}]heptadeca-1(17),3,5,13,15-pentaene-5-carboxylate

2-2. Preparation of GABA-A receptor α1 subunit and ten antiepileptic drugs for Docking

After obtaining the 3D structure of the human GABA-A receptor from the PDB database and antiepileptic drugs from the PubChem database, we performed a crucial step called Dock Prep using UCSF Chimera software. Dock Prep is an essential initial process conducted on both the ligand and receptor before actual docking. This process involves thoroughly cleaning and preparing the molecules. For ligands, Dock Prep involves removing unnecessary water and ion molecules, fixing any structural issues, and creating molecular files suitable for docking. For the receptor, this process may include removing water and extra ions, adjusting the conformation, and removing any unnecessary parts of the structure to optimize it for docking operations.

For the Dock Prep of the antiepileptic drugs' structures, the input files underwent the Dock Prep process using UCSF Chimera software (version 1.17.1). In this process, hydrogens were systematically added to the structure, and partial charges were assigned to the molecule. Subsequently, using UCSF Chimera software, we excluded all chains except for the α1 subunit (chain B) of the human GABA-A receptor due to its extensive structure. This focused approach allowed us to concentrate on the α1 subunit for further analysis and molecular docking (Figure 1). Moreover, ligands, water molecules, and extraneous ions were eliminated to streamline the structure. After the removal of redundant components, the input file underwent Dock Prep using UCSF Chimera software. In this phase, hydrogens were incorporated into the structure, and partial charges were assigned to the molecule. UCSF Chimera for Dock Prep leverages a blend of diverse algorithms for hydrogen addition and charge assignment. It integrates an algorithm for hydrogen addition based on protonation status and chemical norms. Additionally, it employs the AM1-BCC method to allocate partial charge based on the atomic and bonding environment of

each atom. This amalgamation of algorithms ensures that structures are primed for docking or other calculations, guaranteeing the accurate assignment of hydrogens and partial charges, essential for precise molecular modeling[26].

Subsequently, the structures underwent energy minimization using UCSF Chimera software. Conducting energy minimization before docking enhances the molecular structure and stabilizes it in the desired conformation. This optimization facilitates heightened accuracy and predictability in docking outcomes, mitigating the probability of structural and energetic inconsistencies. The GABA-A receptor α1 subunit and the ten antiepileptic drugs were individually subjected to Dock Prep and energy minimization to ensure comprehensive preparation prior to docking analysis.

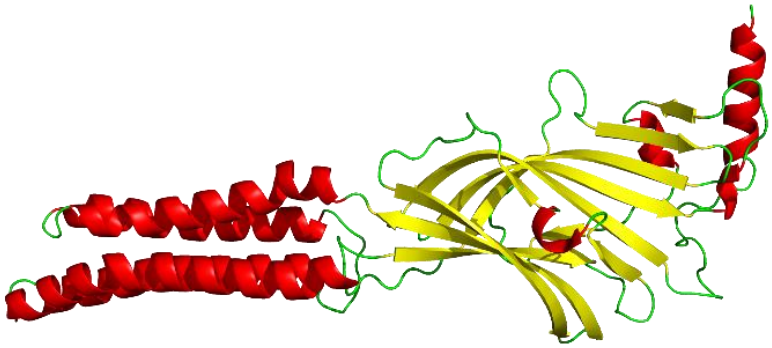


Figure 1. Crystal structure of the human GABA-A receptor α1 subunit, visualization by PyMol[27]**.**

2-3. Conducting Molecular Docking

To explore the binding interactions between ten antiepileptic drugs and the active sites of the human GABA-A receptor α1 subunit, molecular docking was employed. The grid box was positioned at coordinates x=140, y=115, z=132, with dimensions of 100 × 40 × 85, to align with the human GABA-A receptor α1 subunit for the docking process. Unlike conventional docking software that necessitates specific load configurations, AutoDock Vina exhibits versatility, accommodating various load models embedded within the input PDBQT files. Notably, it abstains from load calculations during the docking phase, relying instead on pre-defined loads within the input files, ensuring consistency and accuracy during the simulations. Subsequently, the findings were analyzed using USCF Chimera, LigPlot+ (version 2.2) software, and the PLIP online server.

