IN SILICO DESIGN OF POTENTIAL 1,5-BENZOTHIAZEPINE DERIVATIVES AS AN ANTI- CONVULSANT AGENT BY MOLECULAR DOCKING STUDIES

Ms. Parjane Smita[1], Dr. Kunkulol Rahul [2], Dr. Nandal Dattatray[2]

[1] Pravara Rural College of Pharmacy, Loni BK Tal., Rahata Dist., Ahmednagar, Maharashtra.
[2]Department of Pharmacology, Pravara Institute of Medical Sciences, Deemed University, Loni, Ahmednagar, Maharashtra, India.

ABSTRACT

Epilepsy is characterized by the presence of recurrent seizures. A seizure can be defined as "an episodic disturbance of movement, feeling, or consciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex". One in every three patients with epilepsy is probable to be severely disabled. It is continuing this scenario as an attempt to develop potent and nontoxic anti-convulsant agents. Recently discovery of benzothiazepine derivatives as an anticonvulsant agent is significant area for research in medicinal chemistry as it is free from all side effects which is shown by a developed as an anticonvulsant agent. In this paper, we have presented results of 2D, and 3D docking poses studies of a series of 300 (Three series) molecules containing 1,5-benzothiazepine pharmacophore as anti-convulsant agents. Docking analysis was utilized to predict the mechanism of action of the designed derivatives for anticonvulsant potential. All the molecules exhibited binding score in the range of -82.61 to -118.25 kcal/mol. Most active molecules from Series 1, 2 and 3 exhibited hydrogen bond interactions with LEU282B, LEU282B and LEU282B. Also for the selected standard sodium phenytoin showed the hydrogen bond interaction with LYS637A. It was noted that the docking score of 1a to 10a, 101b to 110b and 201c to 210c was almost same as that of selected standard sodium phenytoin. Protein showed hydrogen bonding with all synthesized compound showed potential against the epilepsy with GABA nergic mechanism.

Keywords: Anti-convulsant; 1,5-benzothiazepine; V-Life MDS 4.3.

INTRODUCTION

Epilepsy is characterized by the presence of recurrent seizures. A seizure can be defined as "an episodic disturbance of movement, feeling, or consciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex" [1]. Epileptic convulsions are expected to have negative consequences on the patient's psychological and social life such as relationships, education and employment. Uncontrolled seizures are associated with physical and psychosocial morbidity, dependent behaviour, poor quality of life and an increased risk of sudden unexpected death. Therefore, it is often recommended to begin treatment of epilepsy with antiepileptic drugs (AEDs) as soon as the patient has reported more than one documented or witnessed seizure bearing in mind that the goal of treatment should be to maintain as normal a life style through complete seizure control with no or minimal side effects [2].

Anti-convulsant drugs are widely used in the treatment of various central nervous system diseases like bipolar disorder, antipsychotic, impulsive aggression, borderline personality disorder etc. Benzothiazepine is the most vital class of series origin of benzodiazepine pharmacophore. They are differ only in place of sulphur and nitrogen element in the heterocyclic ring system. Particularly benzothiazepines used as a cardiovascular-related diseases vix coronary vasodilation, hypertension etc. Recently it has been used as a anti-convulsant, antipsychotic activity, anti-HIV activity, antimicrobial activity etc. There are various benzothiazepines which have been synthesized and tested for their biological activities (3-6). 1,5 benzothiazepine is a calcium channel blocker also known as Diltiazem [3]. Diltiazem is a non-dihydropyridine (DHP) member of the group of drugs known as benzothiazepine.

Medicinal chemists today are facing many complicated challenges. The most demanding and perhaps the most rewarding one is the rational design of new therapeutic agents for treating human diseases. The definition currently accepted of what molecular modelling can be stated as "molecular modelling is anything that requires the use of a computer to paint, describe or evaluate any aspect of the properties of the structure of a molecule". Methods used in the molecular modelling are regarding automatic structure generation, analysis of three-dimensional (3D) databases and construction of protein models by techniques based on sequence homology, diversity analysis, docking of ligand. Molecular modelling has widened the horizons of pharmaceutical research by providing tools for finding new leads.

