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Design, Molecular Docking and ADME Study of New GABA Derivatives

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Abstract

Gamma-aminobutyric acid (GABA) plays a pivotal role in neuronal regulation within the Brain. This study aims to explore potential interactions between synthesized GABA derivatives and GATI through molecular docking simulations. Initially, GABA's historical significance and Therapeutic applications are outlined. The mechanism of action of GABAergic drugs and the role of GATI are elucidated. Subsequently, using ADME procedures and molecular docking protocols, the Physicochemical properties of synthesized compounds and their binding affinities to GATI are Investigated. Results reveal high gastrointestinal absorption and varying blood-brain barrier Permeability among the compounds. Docking studies show promising interactions, with compound G8 exhibiting notable affinity attributed possibly to hydrogen bond formations. This research offers Insights into potential drug development targeting GATI for modulating GABAergic signaling.

Aim:

Keywords: GABA, GATI Receptor , Molecular dockings, Neuropathy, ADME

Introduction

Gamma-aminobutyric acid (GABA) stands as one of the prevalent neurotransmitters, playing a pivotal role in regulating neuronal activity within the brain "!, The initial stage of its breakdown involves catalysis by aminobutyrate transaminase (ABAT, also known as GABA transaminase or 4-aminobutyrate aminotransferase). A decline in GABA levels, in comparison to the normal range, has been identified as a significant indicator in various neurological I disorders (21, These disorders encompass Alzheimer's disease l3l, 41 epilepsy and Parkinson's disease 151, Over the years, advancements in comprehending the mechanisms underlying GABAergic inhibition have paved the way for the informed development of several antiseizure medications (some medications have components of the GABA system, with noteworthy examples such as progabide l6l, vigabatrin 11, and tiagabine lS1, While rational design has been instrumental in creating some of these ASMs, including those mentioned, it's important to note that numerous other ASMs, like barbiturates, valproic acid, benzodiazepines, felbamate, topiramate, and stiripentol, exert their effects on GABAergic transmission without being guided by deliberate target-based strategies. Instead, their discovery was often by chance or resulted from

Phenotypic screening in animal models of seizures and epilepsy.

Mechanism of Action:

GABAergic drugs influence GABA transmission through various mechanisms, including direct GABA Receptor Agonists: Mimic GABA by binding and activating GABA receptors (e.g. muscimol, benzodiazepines) .GABA Transaminase Inhibitors: Prevent GABA breakdown, increasing overall brain levels (e.g., vigabatrin) (1, Positive Allosteric Modulators: Bind to GABA receptors, enhancing their response to GABA (e.g., benzodiazepines on GABA-A). Selective GABA Reuptake Inhibitors: Block GABA transporters (GAT),. prolonging GABA's presence in the synapse (e.g., tiagabine) 2), Tiagabine's unique status as the sole clinically approved GAT-1 selective inhibitor 13l demonstrates the remarkable therapeutic potential of This exclusivity highlights the vast, untapped targeting specitic GABA transporter lCARA eUntake inhibitors, Each GABA transporter opportunity r the development of subtype, beyond just GAT-1, might hold untapped potential for addressing a range of neurological conditions, making their

exploration an exciting frontier in drug development.

Chemistry :

The effective administration of gamma-aminobutyric acid (GABA) through peripheral Means is constrained by limitations stemming from its inability to readily traverse the blood-brain Diffusion barrier (BBB) except at exceptionally high doses, which consequently results in Pronounced adverse side effects 14, Moreover, the hydrophilic nature and doubly charged state of GABA molecules at neutral pH render them soluble in water as well as in acidic and basic solutions Preventing CNS penetration |1S,16| Recognizing this challenge, considerable research efforts have been directed towards devising Strategies to overcome the BBB and facilitate the successful delivery of GABA into the central Nervous system (CNS).For instance, modifications such as incorporating hydrophobic moieties at the 3-position of Compounds like gabapentin and pregabalin (look into Table 1) have been pursued with the aim of Enhancing CNS drug uptake. This approach seeks to capitalize on the lipophilic nature of the blood-Brain barrier, thereby promoting increased diffusion of these compounds into the CNS718].

