



(RESEARCH ARTICLE)



Molecular docking of some benzothiazoles derivatives as anticonvulsant agents

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Abstract

Benzothiazole is one of the promising heterocyclic compounds in the medicinal chemistry, endowed with several therapeutic potentials. The present research endeavors the high throughput *in silico* screening of 66 designed benzothiazole derivatives as potent GABA-aminotransferase inhibitors in Molegro virtual docker software (Version 6.0) using 1OHV as PDB. The docking results showed mol dock score of -73.63 and -62.45 for the standard drugs phenytoin and carbamazepine respectively, on the other hand, the benzothiazole derivatives SDZ3, SDZ4, SDZ5, SDZ6, SDZ13, SDZ16, SDZ19, SDZ21, SDZ32, SDZ51, and SDZ64 exhibited excellent mol dock score, ranged from -104.23 to -121.56. Apart from mol dock score, excellent hydrogen bonding with amino acids of PDB was observed in most of the studied compounds. Compound SDZ4, SDZ8, SDZ11, SDZ31, SDZ57, SDZ58, SDZ59, SDZ60, SDZ61, SDZ63, SDZ64, SDZ65, and SDZ66 showed 5 to 7 hydrogen bond interactions, however, the standard drug phenytoin showed H-bond interaction with 2 amino acid; N-Glu109 and N-Asn110 with bond length 2.86 Å and 3.10 Å respectively, and 2 interaction with N-Asn110 and O-Cys47 with bond length 3.00 Å, and 3.35 Å respectively were observed in carbamazepine. Thus, the present study affirmed the significant anticonvulsant potential of some designed benzothiazole derivatives based on their mol dock values and other parameters when studies *in silico* and the obtained results will provide data support and offer perspectives in future researches to develop a potent anticonvulsant agent from these benzothiazole derivatives.

Keywords: Anti-convulsant activity; Benzothiazole; Carbamazepine; *In silico*; Phenytoin

1. Introduction

Traditional techniques are the extremely time-consuming and expensive methods to discover a new drug, so to overcome these disadvantages of ancient strategies, simpler and rational approaches have been introduced that supports the provision of structural details through virtual screening. Virtual screening approaches can be based on either structure-based or ligand-based drug design techniques. The structural approach to drug explains molecular linking up while ligand-based approaches discuss the interaction between quantitative structure response (QSAR) and pharmacophore modeling [1].

The molecular docking approach highlights the connection amid the material and the target molecule, which consequently envisage the binding affinity of molecules to build a stable supermolecule complex by determining the most well-liked direction with minimal free energy [2]. Although shape complementarities and simulation are two basic perspectives employed in molecular docking yet it is classified into three distinct categories illustrated in Figure 1. The present study was aimed to study *in silico* molecular docking of certain developed benzothiazoles derivatives as potent anticonvulsant agents.

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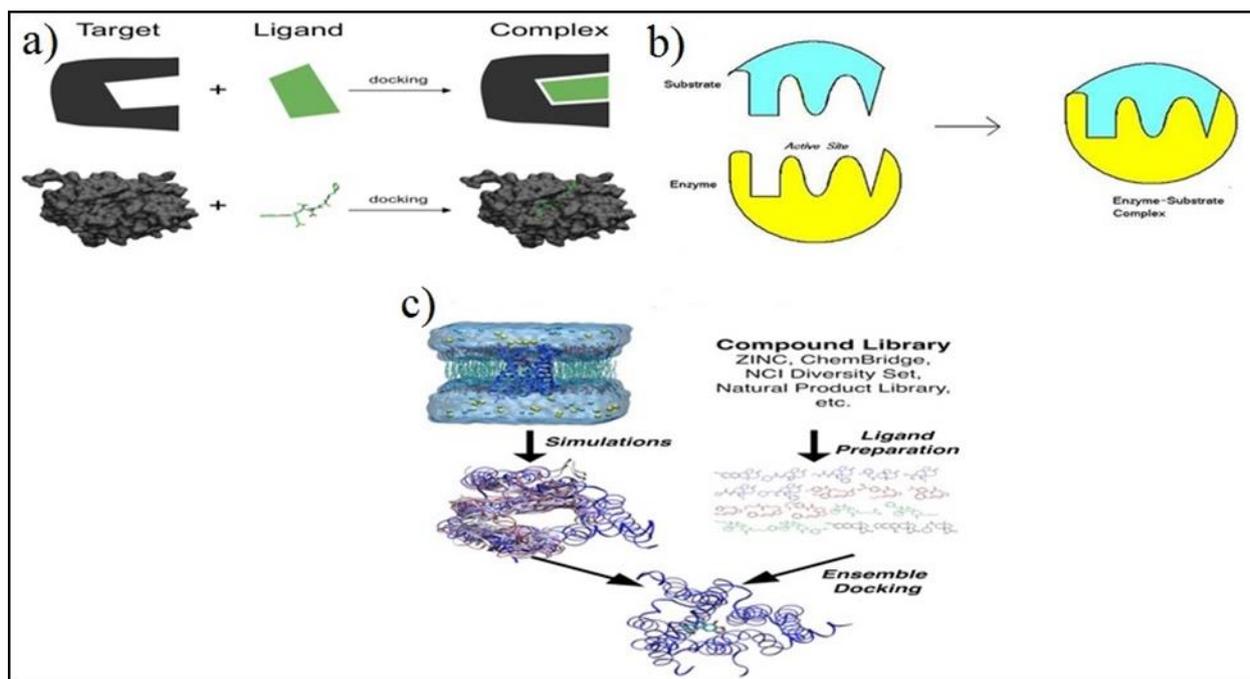


Figure 1 Techniques of molecular docking: (a) Induced work docking [3]; (b) Lock and key docking [4]; and (c) Ensemble docking [5]

Benzothiazole is a heterocyclic organo-sulfur product that is weakly basic. They are commonly used in bioorganic and medicinal chemistry of product development use. Sulfur and nitrogen atoms represent the central component of thiazole and other pharmacologically and biologically active compounds. The standard benzothiazole structure consists of a benzene ring fused with a 4, 5 thiazole position which is shown in Figure 2. The two rings combined and form the basic nucleus 1, 3-benzothiazole [6]. The 1,3-benzothiazole ring has been observed to be a flexible pharmacophore to increase the level of the entire brain GABA, probably by Gamma-aminobutyric acid aminotransferase (GABA-AT) enzyme inhibition [7].