Validation of Docking Protocol and Pose Selection:

To ensure the reliability and reproducibility of the docking results, each ligand was subjected to 100 independent docking runs. The resulting poses were clustered based on their root-mean-square deviation (RMSD) with a cut-off of 2.0 Å. The representative pose from the largest cluster (indicating the most stable and reproducible binding mode) and with the most favorable binding affinity score was selected for detailed interaction analysis. The average RMSD values of the top-ranked poses relative to the initial coordinate are reported in Table 2.

3. Results

The molecular docking results from AutoDock Vina, analyzed using UCSF Chimera, are presented in Table 2. The binding affinity score reflects the predicted strength of interaction between the ligand and receptor, with more negative values indicating stronger affinities. The RMSD (Root-Mean-Square Deviation) values for I.b. (initial bound) and u.b. (unbound) measure the deviation between the ligand's initial position and its best-docked state, as well as between the unbound reference state and the best-docked state. These values provide insights into the stability and reliability of the docking. Additionally, the total number of hydrogen bonds (HBonds) formed between the ligand and receptor, along with the number of ligand and receptor atoms involved in these bonds, are reported. This information offers a clearer understanding of the molecular interactions and helps assess the stability and affinity of the ligand-receptor complexes.

Table 2. Summary of molecular docking results from AutoDock Vina using UCSF Chimera.

Compound Number	Binding Affinity Score (kcal/mol)	RMSD I.b. (Å)	RMSD u.b. (Å)	HBonds (all)	HBond Ligand Atoms	HBond Receptor Atoms
1	-5	0	0	1	1	1
2	-7.5	0	0	0	0	0
3	-6	0	0	2	2	2
4	-6.1	0	0	1	1	1
5	-6.6	0	0	0	0	0
6	-7.3	0	0	0	0	0
7	-7.2	0	0	0	0	0
8	-7.8	0	0	0	0	0
9	-7.6	0	0	1	1	1