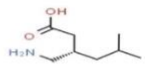
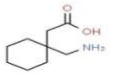
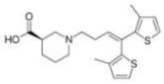
Pregabalin	
Gabapentin	
Tiagabine	

Table (1): (Chemical Structure of Pregabalin, Gabapentin and Tiagabine)

Suggested molecules

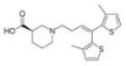
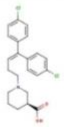
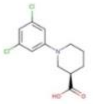
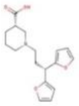
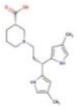
Reference (TGI)	
G 1	
G 2	
G 3	
G 4	
G 5	
G 6	
G 7	
G 8	

Table (2): Suggested molecules

ADME procedures :

Pharmacokinetic properties of Absorption, Distribution, Metabolism, and Elimination (ADME) were studied along with other physicochemical properties of the newly designed compounds using the SwissADME server. This server is a free website used to study the physicochemical parameters, the medicinal chemistry facilities, and the

bioavailability radar which are very important for the design and synthesis of new compounds.

The Docking Studies:

A fully licensed Cambridge Crystallographic Data Centre (CCDC)genetic optimization for ligand Docking (GOLD) Suite (2024.1) was utilized to estimate the docking results for the virtually Designed compounds. CCDC Hermes was used to evaluate the protein, ligands, hydrogen bonding Interactions, short contacts, and bond length calculation.

Preparation of ligands and target :

Cryo-EM structure of human GABA transporter GATI bound with tiagabine (7Y7Z) was downloaded from the Protein Data Bank (PDB). The chemical structures for the designed compounds were generated using ChemOfficesoftware (version 20) and con verted into 3D structures using CheBio3D (v. 20). The energy was minimized via the MM2 force field.

Molecular docking protocol :

The preparation of (7Y7Z) protein was carried out using Hermes software in the CCDC GOLD suite. The active site required for the interaction was designated depending on the binding of Tiagabine. The protein binding site residues were characterized within the distance of (10 A°) of the standard Reference (ligand) for the docking process. The default settings were selected for the rest of the docking process parameters. The number of generated poses was set as 10, while the top- ranked solution was kept as default. Also, the early termination choice was turned off. Chemscore kinase was used as a configuration template. While the piecewise linear potential (ChemPLP) was used as a scoring function. Finally, the generated results were saved as mol.2 files. The results that showed the best binding manner, the free energy of binding, and docked poses, were studied precisely to define the best binding and interaction of our designed Reference (ligand) with amino acid residues of the GATI receptor.

Results and Discussion

Interpretation of ADME study Notably, the compounds generally exhibit high gastrointestinal absorption, with varying degrees Of BBB permeability and bioavailability scores. Lipinski violation is minimal across most Compounds, with G4 being an exception due to its high LogP.

Table (3): ADME Study Results of the Suggested molecules

comp.	TPSA	H-acceptor	H-donors	MR	log P	GT absorption	BBB	Bioavailability score	Lipinski violation	M.wt
G1	40.54	2	2	46.56	0.84	High	Yes	0.85	Yes 0 violation	155.19
G2	40.54	2	1	67.48	2.31	High	Yes	0.85	Yes 0 violation	239.70
G3	40.54	3	1	60.99	1.19	High	yes	0.55	Yes 0 violation	197.27
G4	40.54	3	1	115.96	4.52	High	Yes	0.55	Yes, 1 violation MLOGP> 4.15	404.33
G5	40.54	2	1	72.49	2.84	High	Yes	0.85	Yes,0 violations	274.14
G6	77.84	4	2	69.84	1.25	High	No	0.56	Yes;0 violation	249.26
G7	66.82	5	1	85.35	1.82	High	Yes	0.55	Yes;0 violation	303.35
G8	72.12	3	3	99.45	2.22	High	Yes	0.55	Yes;0 violation	329.44

Figure (1): Boiled Egg of the Suggested Molecules

Analysis of studies using molecular docking

The G8 mnolecule demonstrates pronounced affinity and exhibits promising outcomes, potentially Attributable to its capacity to generate numerous hydrogen bonds, possibly facilitated by the Presence of amine groups (NH). Moreover, investigations indicate that compounds exhibiting the Highest scores typically manifest a compact configuration conducive to hydrophobic interactions.

For instance, the G4 molecule, characterized by a dual benzene ring structure, is anticipated to Display elevated hydrophobic interactions. Nevertheless, its high LogP renders it non-compliant With Lipinski's rule.

Table (4): GAT1 Compounds Binding Energy.