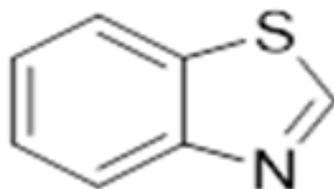


Figure 2 Structure of benzothiazole with basic ring

2. The targets for anticonvulsant drug discovery

A pyridoxal 5'-the phosphate-dependent enzyme. GABA-AT is responsible for the degradation of the GABA inhibitor. GABA-AT is a reliable aim for anti-epileptic medications since its systematic inhibition raises the production of GABA in the brain [8,9]. The neurotransmitter has 3 specific receptors: GABA_A, GABA_B, and GABA_C. GABA_A receptors, linked to binding sites in the form of a receptive complex for benzodiazepines and barbiturates, the regular opening of in the chloride channel (post-synaptic channel connected to Cl⁻). When GABA is connected to the receptor group, it opens up and the chloride anions are hyperpolarized into the neuron. GABA_B (pre-synaptic autoreceptors, K⁺ currents mediated) receptors are metabotropic, associated with a cascade with second messages, while the physiological significance of ionotropic GABA_C receptors is usually unknown, primarily in the retina. Tiagabine and Vigabatrin is the new anticonvulsant drug acting via the GABA-ergic mechanism. The former prevents the synthesis of GABA through neuronal and glial, while the latter raises GABA synaptic levels by GABA-AT inhibition. Gabapentin, designed simply to come into the brain as a precursor of GABA, has been shown to extend GABA synaptic brain. It reduces the influx of Ca²⁺ into neurons through a certain subunit of voltage-dependent calcium channels. A standard anticonvulsant drug usually inhibits sodium currents (Carbamazepine (CBZ), Phenytoin (PTN), phenobarbital, valproate), or enhance GABA-ergic

inhibition (benzodiazepines, phenobarbital, valproate), whereas ethosuximide mainly controls the absence seizures, by reducing calcium currents via T-type calcium channels". Current anticonvulsant drugs (lamotrigine and oxcarbazepine) often produce anticonvulsant action by the suppression of voltage-dependent Na⁺ channels. Due to the consequence of glutamate-mediated excitation, some antiepileptics are targeted at glutamatergic receptors (phenobarbital, felbamate, and topiramate). They inhibit metal currents in conjunction with them. Zonisamide, which appears to share the same mechanism, reduces free radicals jointly [10].

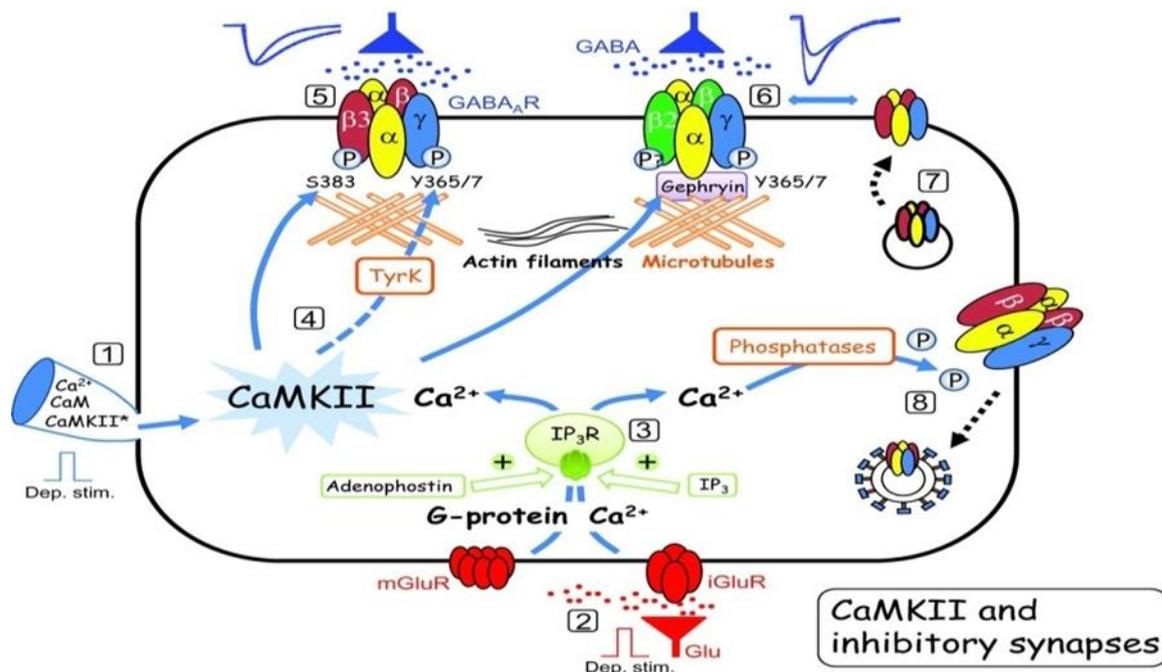


Figure 3 Targets for anticonvulsant drugs

The present research endeavors the high throughput *in silico* screening of 66 designed benzothiazole derivatives as potent GABA-AT inhibitors in Molegro virtual docker software (version 6.0) using 1OHV as PDB and compared with two standard anticonvulsant drugs i.e. Carbamazepine (CBZ) and Phenytoin (PTN).

3. Material and Methods

Docking could be a technique to work out potential binding modes of a substance to the receptor site. Studies of docking with a group of experimental benzothiazole derivatives were carried out using Molegro virtual docker 6.0 on GABA subunits of 1OHV. The X-ray structures of that were retrieved from the Protein Data Bank. Each ligand was determined to interact with the 1OHV active location, which was the highest mol dock, hydrogen bonding, and rerank scores used during docking. Table 1 demonstrates the general arrangement of the analogs [11–14].

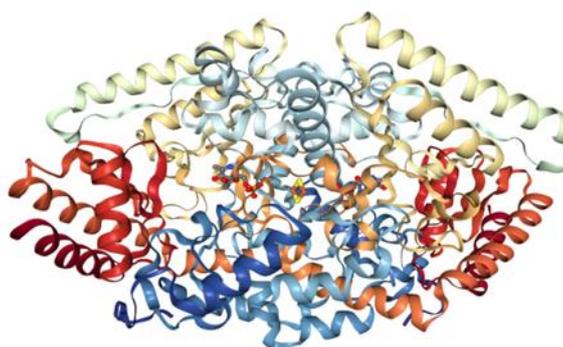


Figure 4 3D view of PDB- 10HV

3.1. The methodology can be divided into the following steps

- Importing a protein file, ligand file, and preparation of ligands
- Preparation and identifications of protein molecule cavities
- Running the docking system using the docking wizard panel
- Determination of poses of protein-ligand complexes
- Calculations of Mol dock score, hydrogen bond interaction, and rerank score

3.1.1. Selection of the compounds and ligand preparation

The hypothetical compounds were selected based on literature. The ligand molecules were prepared by using Marvin Sketch (version 5.11.0) and then molecules were converted to 2D and then converted to 3D using build and optimize the method and then clean in 3D then add explicit hydrogens. The resulting structure will be saved in MDL Molfile (*.mol) format. Single, low energy, 3D structure with appropriate chiralities will be created for each successfully proposed structure. Then the generated structures were imported into the workspace of docking software Molegro Virtual Docker 6.0. The molecule can be incorporated into the MVD using MDL (sdf/sd/mol/mdl) file format which contains bonding formation. In this step, the preparation of molecules was assigned bonds, bond order and hybridization, charges, explicit hydrogens, and flexible torsion in ligands.