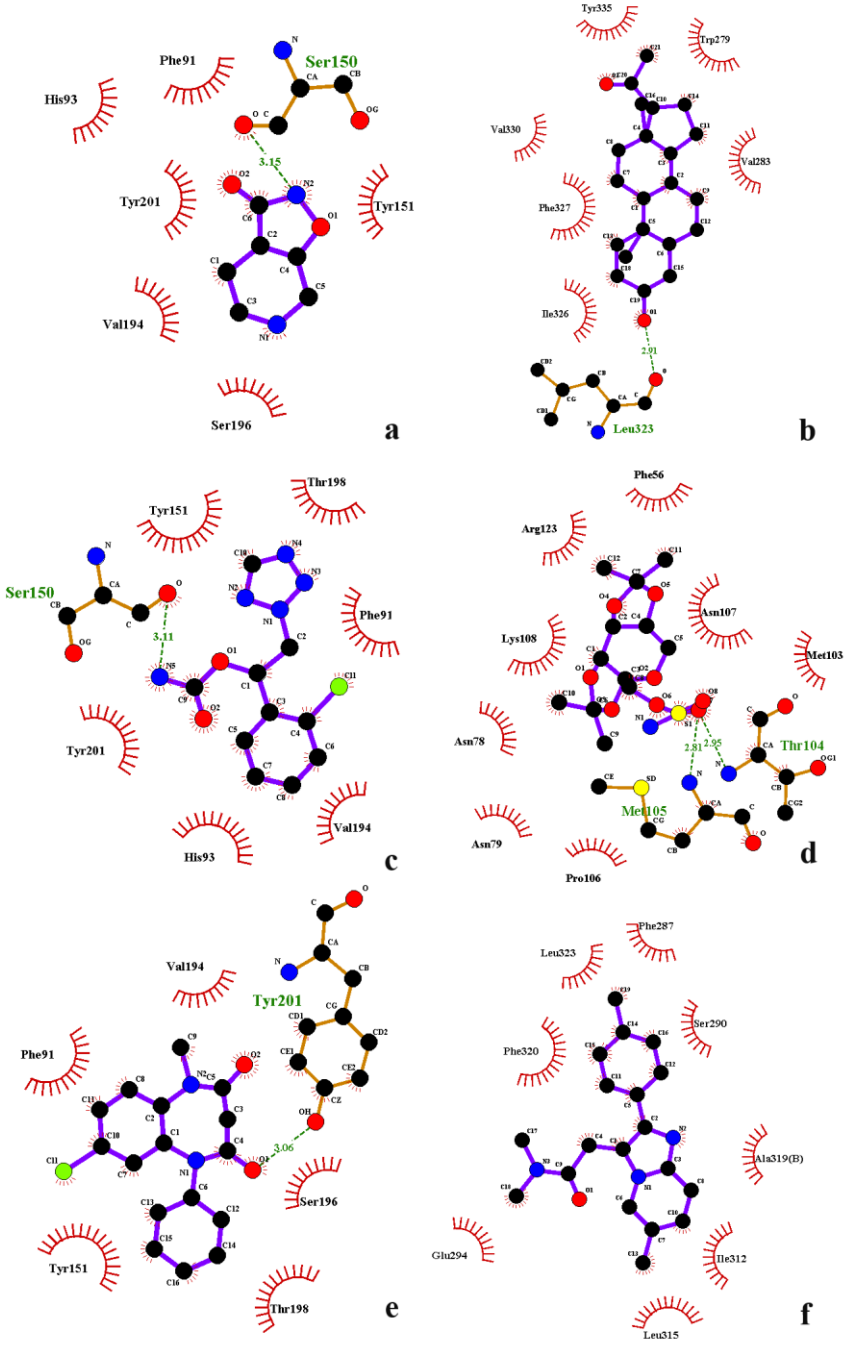
10	-6.6	0	0	0	0	0

Table 3 provides a comprehensive overview of all amino acids involved in interactions between the GABA-A receptor α1 subunit and the ten antiepileptic drugs, as identified by the PLIP server. These results highlight a range of molecular interactions, including hydrogen bonds, hydrophobic interactions, π-stacking, and π-cation interactions. Hydrogen bonds, formed between hydrogen atoms and electron-rich atoms such as oxygen, nitrogen, and fluorine, play a key role in stabilizing molecular structures. Hydrophobic interactions involve the nonpolar regions of molecules, contributing to the overall stability of the complex. π-Stacking refers to the interactions between aromatic rings, while π-cation interactions occur between aromatic rings and positively charged ions. These interactions significantly contribute to the structural integrity and the establishment of sturdy bonds between molecules. Furthermore, Figure 2 illustrates the receptor-ligand interactions generated using LigPlot+ software. The diagram highlights both hydrogen bonds and hydrophobic interactions between the receptor and the ligand, providing a clear visual representation of these key molecular interactions.

Table 3. Summary of possible molecular interactions between the GABA-A receptor α1 subunit and ten antiepileptic drugs, identified via Protein-Ligand Interaction Profiler server.

Compound Number	Involved amino acids in forming interactions			
	Hydrogen Bonds	Hydrophobic Interactions	π-Stacking	π-Cation Interactions
1	His93, Ser150	Val194	-	-
2	Tyr335	Trp279, Val283, Ile326, Phe327, Val330	-	-
3	His93, Ser150, Thr198	Phe91, His93, Val194	Tyr151	His93
4	Met103, Thr104, Met105, Asn107	Phe56, Asn78, Asn107, Arg123	-	-
5	Tyr201	Tyr151, Thr198	Phe91	-
6	-	Phe287, Ile312,	Phe320	-

		Phe320, Leu323		
7	-	Phe287, Leu323	Phe320	-
8	-	Trp279, Ala286, Leu323, Phe327, Val330	Phe287	-
9	His93, Ser197	His93, Val194, Tyr201	Phe91	Lys147
10	Asn79	Phe56, Asn78, Met105, Asn107, Arg123	-	-


Phe91
Ser150
His93
Tyr201
Tyr151
Val194
Ser196
3.15
a
Tyr335
Trp279
Val330
Val283
Phe327
Ile326
Leu323
2.91
b
Thr198
Tyr151
Ser150
Phe91
Tyr201
Val194
His93
3.11
c
Phe56
Arg123
Asn107
Lys108
Met103
Asn78
Thr104
Met105
Asn79
Pro106
2.81
2.95
d
Val194
Tyr201
Phe91
Ser196
Tyr151
Thr198
3.06
e
Phe287
Leu323
Ser290
Phe320
Ala319(B)
Glu294
Ile312
Leu315
f

