

Designing of Hybrid form of Benzothiazole-quinazoline as GABA-A Inhibitor with Anticonvulsant Profile: An *in-silico* Approach

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Abstract Epilepsy is a common but serious brain disorder. It is universal, with no age, sex, geographical, social class or racial boundaries. One of the most important mechanisms for handling it is the inhibition of the GABA-A receptor. In same context while studying the treatment of epilepsy we found the significant effects of the derivatives of the benzothiazole and quinazolines, this promotes us to develop a hybrid form of these two moieties by the means of *in-silico* resources with antiepileptic/anticonvulsant effects. Molecular docking approaches are routinely used in modern drug design to help understand drug-receptor interaction. This study has been performed with the help of Chemdraw Ultra 7.0, AutoDock Vina (Python Prescription 0.8), and PaDEL software. Results revealed that ligand-protein interaction affinity of all designed 10 hybrid molecules ranges from -6.8 Kcal/mol to -6.2 Kcal/mol which is approximately double as compared to pre-existing GABA-A inhibitor i.e. γ -aminobutyric acid (CID: 119, ligand-protein interaction affinity is -3.2 Kcal/mol).

Keywords: Benzothiazole-quinazolines, docking, GABA-A inhibitors, γ -aminobutyric acid, protein-ligand interaction affinity

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1. Introduction

Epilepsy is a common but serious brain disorder. It is universal, with no age, sex, geographical, social class or racial boundaries. Epilepsy imposes a large economic burden on health care systems of countries. There is also a hidden burden associated with stigma and discrimination against the patient and even his/her family in the community, workplace, and school and home. Many patients with epilepsy suffer severe emotional distress, behavioral disorders and extreme social isolation [1]. Epilepsy is usually defined as a tendency to recurrent seizures. The word "epilepsy" is derived from Latin and Greek words for "seizure" or "to seize upon". This implies that epilepsy is an ancient disorder; indeed, in all civilizations it can be traced as far back as medical records exist. In fact, epilepsy is a disorder that can occur in all mammalian species, probably more frequently as brains have become more complex. Epilepsy is also remarkably uniformly distributed around the world. There are no racial, geographical or social class boundaries. It occurs in both sexes, at all ages, especially in childhood, adolescence and increasingly in ageing populations [2]. The term seizure refers to a transient alteration of behavior due to the disordered, synchronous, and rhythmic firing of population of the brain neurons [3]. The meaning of the term seizure needs to be carefully distinguished from that

of epilepsy. Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process. This definition implies that a person with a single seizure, or recurrent seizures due to correctable or avoidable circumstances, does not necessarily have epilepsy. Epilepsy refers to a clinical phenomenon rather than a single disease entity, since there are many forms and causes of epilepsy. However, among the many causes of epilepsy there are various epilepsy syndromes in which the clinical and pathologic characteristics are distinctive and suggest a specific underlying etiology [4].

The GABA-A receptor is an ionotropic receptor and ligand-gated ion channel. Its endogenous ligand is γ -aminobutyric acid (GABA (CID: 119)), the major inhibitory neurotransmitter in the central nervous system. Upon activation, the GABA-A receptor selectively conducts Cl^- through its pore, resulting in hyperpolarization of the neuron. This causes an inhibitory effect on neurotransmission by diminishing the chance of a successful action potential occurring [5].

Candidates from benzothiazoles for designing novel anticonvulsant agents emerge with promising effects. The endocyclic nitrogen and sulphur functions present in the heterocyclic nucleus have been shown to be critical for anticonvulsant activity. [6,7] Harish Rajak et al confirmed by the preliminary pharmacological animal models that semicarbazones containing quinazoline ring emerges with a novel anticonvulsant series [8].

On studying the above mentioned literature about the anticonvulsant behavior of benzothiazoles and quinazolines promoted us to theoretically develop a hybrid of these two moieties by the means of *in-silico* resources.

Rational drug design helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compound, out of them one method is the docking of the drug molecule with the receptor. The therapeutic action of the clinical drug will be effective when the biochemical pathway of the enzyme can be exploited [9,10,11,12].