3.1.2. Compound selection

Based on literature data, we selected 66 hypothetical compounds and docking studies were performed using (PDB ID 1OHV) for anticonvulsant activity using Molegro Virtual Docker. The structure of all the 66 selected compounds is illustrated in Table 1.

3.1.3. Set of hypothetical compounds

A docking study was performed with a set of hypothetical benzothiazole derivatives. The basic moiety of compounds is shown in Figure 5

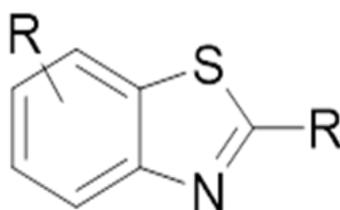


Figure 5 Basic moiety of developed compounds

3.1.4. Protein preparation

In Molegro Virtual Docker the step protein preparation is automatically done. Docking is a computational method for predicting modes of action of small organic molecules to protein receptors. It produces a picture of the active site with an interface point known as the grid. It holds the ligand in the receptor-binding region. Different forms of interactions between receptor and ligand van der Waal interactions, aromatic interactions are known to be used to quantify binding strength. The number of protein receptor (PDB) used in this study are PDB ID: 1OHV. The PDB's used for docking were produced from RCSB (protein data bank).

3.1.5. Ligand docking

The ligand docking was accomplished by producing many ligands poses at the active site and a posing score to classify one or more poses that roughly resemble the bioactive conformation defined by X-ray crystallography. The Mol dock scoring function (Mol Dock Score), The E-score is determined by the following terms of energy:

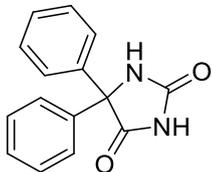
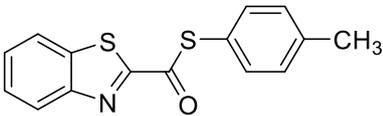
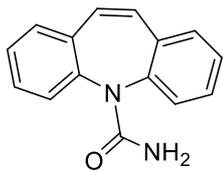
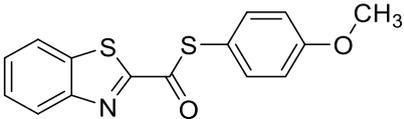
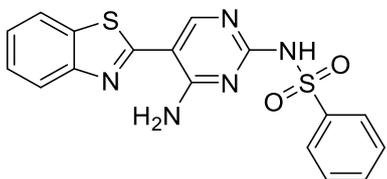
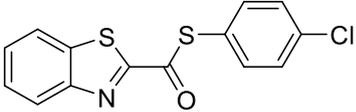
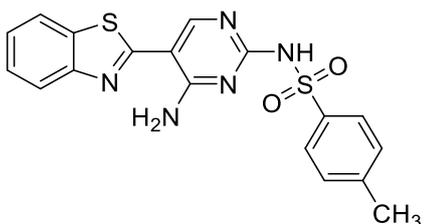
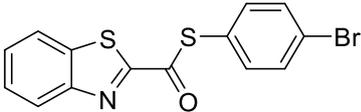
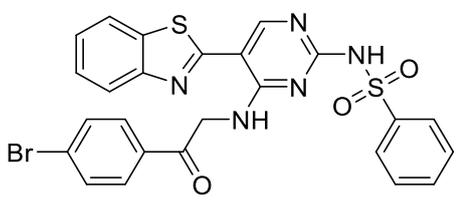
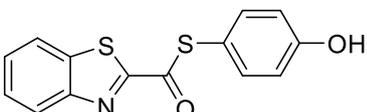
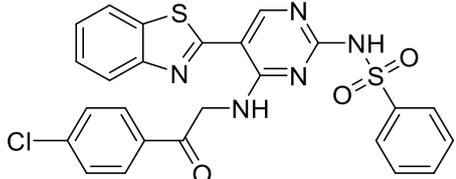
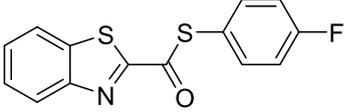
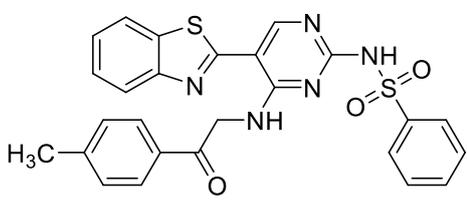
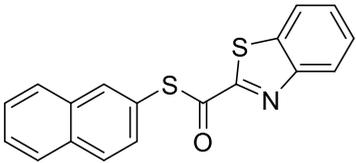
$$E_{score} = E_{inter} + E_{intra} \quad \text{(Equation 1)}$$

Where E_{intra} is the inter energy of the ligand;

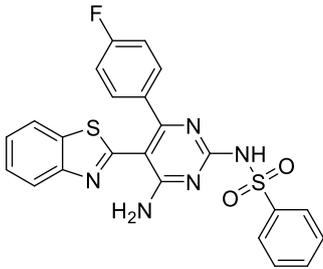
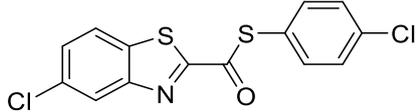
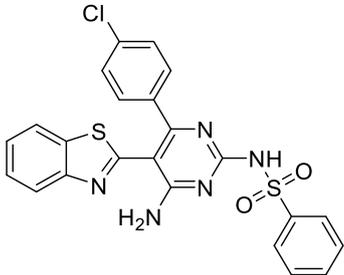
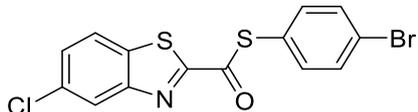
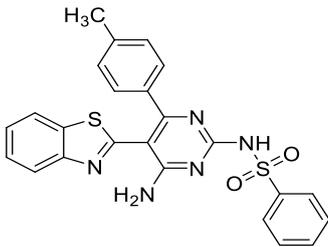
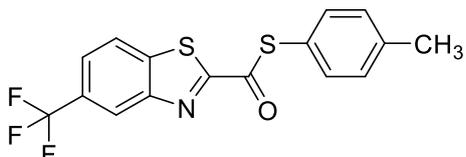
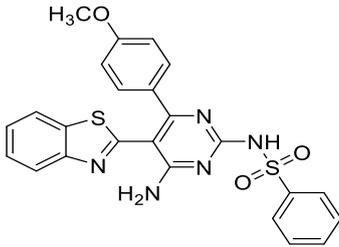
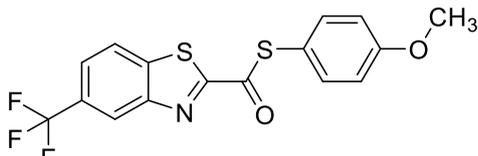
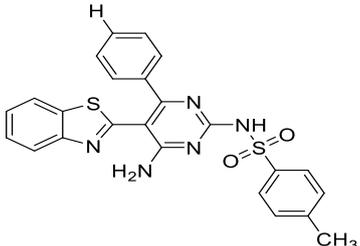
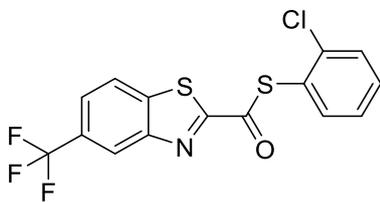
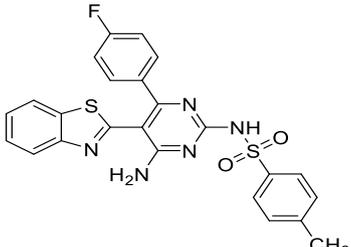
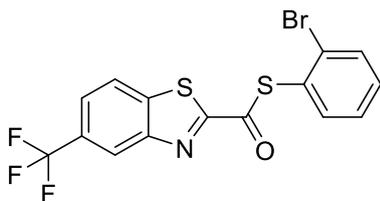
E_{inter} is the ligand-protein interaction energy