Thus, today, molecular modelling is regarded as a field concerned with the use of all sort of different strategies to model and to deduce information of a system at the

DOI: 10.31878/ijcbr.2019.53.6

eISSN: 2395-0471
pISSN: 2521-0394

Correspondence: Parjane Smita, Pravara Rural College of Pharmacy, Loni BK Tal. Rahata Dist. Ahmednagar, Maharashtra, India. Email: parjanesmita23@gmail.com

atomic level. On the other hand, this discipline includes all methodologies used in computational chemistry, like computation of the energy of a molecular system, energy minimisation Monte Carlo methods or molecular dynamics. In other words, it is possible to conclude that computational chemistry is the nucleus of molecular modelling. Identification of bio-molecular moieties involved in the interaction with a specific receptor permits to understand the molecular mechanism responsible of its particular biological activity. In turn, this knowledge is aimed at designing new active molecules that can be successfully used as drugs. Because simulation accuracy is limited to the precision of the constructed models, when it is possible, computational simulations have to be compared with experimental results to confirm model accuracy and to modify them if necessary, in order to obtain better representations of the system [4-6].

The developments of new anti-convulsant therapeutic agents are one of the fundamental goals in medicinal chemistry. In recent years there has been concerned search for the discovery and development of potent and selective against anti-convulsant agents. Heterocyclic compounds comprise the dominant family of organic compounds. These are enormously essential with a wide range of synthetic, pharmaceutical and industrial applications and are famous for their biological activities. There is an extensive spectrum of biological activities shown by many compounds containing five-membered heterocyclic rings in their structure.

Therefore we attempt to identify the potential molecule for the synthesis of 1,5-benzothiazepine as an anticonvulsant using V-Life MDS 4.3 software for the execution of synthesis of selected moiety. From the present work, we find out the physicochemical and interactive parameters responsible for the anticonvulsant action of new 1,5-benzothiazepine as anti-convulsant agents from the docking studies,

MATERIAL AND METHODOLOGY

Equipments: All computational studies were performed using V-Life Molecular Design Software Version 4.3. Docking study were generated using a training set of 300 molecules.

Molecular docking studies: V Life MDS version 4.3 software was employed to assess the structure of the enzyme-inhibitor complex. In our study, three series of 1,5 benzothiazepine were selected for docking studies (**Figure 1a, 1b** and **1c**) Three hundred structure of 1,5-benzothiazepine expected derivatives were tested and also shown in **Table 1, 2** and **3**.VLifeMDS version 4.3 expected binding free energies of enzyme-inhibitor complexes and the binding energies of both the bound and unbound states using semi-empirical free energy force field. The 3D structures of following PDBs were acquired from RCSB Protein Data Bank. The PDB id is, 3IP9 (Structure of Atu2422-GABA receptor in complex with GABA shown in **Figure 2**) [7]. The 3D structures of selected 1,5-benzothiazepine derivatives were drawn in ACD-Chemsketch and converted into 3D mol. format. The automated docking model was generated using Vlife MDS Tool. The co-crystallized ligand was used to generate the grid box for catalytic inhibition mode. The selected grid box size was 60×60×60. PyMOL 1.7.4 and LigPlot+ were adopted to acquire the number of H-bonds and van der Waals interacting residues. To determine the binding affinities between the ligand and receptor, the amino acids with the binding pockets was predicted at Q-site finder server [8].

RESULTS

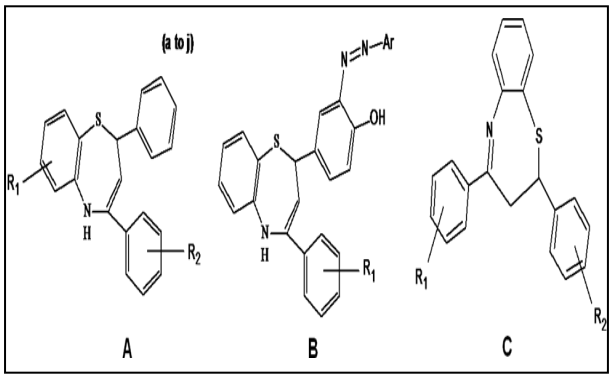


Fig 1. Selected 1,5-benzothiazepine series for the docking study

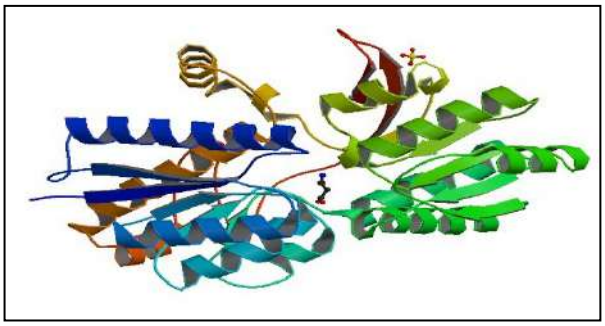


Fig 2. Target structure PDB code 3IP9 (Structure of Atu2422-GABA receptor in complex with GABA)

Docking Study: Molecular docking approach was utilze to guess the enzyme inhibitor interaction geometrics for the selected compounds. The docking scores for 1,5-benzothiazepine derivatives (selected 300 substituents on 1,5-benzothiazepine moieties) with interacting 3IP9 (Structure of Atu2422-GABA receptor in complex with GABA) residues including hydrogen bond, van der Waals and hydrophobic interacting residues. Sodium Phenytoin moiety was choose as a standard drug for the docking study.