Docking procedures allows virtually screening a database of compounds and predict the strongest binder based on various scoring functions. It gives way in which two molecules such as drugs and an enzyme receptor fit together and dock to each other well [9,10,11,12].

Molecular docking techniques are used in modern drug design to help understand drug-receptor interaction. It has been shown in the literature that these computational procedures can strongly support and help the design of new, more potent drugs by revealing the mechanism of drug-receptor interaction [9,10,11,12].

2. Materials and Method

2.1. Database and Tools

For carrying out the study, National Center for Biotechnology Information's (NCBI.) website and Protein Data Bank's (PDB) website were used as biological and receptor sources. For designing and optimizing the geometry of the derivatives, Chemdraw Ultra 7.0 [13] was used. For docking studies of derivatives, AutoDock Vina [10,11,12] molecular docking software has been employed and for descriptor calculations PaDEL software has been used [14].

2.2. Molecule Designing and Optimization

The chemical structures of the hybrid derivatives **Figure 1** were drawn using ChemDraw Ultra 7.0 and energy minimization of derivatives was achieved with Chem3D Pro of ChemOffice suit for taking energy of each molecule up to its lowest energy state (highest stability). 3D structure of gamma aminobutyric acid (CID: 119) was retrieved from PubChem compound database at NCBI.