Compound	Score	H-bond	Short Contact
Reference	61.87	Glycine 65 Serine 396	No
G1	34.42	Serine 396 Threonine 400	No
G2	45.26	Isolucine 62	No

G3

G4

G5

G6

G7

G8

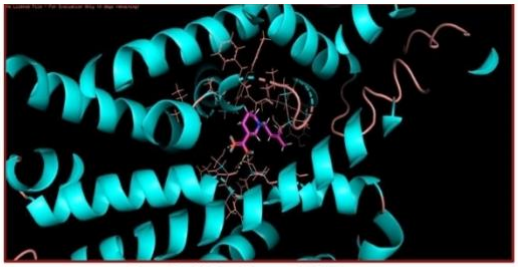


Figure (5): G3 Pose Figure on GAT1 Receptor

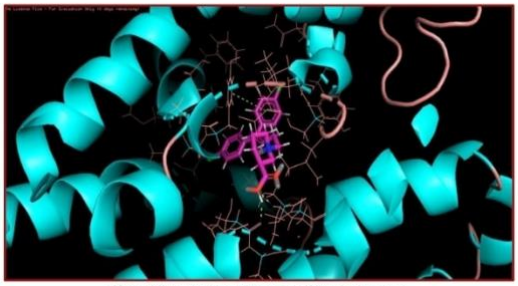


Figure (6): G4 Pose Figure on GAT1 Receptor

Figure (2): References Pose Figure on GAT1 Receptor

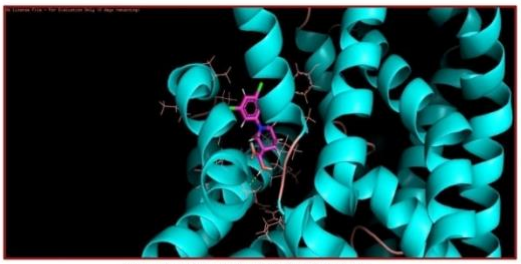


Figure (7): G5 Pose Figure on GAT1 Receptor

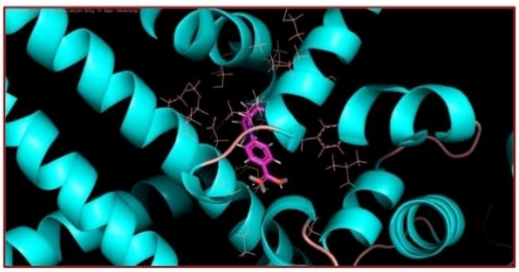


Figure (8): G6 Pose Figure on GAT1 Receptor

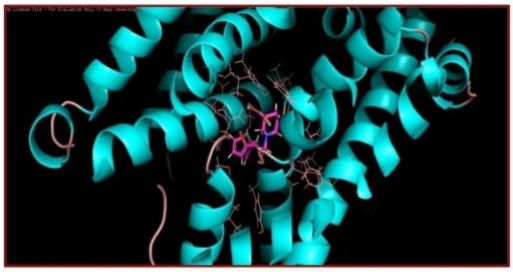


Figure (9): G7 Pose on GAT1 Receptor

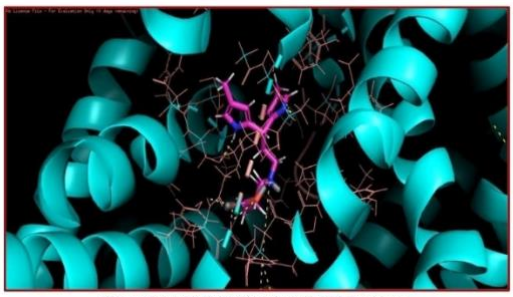


Figure (10): G8 Pose Figure on GAT1 Receptor.

Conclusion

In conclusion, the findings of this study underscore the considerable promise of compound G8 as A prospective GATl inhibitor, exhibiting a notably heightened affinity compared to the reference Ligand, tiagabine. Moreover, the comprehensive assessment of the physicochemical properties of The synthesized compounds reveals a favorable profile, particularly in terms of gastrointestinal Absorption and blood-brain barrier (BBB) permeability, with all compounds demonstrating Satisfactory permeation except for G6. These encouraging results not only highlight the potential Of G8 as a lead candidate for further optimization but also suggest a broader potential for the Development of novel GATI inhibitors. Consequently, this research contributes valuable insights Into the ongoing endeavor to expand the pharmacological arsenal targeting GABAergic signaling Pathways, thereby advancing therapeutic strategies for neurological disorders.

Recommendation

The process involves identifying a promising GABA derivative through docking simulations, Synthesizing and purifying it for testing. In vitro binding assays confirm its affinity for the GABA receptor, followed by functional assays on cellular models. Selectivity studies ensure it Targets the desired receptor with minimal off-target effects. Promising in vitro results lead to in Vivo studies in animal models to evaluate efficacy, pharmacokinetics, and toxicity. Medicinal Chemistry optimization refines the compound for improved drug-like properties, preparing for Preclinical development.

Acknowledgment

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