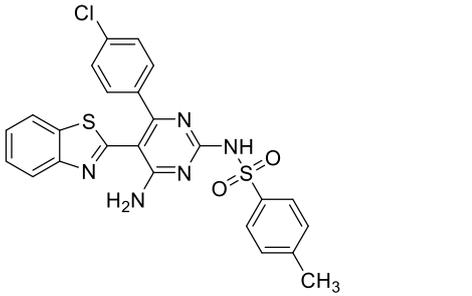
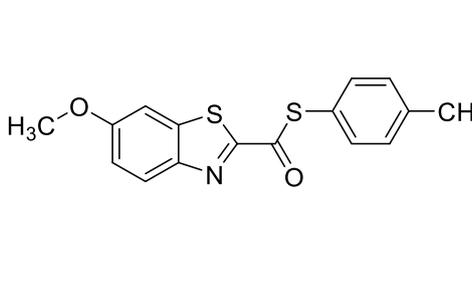
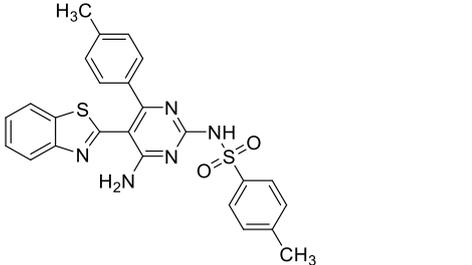
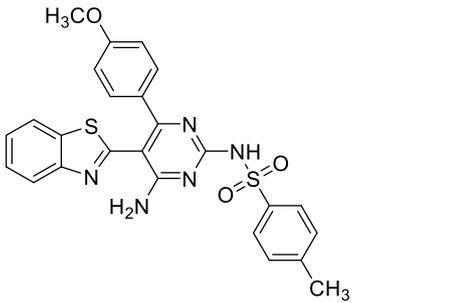
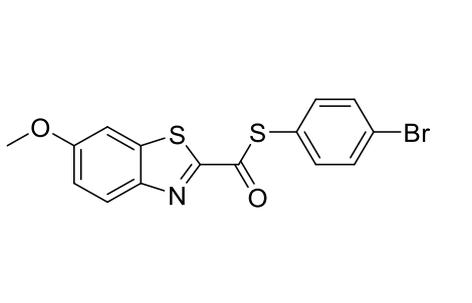
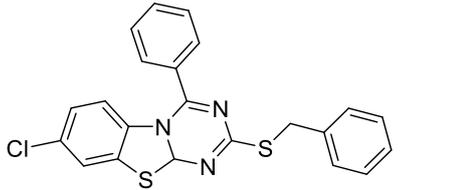
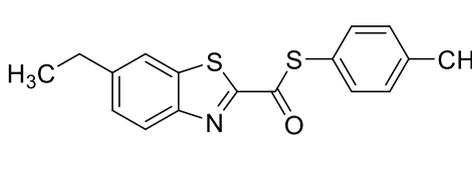
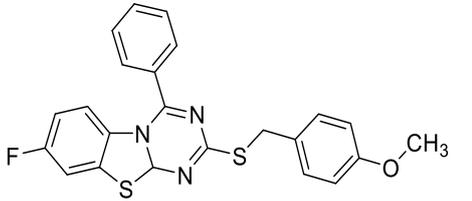
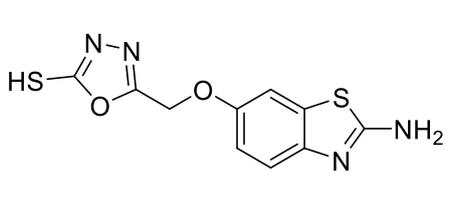
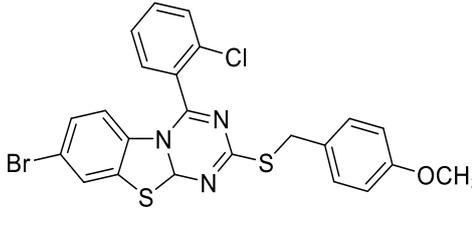
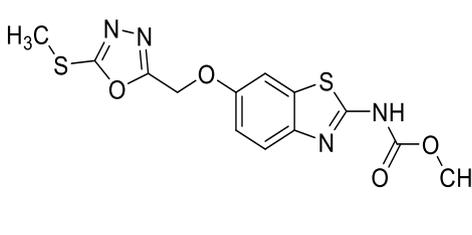
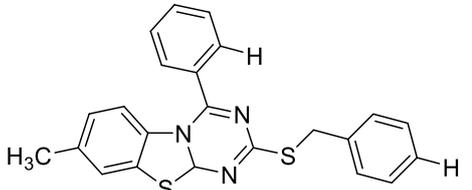
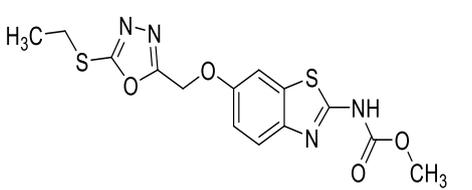
Molegro Virtual Docker (Version 6.0) software is used to analyze binding modes of compounds with internal ligand PLP-600. The interactions of standards (PTN, CBZ) and test compounds were compared and the score tabulated as mol dock score, re-rank score, and the number of hydrogen bond interactions. The docking energies of the ligands were negative, which shows the stable binding interaction between the receptor and the ligands.