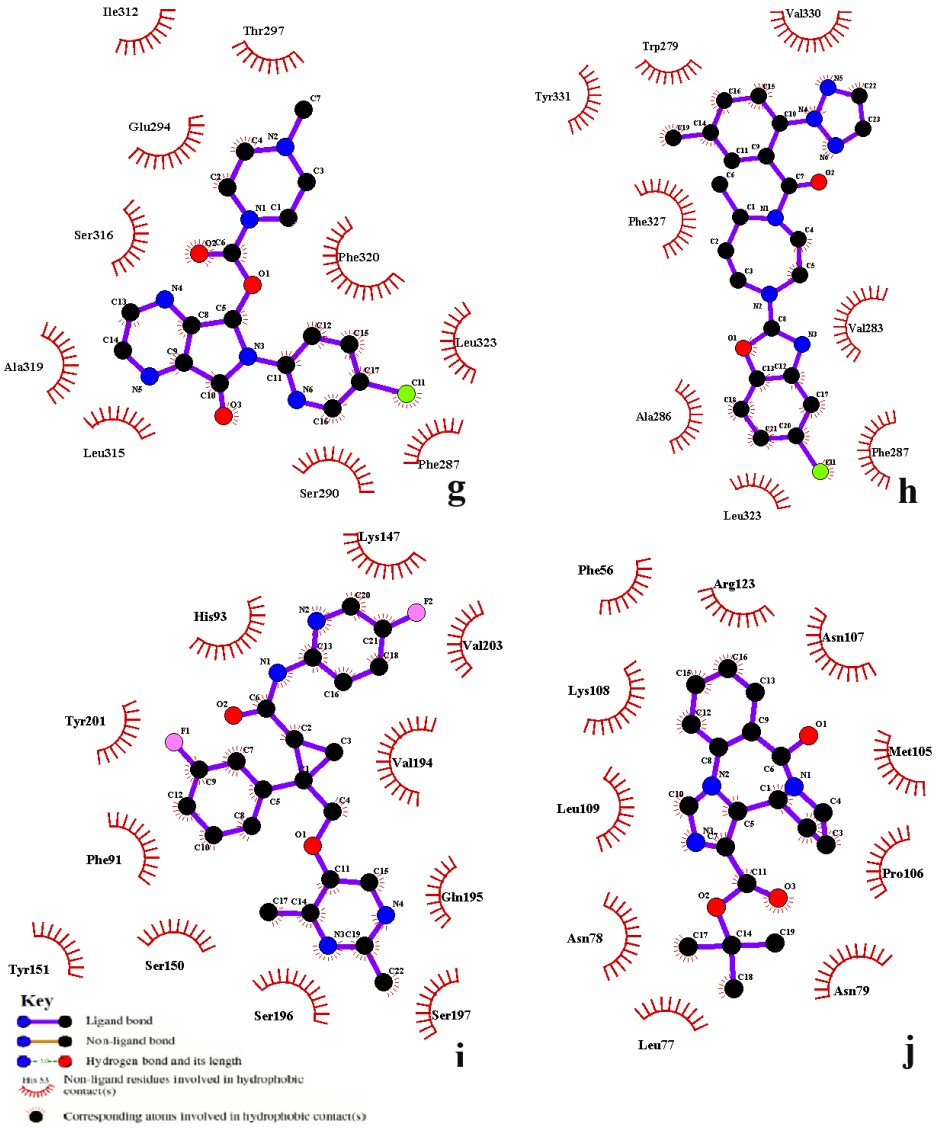


Figure 2. Possible interactions of the human GABA-A receptor α1 subunit and ten antiepileptic drugs—Gaboxadol (a), Allopregnanolone (b), Cenobamate (c), Topiramate (d), Clobazam (e), Zolpidem (f), Eszopiclone (g), Suvorexant (h), Lemborexant (i), and Bretazenil (j)— using LigPlot+ software.

4. Discussion

In this study, a comprehensive molecular docking analysis was conducted to

investigate the interactions between ten antiepileptic drugs—five approved and five emerging—with the GABA-A receptor alpha-1 subunit. The use of AutoDock Vina provided detailed insights into the binding affinities, hydrogen bond interactions, and molecular orientations of these drugs within the receptor's active site. The results highlight both the efficacy of current antiepileptic drugs and the potential of emerging drugs in modulating GABA-A receptor activity, which is critical for controlling seizure activity in epilepsy patients.

