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VIRTUAL SCREENING OF DERIVATIVES CONTAINING 2-AMINO-BENZOTHIAZOLE AS ANTICONVULSANT AGENTS

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ABSTRACT

A new series of 6-subtituted 2-aminobenzothiazole derivatives were designed for their anticonvulsant activity. In order to predict their anticonvulsant activities the virtual screening was performed for all the designed compounds using binding affinities to beta-3 subunit of $GABA_A$ receptor. The data obtained from the virtual screening was analyzed by comparing the scores of designed compound with the score of the reference molecule. In the present study molegro virtual docker (MVD) version 6.0 were used as designing software while the riluzole (2-amino-6-trifluoromethoxybenzothiazole) were taken as reference molecule for the structural similarity with designed compound. Compound 14 showed the highest rerank score (-98.98), mol dock score (-118.98) and h-bond (-3.28) when compared to reference ligand rerank score (-57.74), mol dock score (-76.16) and h-bond (-2.08) for anticonvulsant activities of this series. The results obtained provide information about the most active compounds i.e. compound 14 which could be a useful information for future design and investigation to construct more active analogs.

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INTRODUCTION:

Epilepsy is a most common hyper synchronous brain disorders which is characterized by recurrent spontaneous seizures of cerebral origin[1]. It is a common neurological condition, affecting 0.5-1% or 45-100 million people of the population worldwide. Some of the conventional antiepileptic drugs like benzodiazepine, phenytoin, primidone, and phenobarbital, are widely used but exhibit unfavorable side effects like headache, nausea, vomiting, blurred vision, insomnia, restlessness, etc. and thus fails to adequate control of seizures. Benzothiazoles and its derivative such as 2-aminobenzothiazole represent a class of heterocyclic scaffold that consists of a five-membered 1,3-thiazole ring fused to a benzene ring. Benzothiazoles contain an extended π-delocalized system that binds to DNA molecules via π–π interactions. Because of this interaction, it demonstrates complex biological properties such as antimicrobial, anticancer, anti-inflammatory, antidiabetic, anticonvulsant activities. $GABA_AR$'s belong to a superfamily of pentameric ligand-gated ion channels (pLGICs) which is also known as the Cys-loop receptors, that include the cation-selective nicotinic acetylcholine receptors (nAChRs) and serotonin type-3 receptors (5HT3Rs), as well as anion-selective glycine receptors (GlyRs).

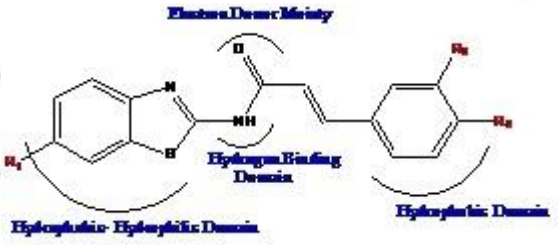


Figure 1: Pharmacophoric features of the titled compounds

MATERIALS AND METHODS:

Molecular docking Study

The amino acid primary sequence of beta-3 subunit of gamma aminobutyric acid (PDB ID:4COF) was retrieved from the Protein Data Bank. The docking studies were carried out using the Molegro Virtual Docker (MVD), a program for predicting the most likely conformation of how a ligand will bind to a macromolecule. In docking studies the calculated cavity was used as active site.

Structure drawing and energy minimization:

CS Chem Office 8.0 was used for the sketching of molecules. The sketched 2D structures were transformed

into 3D structures using module of the program (Chem3D Ultra 8.0). The 3D structures were then subjected to energy minimization using molecular mechanics (MM2) and re optimized via MOPAC until the RMS gradient attained a value smaller than 0.0001 kcal/mol Å.

Docking Procedure:

Protein structure of beta-3 subunit of gamma aminobutyric acid (PDB ID: 4COF)[2] was downloaded from the Protein Data Bank. Protein model of *$GABA_A$*.

Protein ligand docking studies were carried out based on the basis of crystal structure of protein Pdb 4COF and ligand binding.

Docking studies shows that Gln224, Gln185, Glu52, Tyr143, Val53, Ser51, Leu268, Thr271, Thr225, Arg216, Ile264 present in the protein structure of A-chain of beta-3 subunit of GABAA are highly conserved and might play a major role in substrate binding. Standard drug riluzole is also found to be bind to these amino acids.

Table 1: Substitution on title compound**,** Mol dock score, rerank score, hydrogen bond energies, of designed compounds and reference ligand