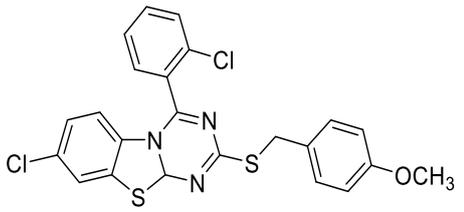
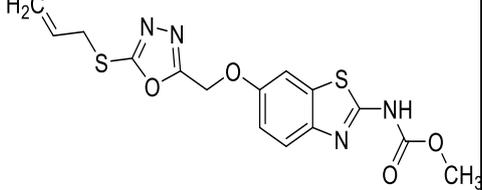
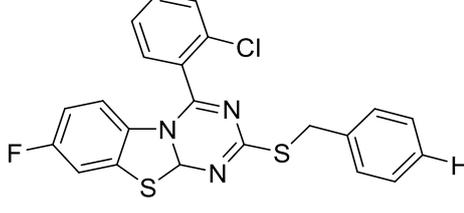
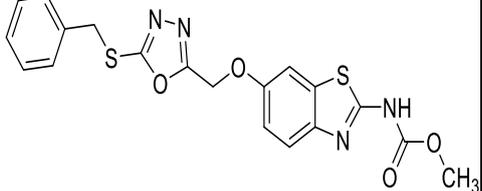
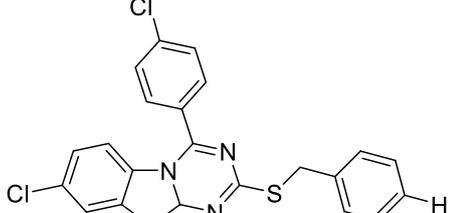
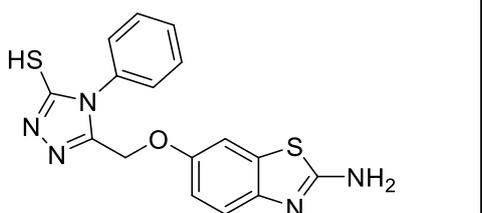
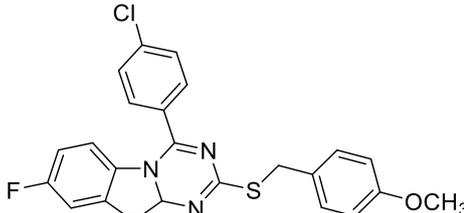
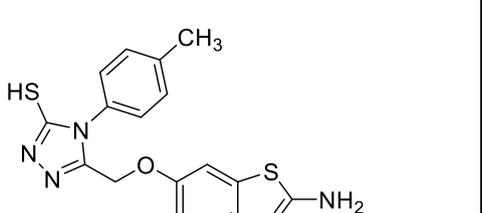
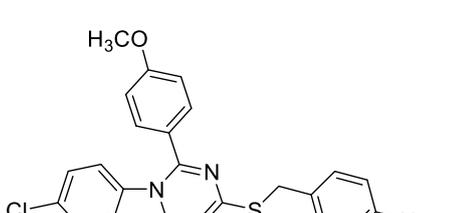
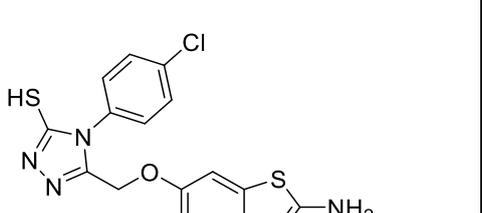
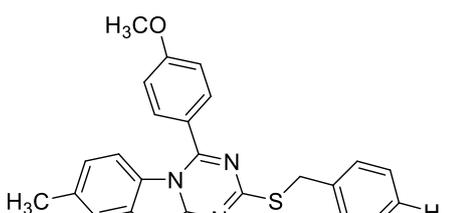
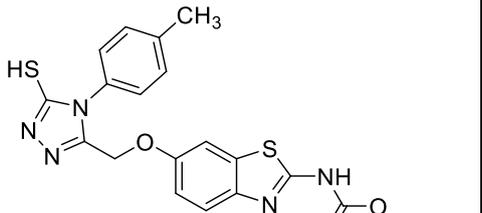
Table 1 Hypothetical compounds used for docking analysis

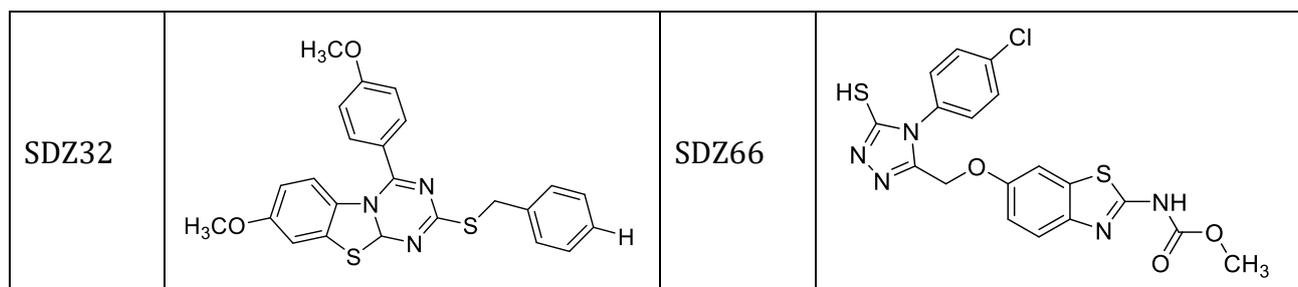
Compound Name	Structure of compounds	Compound Name	Structure of compounds
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CBZ		SDZ34	
SDZ1		SDZ35	
SDZ2		SDZ36	
SDZ3		SDZ37	
SDZ4		SDZ38	
SDZ5		SDZ39	