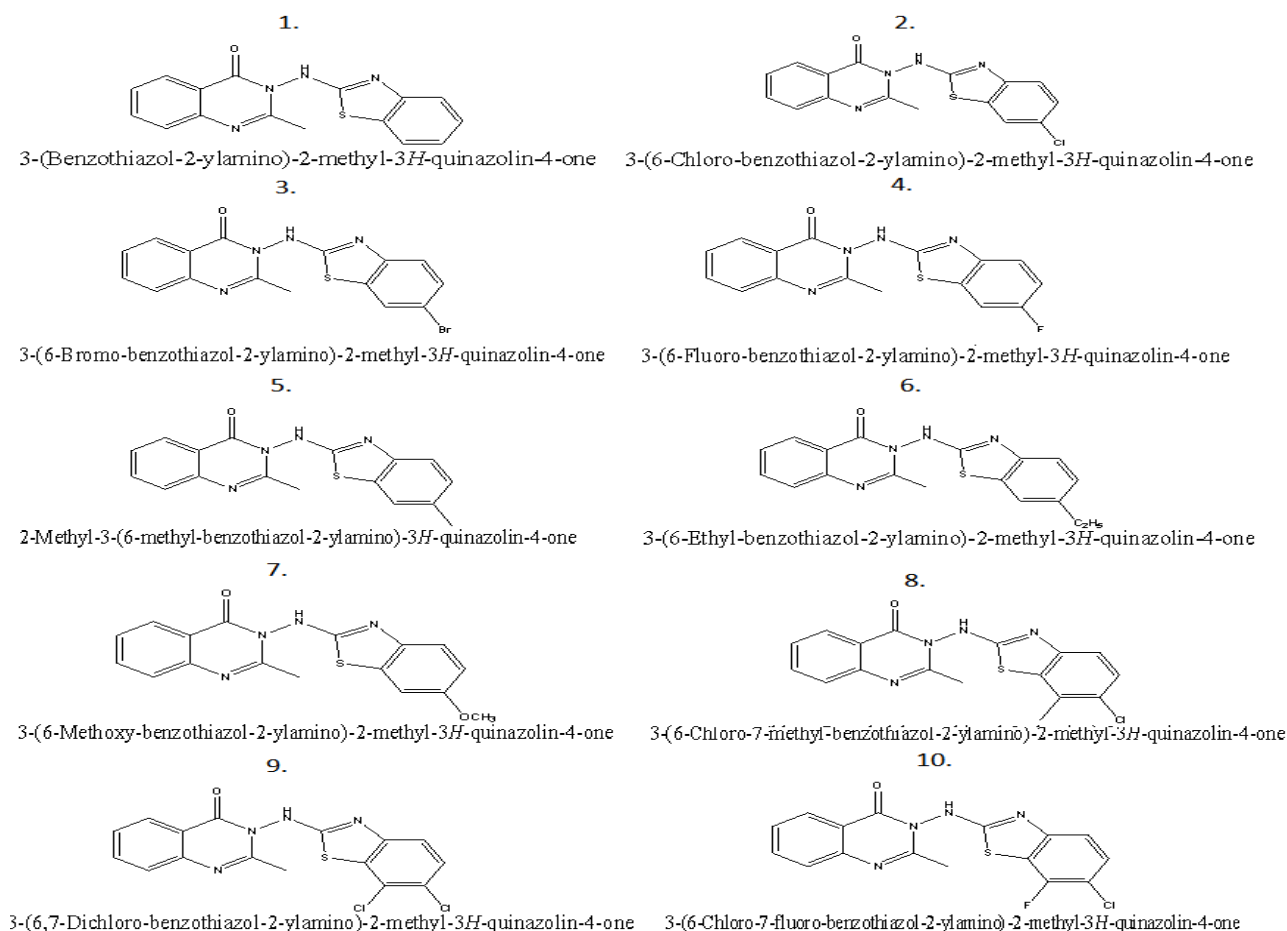


Figure 1. Chemical structures of the hybrid derivatives

2.3. Docking Studies

The docking analysis of hybrid derivatives with GABA-A was carried out by AutoDock Vina. The incorporation of various algorithms makes it a very good tool, as docking search algorithm is based on evolutionary algorithm. It is an iterative optimization technique inspired by Darwinian evolution theory. Evolutionary algorithm consists of population of individuals, which is exposed to

random variation by means of variation operators, like mutation and recombination.

The designed hybrid benzothiazole-quinazolinone derivatives were docked into binding site of GABA-A receptor. For this study, X-ray crystal structure of GABA-A receptor was retrieved from protein data bank.

3. Results and Discussion

3.1. Docking Results

3.1.1. Binding site Analysis

The experimental analysis of binding site shows that PHE 334, TRP 266 and SER 137 could be the catalytic site residue present in the structure of GABA-A receptor.

3.1.2. Docking Studies of Hybrid Benzothiazole-Quinazoline Derivatives with GABA-A Receptor

The protein-ligand interaction affinity of hybrid benzothiazole-quinazoline inhibitors were given by

AutoDock Vina for best pose of novel inhibitors. The best pose ligand-protein interaction affinity of 10 molecules was found to be as -6.2 Kcal/mol, -6.5 Kcal/mol, -6.3 Kcal/mol, -6.4 Kcal/mol, -6.4 Kcal/mol, -6.8 Kcal/mol, -6.4 Kcal/mol, -6.8 Kcal/mol, -6.7 Kcal/mol and -6.5 Kcal/mol respectively. Here, negative values for interaction energy would reflect the positive docking approach. Number of hydrogen bonds and other binding details are given in Table 1 and docking images are given in Figure 2.