Ligand	R1	R2	R3	Mol Dock Score	Re rank Score	H-Bond
Comp.1	H	H	H	-107.14	-89.04	-1.09
Comp.2	H	H	Cl	-106.10	-84.25	-1.11
Comp.3	H	H	OH	-106.27	-90.71	-0.85
Comp.4	H	OH	OCH_3	-111.80	-93.71	-085
Comp.5	H	H	OCH_3	-107.75	-90.11	-2.54
Comp.6	Cl	H	H	-110.61	-95.64	-4.55
Comp.7	Cl	H	Cl	-106.61	-88.97	-1.04
Comp.8	Cl	H	OH	-107.21	-87.13	-0.99
Comp.9	Cl	OH	OCH_3	-112.40	-92.57	-1.29
Comp.10	Cl	H	OCH_3	-112.65	-92.07	0
Comp.11	NO_2	H	H	-114.28	-96.33	-1.22
Comp.12	NO_2	H	Cl	-116.32	-96.01	-4.95
Comp.13	NO_2	H	OH	-111.80	-98.98	-3.28
Comp.14	NO_2	OH	OCH_3	-118.98	-98.98	-3.28
Comp.15	NO_2	H	OCH_3	-114.70	-84.46	-6.90
Comp.16	CH_3	H	H	-105.42	-87.45	-0.99
Comp.17	CH_3	H	Cl	-104.30	-80.76	-2.41
Comp.18	CH_3	H	OH	-106.08	-85.79	-3.71
Comp.19	CH_3	OH	OCH_3	-111.12	-89.80	-3.33
Comp.20	CH_3	H	OCH_3	-111.99	-89.52	-4.82
Reference				-76.16	-57.74	-2.08

Table 2 Common types of interactions between protein structures of GABAA with most active comp (comp.14) and reference comp (riluzole).

S. No.	Interaction	Residue
1.	Hydrogen Bond Interaction	Tyr143
2.	Steric Interaction	Gln224, Thr271, Tyr143

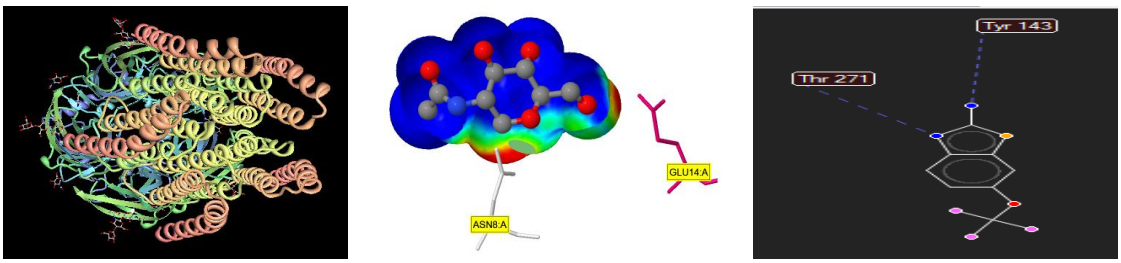
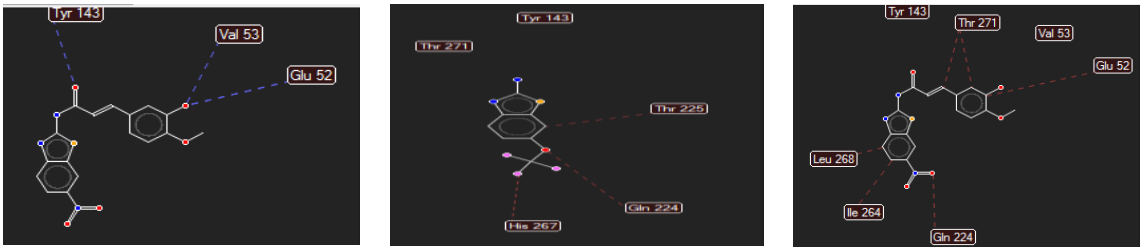


Figure 2: 3D-Structure of $GABA_A$ Enzyme Binding Pocket of $GABA_A$ Enzyme H-Bond Interaction of Reference Ligand



H-Bond Interaction of Most Active Ligand Steric Interaction of Reference Ligand Steric Interaction of Most Active Ligand

RESULTS AND DISCUSSION:

Evaluation of the docking results was based on protein-ligand complementarity considering steric and electrostatic properties. By analyzing the hydrogen bond formed between the fifteen compounds and the active site of A- chain of protein we observed almost the compounds and riluzole exhibited hydrogen bonds with Tyr143. By analyzing the steric interaction formed between all the compounds and the active site of A-chain of protein we observed:(i) compound 1, 2 and 3 exhibited electrostatic bonds with Gln224, Leu268, Thr271, Glu52, Thr225, Gln185, Gln185 (ii) compounds 4,5 and 6 exhibited electrostatic bonds with Gln224, Leu268, Tyr143, Gln185, Arg216, Glu52, Ile264, Arg216 (iii) compounds 7,8 and 9 exhibited electrostatic bonds with Gln224, Leu268, Gln185, Thr271, Glu52, Ile264 (iv) compounds 10,11 and 12 exhibited electrostatic bonds with Gln224, Ile264, Glu52, Thr271, Gln185, Arg216, Tyr143. Compound 14 experiences a lower intermolecular energy in terms of Mol docks score and rerank score or more stable complex because the distance between the two aromatic rings is larger. The neat results of the above interactions are given in terms of mol dock score, rerank score and hydrogen binding energies toward the active site of A-chain of beta-3 subunit of $GABA_A$ as depicted in Table 1. According to these values, compound 14 presented an estimated affinity to the 4COF active site higher than the standard compound riluzole the most promising reference compound.

CONCLUSIONS:

The scoring results reveal the higher negative mol dock score and rerank score of the test compounds (especially compound 14) in comparison to riluzole. It was also observed that the commercial drug riluzole and all the 20 designed compounds binds to the specific binding sites and shows only one hydrogen bond interaction i.e. Tyr143. Here docking study provides an important insight in designing the structures of the most potent compound and subsequent construction of library of such derivatives.

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