SDZ6		SDZ40	
SDZ7		SDZ41	
SDZ8		SDZ42	
SDZ9		SDZ43	
SDZ10		SDZ44	
SDZ11		SDZ45	
SDZ12		SDZ46	

SDZ13		SDZ47	
SDZ14		SDZ48	
SDZ15		SDZ49	
SDZ16		SDZ50	
SDZ17		SDZ51	
SDZ18		SDZ52	

SDZ19		SDZ53	
SDZ20		SDZ54	
SDZ21		SDZ55	
SDZ22		SDZ56	
SDZ23		SDZ57	
SDZ24		SDZ58	
SDZ25		SDZ59	

SDZ26		SDZ60	
SDZ27		SDZ61	
SDZ28		SDZ62	
SDZ29		SDZ63	
SDZ30		SDZ64	
SDZ31		SDZ65	



4. Results and discussion

The most significant aspects of docking are the association of the ligand with the putative binding site of the enzyme. In this article, we studied the docking of the sixty-six test compounds using PDB (1OHV) with GABA-AT inhibitors taking PTN and CBZ as standard. All hypothetical compounds were found to possess moderate results for anticonvulsant activity. But out of sixty-six compounds, 22 compounds (SDZ4, SDZ6, SDZ7, SDZ8, SDZ11, SDZ14, SDZ17, SDZ18, SDZ19, SDZ20, SDZ21, SDZ31, SDZ57, SDZ58, SDZ59, SDZ60, SDZ61, SDZ62, SDZ63, SDZ64, SDZ65, and SDZ66) which we selected were found to possess best results for anti-epileptic activity. The standard drugs PTN and CBZ showed mol dock score -73.63 and -62.45 respectively, was found comparatively lower than the hypothetical compounds. Out of these sixty-six compounds, eleven compounds SDZ3, SDZ4, SDZ5, SDZ6, SDZ13, SDZ16, SDZ19, SDZ21, SDZ32, SDZ51, and SDZ64 showed very good mol dock score ranging between -104.23 to -121.56 while compounds SDZ12, SDZ14, SDZ15, SDZ18, SDZ20, SDZ22, SDZ23, SDZ24, SDZ27, SDZ31, SDZ52, and SDZ63 showed mol dock score ranging between -100.45 to -103.91 as compared to standard mol dock score values -73.63 and -62.45 respectively. It is concluded that the mol dock values of most of the test compounds were found greater than standard drugs except compounds SDZ38 and SDZ54. Most of the test compounds showed a very good number of hydrogen bond interactions viz compound SDZ4, SDZ8, SDZ11, SDZ31, SDZ57, SDZ58, SDZ59, SDZ60, SDZ6, SDZ63, SDZ64, SDZ65 & SDZ66 which showed 5 to 7 number of hydrogen bond interactions as compared to standard drug interactions values 2 respectively. Test compounds that showed 4 number of hydrogen bond interactions are SDZ6, SDZ7, SDZ14, SDZ17, SDZ18, SDZ19, SDZ20, SDZ21, and SDZ62. The standard drug PTN showed H-bond interaction with amino acid N-Glu109, N-Asn110 with bond length 2.86 Å and 3.10 Å while CBZ showed interaction with N-asn110, O-Cys47 with bond length 3.00 Å and 3.35 Å respectively. Most of the test compounds were found to showed interaction with the same amino acids Glu50 and Asn110 and showed very acceptable bond length. The docking output of 66 compounds is given in Table 2 with details of interacting amino acids, bond length, no. of hydrogen bond interaction, Mol dock score, and re-ranks score. Figure 6 represents the drug-receptor interaction of standards drugs (PTZ and CBZ), whereas ligand-receptor interactions of compounds having good Mol dock scores were illustrated in Figure 7 and Figure 8.

Table 2 Ligand–receptor interaction of Benzothiazoles, Phenytoin, and Carbamazepine as standard drugs on PDB ID: (1OHV) using Molegro software.

Compound No.	Interaction of amino acid with H-bond (Å) having the shortest bond length	Number of hydrogen bonds	Mol dock score	Re-rank score
PTN	N-Asn110 (3.10); N-Glu109(2.86)	2	-73.63	-60.75
CBZ	N-Asn110(3.00); O-Cys(3.35)	2	-62.45	-53.39
Internal ligand PLP-600 [A]	N-Glu109(3.00); N-Asn110(3.44); O-Glu50(2.61)	3	-47.66	-45.75
SDZ1	O-Glu50 (2.67); O-Gln92(2.86)	2	-78.61	-61.35
SDZ2	O-Glu109 (3.49); N-Asn48(2.80); O-Glu50(3.51)	3	-84.82	-63.44
SDZ3	N-Lys114(2.73); N-Asn110(3.21); N-Glu109(3.57)	3	-114.75	-79.84
SDZ4*	N-Asn48(2.80); N-Asn48(2.86); N-Asn110(3.26); N-Glu109(3.34);	5	-112.81	-72.46

	O-Glu50(2.70)			
SDZ5	N-Asn110(3.17); O-Glu109(2.60)	2	-117.74	-79.14
SDZ6*	N-Lys114(2.60); O-Asn93(3.32); N-Glu109(2.94); N-Asn110(2.79)	4	-113.55	-82.74
SDZ7*	O-Thr96(2.85); O-Glu50(2.96); N-Glu109(3.56); O-Cys47(2.60)	4	-75.66	-56.96
SDZ8*	O-Cys47(2.60); O-Glu50(2.96); O-Asn110(3.11); O-Thr96(2.84); N-Glu109(3.56)	5	-75.21	-56.86
SDZ9	O-Asn110(3.10); O-Glu117(2.71); NAsn110(3.43)	3	-81.67	-54.59
SDZ10	N-Asn110(2.62); O-Gln92 (3.31)	2	-86.11	-59.12
SDZ11*	O-Asn93(2.60); O-Gln92(2.66); O-Gln50(3.04); N-Asn110(2.77); N-Glu109(3.10)	5	-85.67	-65.61
SDZ12	O-Asn110 (3.03); O-Asn93 (2.13)	2	-103.58	-72.15
SDZ13	N-Asn48(3.11)	1	-113.40	-76.29
SDZ14*	O-Glu50(3.28); O-Glu109(3.19); O-Thr96(2.69); O-Asn110(2.48)	4	-101.51	-70.79
SDZ15	N-Asn48(3.11); O-Asn48(3.24); O-Glu109(2.67)	3	-103.46	-74.44
SDZ16	O-Asn110(2.88); N-Glu109(3.10); N-Asn110(2.55)	3	-110.43	-77.27
SDZ17*	O-Glu50 (3.10); O-Gln92(2.86); N-Asn93(3.10); N-Gln92(2.82)	4	-99.96	-50.79
SDZ18*	O-Glu150(3.10); O-Asn110(2.43) O-Glu109(3.30); O-Thr96(2.60)	4	-103.91	-68.97
SDZ19*	O-Glu109(3.10); O-Glu50(3.33); O-Asn110(2.56); O-Thr96(2.74)	4	-104.23	-76.78
SDZ20*	O-Glu109 (3.14); O-Asn110(2.56); O-Thr96(2.90); O-Glu50(2.70)	4	-100.45	-71.19
SDZ21*	N-Asn110(3.10); O-Glu109(3.29); N-Glu92(3.50); N-Glu109(3.51)	4	-121.56	-68.06
SDZ22	-----	No interaction	-101.81	-78.05
SDZ23	N-Asn110 (2.97); N-Glu109(3.11)	2	-101.41	-53.85
SDZ24	-----	No interaction	-103.79	-57.96
SDZ25	-----	No interaction	-96.62	-60.57
SDZ26	O-Thr96(3.24)	1	-95.65	-51.43
SDZ27	-----	No interaction	-102.77	-62.89
SDZ28	-----	No interaction	-100.21	-63.54
SDZ29	N-Asn48(3.37); N-Asn48(3.10);	3	-94.32	-60.92