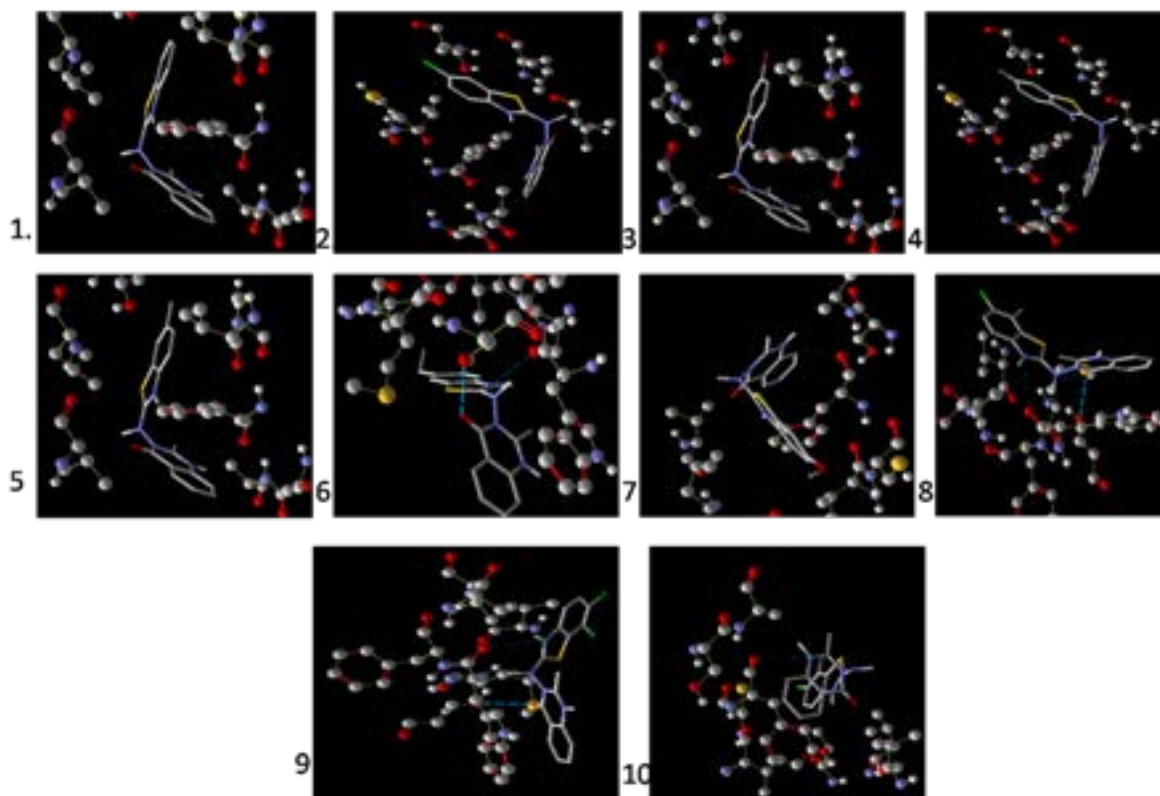


Figure 2. Docked photographs of hybrid benzothiazole-quinazoline derivatives with GABA-A receptor

Table 1. Docking results of hybrid benzothiazole-quinazoline derivatives and γ -aminobutyric acid (CID: 119)

Ligand	Receptor	Affinity Kcal/mol	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Elem.	At. ID.	Type	Res.	Elem.	At.ID.	Type
1	GABA(A) alpha-1	-6.2	1	N	06	Donor	PHE	O	334	Acceptor
2		-6.5	1	N	06	Donor	PHE	O	334	Acceptor
3		-6.3	1	N	06	Donor	PHE	O	334	Acceptor
4		-6.4	1	N	06	Donor	PHE	O	334	Acceptor
5		-6.4	1	N	06	Donor	PHE	O	334	Acceptor
6		-6.8	2	N	20	Acceptor	TRP	O	266	Acceptor
		N		20	Donor	SER	O	137	Both	
7		-6.4	1	N	04	Donor	PHE	O	334	Acceptor
8		-6.8	2	N	20	Donor	TRP	O	266	Acceptor
		O		14	Acceptor	SER	O	137	Both	
9	-6.7	2	N	20	Donor	TRP	O	266	Acceptor	
	O		14	Acceptor	SER	O	137	Both		
10	-6.5	1	N	04	Donor	PHE	O	334	Acceptor	
CID_119	-3.2	5	N	07	Donor	LEU	O	127	Acceptor	
			O	04	Both	SER	O	135	Acceptor	
			O	04	Both	ALA	O	216	Acceptor	
			O	04	Both	THR	O	240	Both	
			O	03	Acceptor	THR	O	240	Both	

3.2. Comparison of Docking Results with Pre-existing GABA-A Inhibitor γ -aminobutyric acid (GABA CID: 119)

On docking studies and docking analysis of γ -aminobutyric acid with the GABA-A, interacting residues (amino acids) are found as THR 311, ALA 308, LEU 296, SER 299, ALA 312, TRP 315 and SER 297 [Figure 3](#).