Table 2 summarizes the binding affinity scores and RMSD values from the molecular docking simulations. Binding affinity, as indicated by the negative values, reflects the strength of the interaction between the AEDs and the GABA-A receptor α1 subunit. More negative values correspond to stronger binding. All drugs had an RMSD of 0 Å, as we chose the first docking results, which were the best. This indicates that the docking simulations provided consistent and reliable binding positions every time. This RMSD value emphasizes the accuracy and dependability of our results.

Gaboxadol exhibited a binding affinity score of -5 kcal/mol. Despite its known efficacy in enhancing GABA-A receptor activity, the relatively weaker binding affinity in this study suggests that it may not be as tightly bound as other AEDs. The moderate binding affinity predicted for Gaboxadol in this static model provides a molecular snapshot of its interaction. However, the clinical profile of a drug, including its discontinuation due to adverse effects, is a complex multifactorial outcome influenced by pharmacokinetics, off-target effects, and dynamic receptor modulation in vivo, which are not captured by docking alone. Thus, while our data describes its binding pose, it cannot directly explain clinical outcomes[7]. Allopregnanolone demonstrated a higher binding affinity score of -7.5 kcal/mol, indicating a strong interaction with the receptor. This aligns with its clinical use as an effective GABA-A receptor modulator, particularly in conditions like epilepsy and postpartum depression[8]. Cenobamate and Topiramate showed similar binding affinities of -6 and -6.1 kcal/mol, respectively. Both drugs are known for their dual mechanisms of action—Cenobamate also inhibits sodium channels while Topiramate affects multiple targets. Their moderate binding affinities reflect their broad-spectrum efficacy and highlight their dual functionality[6],[9]. Clobazam had a binding affinity of -6.6 kcal/mol. As a benzodiazepine, its binding affinity is consistent with its role in enhancing GABA-A receptor activity, though its therapeutic use is limited by tolerance and sedation issues[10].

Zolpidem and Eszopiclone exhibited binding affinities of -7.3 and -7.2

kcal/mol, respectively. These results suggest that these drugs may have strong interactions with the GABA-A receptor α1 subunit, aligning with their selective modulation and potential utility in targeting specific seizure subtypes[11]. Suvorexant and Lemborexant had binding affinities of -7.8 and -7.6 kcal/mol, respectively. These dual orexin receptor antagonists, while primarily targeting sleep disorders, show promising interaction profiles that may extend their utility in epilepsy, especially in patients with comorbid sleep issues[12]. Bretazenil had the lowest binding affinity score of -6.6 kcal/mol among the emerging drugs. Its partial agonist activity might explain this, as it offers a more selective effect compared to full agonists[13].

Table 3 and Figure 2 present a detailed overview of the molecular interactions between the GABA-A receptor α1 subunit and ten antiepileptic drugs, analyzed using the Protein-Ligand Interaction Profiler server and LigPlot+ software. This section delves into the nature of these interactions, highlighting the diversity and specificity of binding modes exhibited by these drugs.

Hydrogen bonding is a critical factor in stabilizing drug-receptor complexes. Among the antiepileptic drugs, several demonstrate strong hydrogen bonding interactions with the GABA-A receptor α1 subunit. Gaboxadol and Cenobamate both establish hydrogen bonds with key residues such as His93 and Ser150, which are crucial for receptor binding. Cenobamate further interacts with Thr198, enhancing its binding affinity through additional hydrogen bonds. Allopregnanolone also forms hydrogen bonds with Tyr335, though this interaction is less pronounced compared to the others. Topiramate exhibits notable hydrogen bonding with Met103, Thr104, Met105, and Asn107, suggesting a strong interaction with the receptor. Clobazam forms hydrogen bonds with Tyr201, indicating a possible mechanism for its anticonvulsant activity.

In contrast, while Zolpidem, Eszopiclone, and Suvorexant do not engage in hydrogen bonding, Lemborexant and Bretazenil do. Lemborexant forms hydrogen bonds with His93 and Ser197, while Bretazenil interacts with Asn79. This variation in hydrogen bonding indicates potential differences in the binding modes of these drugs. The presence of hydrogen bonds in Lemborexant and Bretazenil suggests that, despite being less-studied, these drugs may share similar binding mechanisms with the approved drugs, highlighting a possible commonality in their interaction with the GABA-A receptor α1 subunit.