	N-Asn48(3.26)			
SDZ30	N-Glu109(2.93); N-Tyr49(3.44)	2	-195.73	-38.99
SDZ31*	N-Asn110(3.08); N-Glu109(3.31); N-Asn48(2.95); N-Asn48(3.31); N-Asn48(3.24)	5	-101.53	-65.52
SDZ32	N-Glu109(2.87)	1	-106.23	-61.19
SDZ33	-----	No interaction	-89.66	-64.73
SDZ34	N-Lys114(2.97)	1	-73.51	-56.33
SDZ35	-----	No interaction	-85.24	-61.58
SDZ36	-----	No interaction	-88.49	-65.07
SDZ37	N-Tyr49(2.81); O-Cys47(1.82)	2	-87.45	-65.84
SDZ38	N-Asn110(3.07); N-Glu109(3.21)	2	-66.51	-51.83
SDZ39	-----	No interaction	-99.91	-69.61
SDZ40	N-Asn110(3.05)	1	-86.41	-63.89
SDZ41	N-Asn110(3.40)	1	-83.43	-47.09
SDZ42	N-Asn110(2.60)	1	-71.04	-58.32
SDZ43	N-Asn110(2.99); N-Glu109(2.82)	2	-63.58	-53.43
SDZ44	N-Glu113(3.10)	1	-87.71	-64.35
SDZ45	N-Asn48(2.93)	1	-72.87	-52.22
SDZ46	-----	No interaction	-94.65	-55.53
SDZ47	N-Asn48(3.31)	1	-93.74	-63.53
SDZ48	N-Asn110(3.55)	1	-95.26	-65.48
SDZ49	-----	No interaction	-92.66	-62.94
SDZ50	N-Asn48 (2.95)	1	-77.24	-61.43
SDZ51	-----	No interaction	-118.29	-68.69
SDZ52	-----	No interaction	-102.83	-39.19
SDZ53	N-Tyr49 (2.93)	1	-80.71	-39.13
SDZ54	N-Asn110(3.27); Glu109(3.110)	2	-70.21	-53.495
SDZ55	Asn110(3.09); N-Asn110(3.10); N-Glu109(3.20)	3	-69.85	-54.10
SDZ56	N-Asn110 (3.20)	1	-76.51	-58.24
SDZ57*	O-Cys47(1.47); N-Glu109(3.15); N-Asn48(3.46); N-Asn110(3.10); N-Asn110(2.76)	5	-74.14	-55.43
SDZ58*	O-Thr96 (3.10); O-Asn110 (2.64); N-Asn48(2.69); N-Asn48 (3.17); N-Asn48 (3.07); N-Asn48(2.91)	6	-78.17	-47.33
SDZ59*	O-Asn110(2.60); O-Thr96 (2.92); N-Asn48(3.07); N-Asn48(2093); N-Asn48(3.08); N-Asn48 (2.76)	6	-85.13	-61.33

SDZ60*	O-Glu92(3.30); O-Asn93(3.15); N-Asn48(3.02); N-Asn48(3.10); N-Asn48(3.09); N-Asn48(3.35)	6	-84.87	-68.13
SDZ61*	N-Lys114(3.00); N-Lys114(3.12); N-Asn48(2.85); N-Asn48(2.85); O-Glu50(3.37)	5	-96.28	-63.94
SDZ62*	O-Cys47(2.88); N-Glu109(3.11); N-Asn110(3.19); N-Asn110(3.14)	4	-87.15	-49.55
SDZ63*	O-Gln33 (3.08); O-Gln50(2.83); N-Glu109(3.47); N-Asn110(3.18); O-Thr96 (3.46); N-Asn110 (2.96); N-Glu109(3.48)	7	-101.75	-43.08
SDZ64*	O-Glu50(2.86); O-Gln33(3.10); N-Asn110(3.13); N-Glu109(3.20); N-Glu109(3.41); N-Asn110(3.07)	6	-104.88	-50.11
SDZ65*	N-Lys114 (3.38); O-Asn93 (2.87); O-Thr96 (3.09); N-Asn48 (3.22); N-Asn48 (2.71); N-Asn48(3.03)	6	-100.01	-73.01
SDZ66*	N-Glu113(2.88); N-Arg116 (3.20); N-Arg116 (3.17); O-Glu50(2.63); N-Asn110(3.26); O-Asn48(3.57)	6	-103.91	-73.48