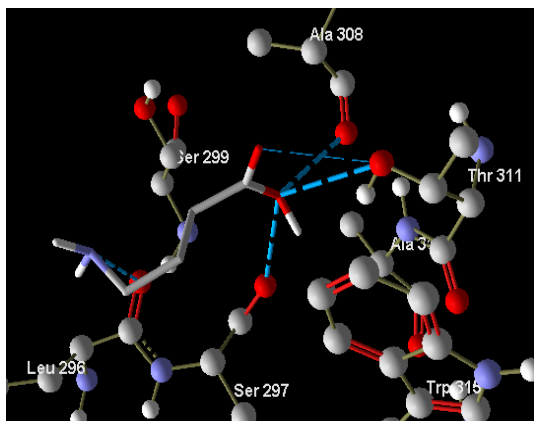


Figure 3. Docking photograph of γ -aminobutyric acid with the GABA-A showing interacting amino acids

On docking analysis, the docked poses of all hybrid benzothiazole-quinazoline derivatives do not superimpose the γ -aminobutyric acid, a pre-existing GABA-A inhibitor which can be clearly seen in [Figure 4](#), but the docking

analysis shows that it nicely docked with protein rather in the catalytic domain for the γ -aminobutyric acid, it means that it binds in the allosteric site of the protein and there is possibilities of making it with anticonvulsant profile.

3.3. Descriptor Studies

All the 10 designed hybrid benzothiazole-quinazoline derivatives have been gone through some descriptor calculation, which are listed in [Table 2](#).

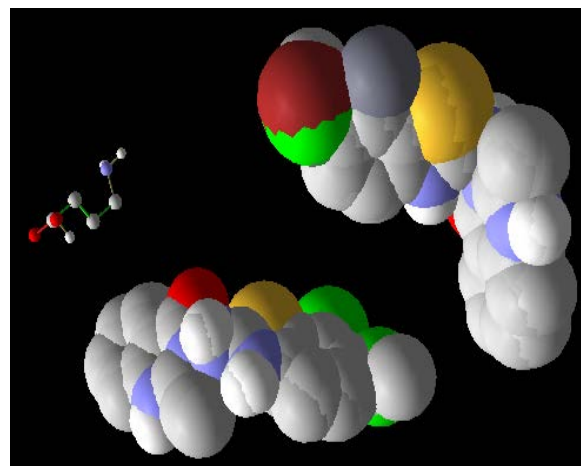


Figure 4. Non-superimposed docking poses of hybrid benzothiazole-quinazoline derivatives (showing with spacefill model) with the pre-existing ligand γ -aminobutyric acid (showing with ball and stick model)

Table 2. Descriptor studies of the hybrid benzothiazole-quinazoline derivatives

S. No.	ALogP	XLogP	Lipinski Failures	Lipo-affinity Index	Eccentric connectivity index	McGowan Volume	Molecular weight
1	1.313	1.429	0	-1.21666	426	1.905	295.9793
2	1.6817	2.006	0	-1.18291	476	2.0489	330.9481
3	1.7657	2.182	0	-1.28653	476	2.1015	374.8976
4	1.2228	1.545	0	0.654387	476	1.9442	314.9777
5	1.7594	1.821	0	-1.25471	476	2.0029	307.9793
6	1.4243	2.285	0	-1.30539	530	2.1008	319.9793
7	0.8144	1.669	0	-1.26816	530	2.0616	323.9742
8	2.1281	2.187	0	-1.30537	497	2.1468	342.9481
9	2.0504	2.583	0	-1.19454	497	2.1928	365.917
10	1.5915	2.122	0	0.739636	497	2.0881	349.9465

4. Conclusion

Docking study of hybrid benzothiazole-quinazoline derivatives proved them potential GABA-A inhibitors. Although a systemic biochemical study is necessary to confirm the findings. When hybrid form of benzothiazole-quinazoline derivatives were docked with GABA-A then all the 10 designed molecules were found with the higher affinity values (more than double affinity value) as compared to the γ -aminobutyric acid, so it could be concluded that these hybrid derivatives may be proved the better inhibitors of GABA-A for the anticonvulsant activity. On comparing the chemical structure of hybrid benzothiazole-quinazoline derivatives with γ -aminobutyric acid, a pre-existing GABA-A inhibitor; there is no structural similarity found except a amine group so it is concluded that this hybrid system may proved a novel class of this category.

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