Hydrophobic interactions are essential for stabilizing the receptor-drug complex by aligning nonpolar regions. Among the approved antiepileptic drugs, Gaboxadol interacts with Val194, which supports its binding but is relatively limited in scope. Allopregnanolone, on the other hand, forms hydrophobic interactions with multiple residues—Trp279, Val283, Ile326, Phe327, and Val330—indicating a broader interaction profile that enhances its binding strength. Cenobamate interacts with Phe91 and Val194, which improves its binding specificity. Topiramate engages with several residues, including Phe56, Arg123, and Asn107, demonstrating a strong and versatile binding capability. Clobazam interacts with Tyr151, which contributes to its effectiveness.

In contrast, the emerging or less-studied drugs exhibit varied hydrophobic interaction patterns. Zolpidem and Eszopiclone primarily interact with Phe287 and Leu323, reflecting a more focused binding approach. Suvorexant shows significant interactions with Trp279, Ala286, and Leu323, suggesting a diverse binding profile. Lemborexant interacts with residues like His93 and Tyr201, indicating a blend of hydrophobic interactions. Bretazenil engages with multiple residues, including Phe56 and Met105, which may overlap with the binding sites of other drugs. These varied hydrophobic interaction profiles highlight the complexity and diversity of receptor-drug interactions.

π-Stacking and π-cation interactions play a role in further stabilizing receptor-drug complexes by involving aromatic and charged residues. Cenobamate stands out with its π-Stacking interaction with Tyr151 and π-Cation interaction with His93, which may enhance its binding specificity to the GABA-A receptor α1 subunit. In contrast, Gaboxadol, Allopregnanolone, and Topiramate do not show π-Stacking or π-Cation interactions, indicating that their binding is likely driven by other forces, such as hydrogen bonds and hydrophobic interactions. Additionally, Clobazam and Lemborexant show π-Stacking interactions with Phe91, while Zolpidem and Eszopiclone interact with Phe320, and Suvorexant interacts with Phe287. Bretazenil does not exhibit either interaction type. These differences in interaction profiles reflect the varied mechanisms through which these drugs stabilize their receptor bindings.

While the molecular docking approach offers valuable insights into drug-receptor interactions, it has limitations. Docking simulations use static models that do not capture the dynamic nature of receptor-ligand interactions or the impact of the cellular environment. Future studies should incorporate molecular dynamics simulations to better understand these

interactions. Furthermore, the most significant limitation of this study is its exclusive focus on the α1 subunit. Epilepsy therapeutics often target receptor assemblies containing α2, α3, β2/3, and γ2 subunits to achieve seizure control with minimal sedation. Our findings, while valuable for comparing binding to the α1 site, represent a simplified model and cannot predict effects on neuronal excitability or clinical efficacy. Future studies must investigate these interactions in the context of physiologically relevant heteromeric receptors (e.g., α1β2γ2, α2β3γ2) to yield translatable insights.

Perspective on Personalized Medicine in Epilepsy:

Contemporary epilepsy management is increasingly moving towards precision medicine, considering the patient's specific epilepsy syndrome, etiology (including genetic mutations in genes like SCN1A, GABRA1), and prior drug response. This docking study provides a population-level, theoretical comparison based on a wild-type receptor structure. A critical future direction would be to model how patient-specific mutations (e.g., in GABRA1) alter the receptor's binding pocket and affinity for these drugs. Such in silico pharmacogenomics approaches could eventually help explain differential drug responses and inform personalized therapeutic strategies, bridging computational predictions with clinical heterogeneity.

5. Conclusion

This study provides a detailed analysis of molecular interactions between ten antiepileptic drugs and the GABA-A receptor α1 subunit through molecular docking simulations. The results underscore the efficacy of both approved and emerging AEDs in modulating GABA-A receptor activity. The binding affinity data, with emerging drugs showing competitive or superior interaction profiles compared to approved AEDs, highlight that novel agents, particularly Suvorexant and Lemborexant, merit further in vitro investigation to explore their unexpected predicted binding to the GABA-A receptor α1 subunit, as revealed by this study. The detailed exploration of hydrogen bonds, hydrophobic interactions, and π-interactions reveals a complex interplay of forces stabilizing drug-receptor complexes, with potential implications for drug design. However, limitations such as the static nature of docking models and a focus on only one receptor subunit indicate the need for future studies incorporating molecular dynamics simulations and exploring interactions with other receptor subunits. This study enhances our understanding of GABA-A receptor modulation by antiepileptic drugs and paves the way for the development of more effective and targeted treatments for epilepsy.

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