*indicate most potent

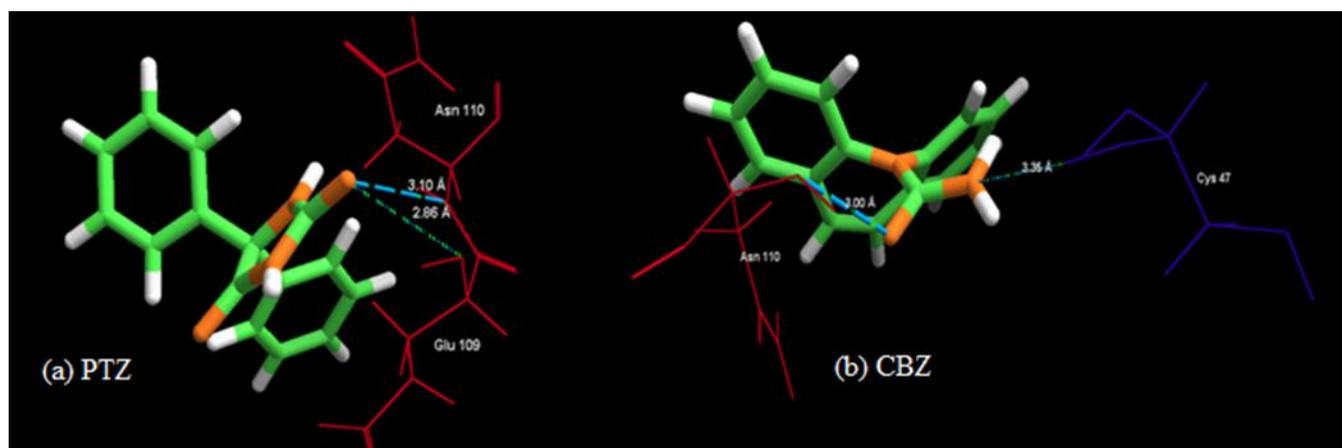


Figure 6 Interaction of standard drug (a) PTN and (b) CBZ with PDB 10HV

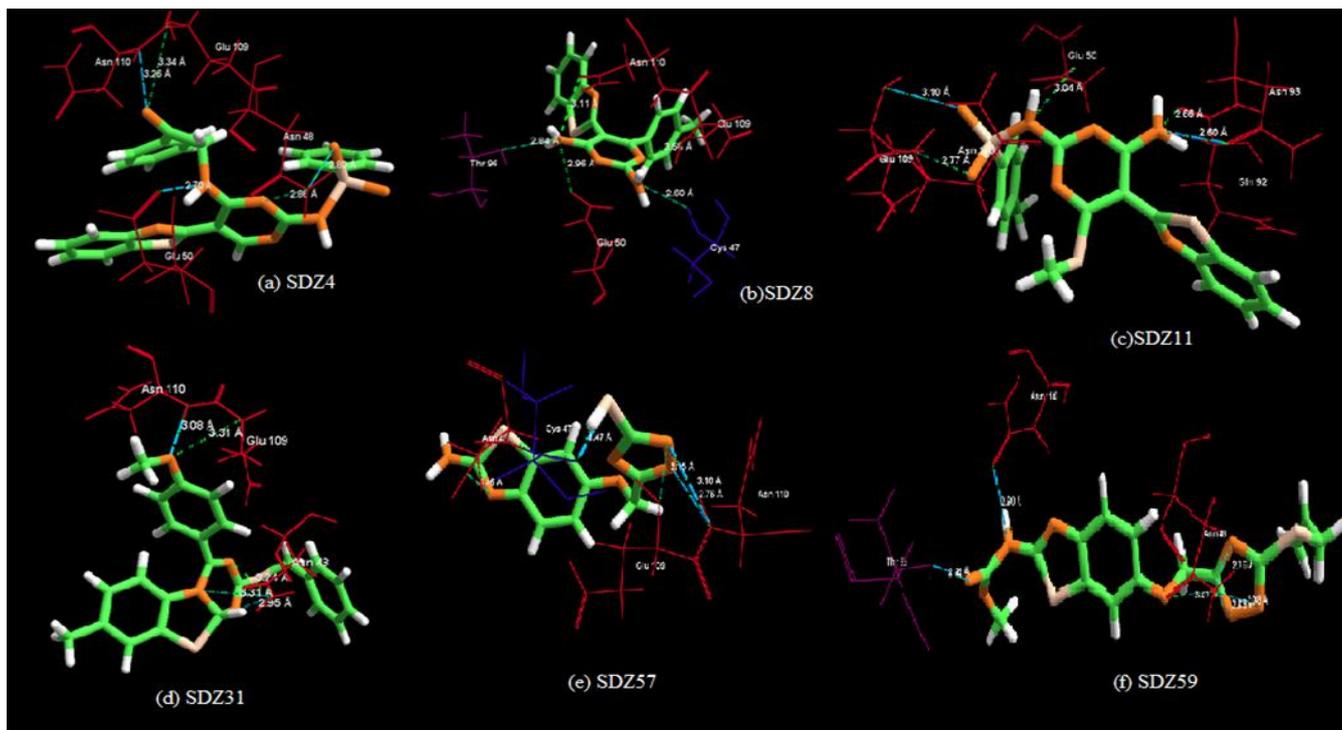


Figure 7 Interaction of compounds (a) SDZ4, (b) SDZ8, (c) SDZ11, (d) SDZ31, (e) SDZ57, and (f) SDZ59 with PDB 10HV.

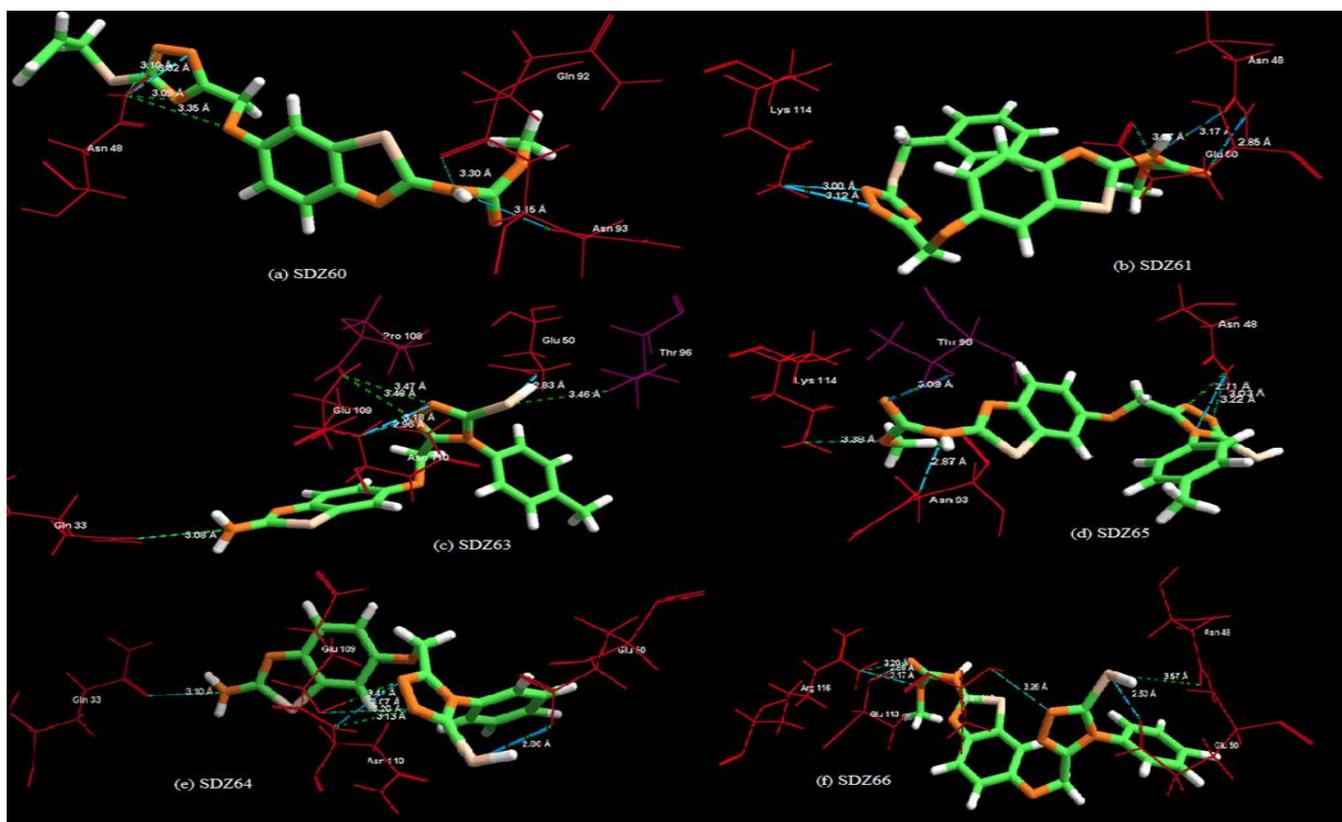


Figure 8 Interaction of compounds (a) SDZ60, (b) SDZ61, (c) SDZ63, (d) SDZ65, (e) SDZ64, and (f) SDZ66 with PDB 10HV.

5. Conclusion

Docking experiments have allowed us to learn how benzothiazole attaches to activate their GABA restrictive behaviors. Such investigations are exceptionally beneficial during the synthesis of selected substances, which efficiently inhibits GABA-AT enzyme. It was also examined from a higher point of view that receptor structure plays a critical role in influencing the drug action. Thus, it can be concluded that the above designed benzothiazole derivatives can hold great importance, particularly as anticonvulsant agents, as identified by in silico methods in the present study.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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