DISCUSSION

Epilepsy is an associated with physical and psychosocial morbidity, dependent behavior, poor quality of life and an increased risk of sudden unexpected death , therefore it an urgent social need to discover a new potential derivative for the treatment of epilepsy. Henceforth we have planned to synthesized new derivative from the class of 1,5 benzothizepine. Generally we have drawn the three series for the synthesis of 1,5 benzothizepine moiety to get higher potential moiety. Three hundred substituents of the selected series were fixed and were screened to get better activity against the epilepsy. As per the discussion in introduction part molecular modeling study is the best option to get the idea about potency of

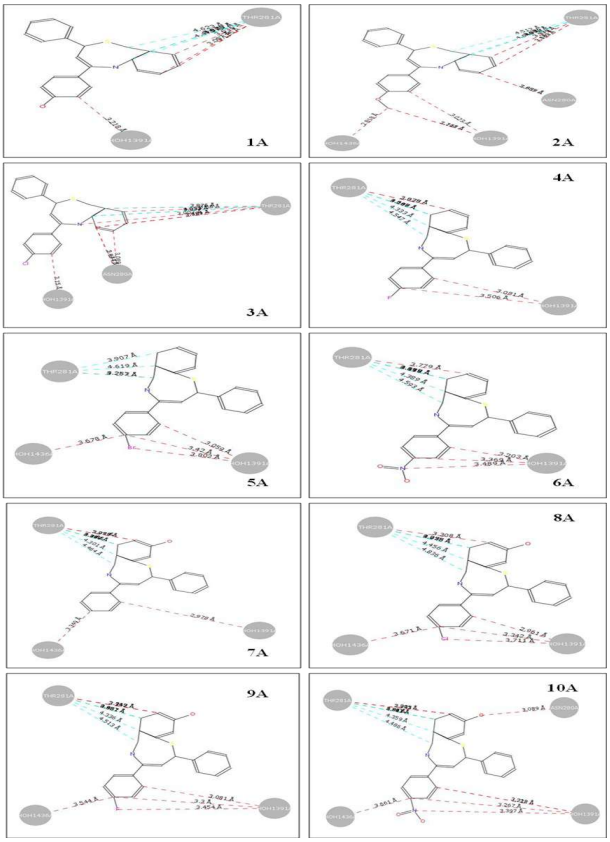


Fig 3. 2D images of 1a-10ainteract with 3IP9 protein

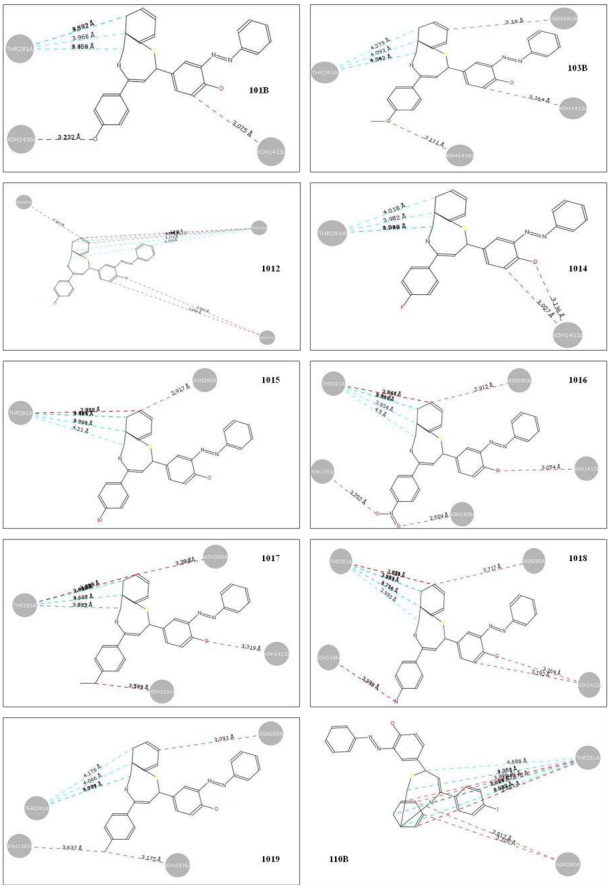


Fig 4. 2D images of 101b-110b bonding with 3IP9 protein

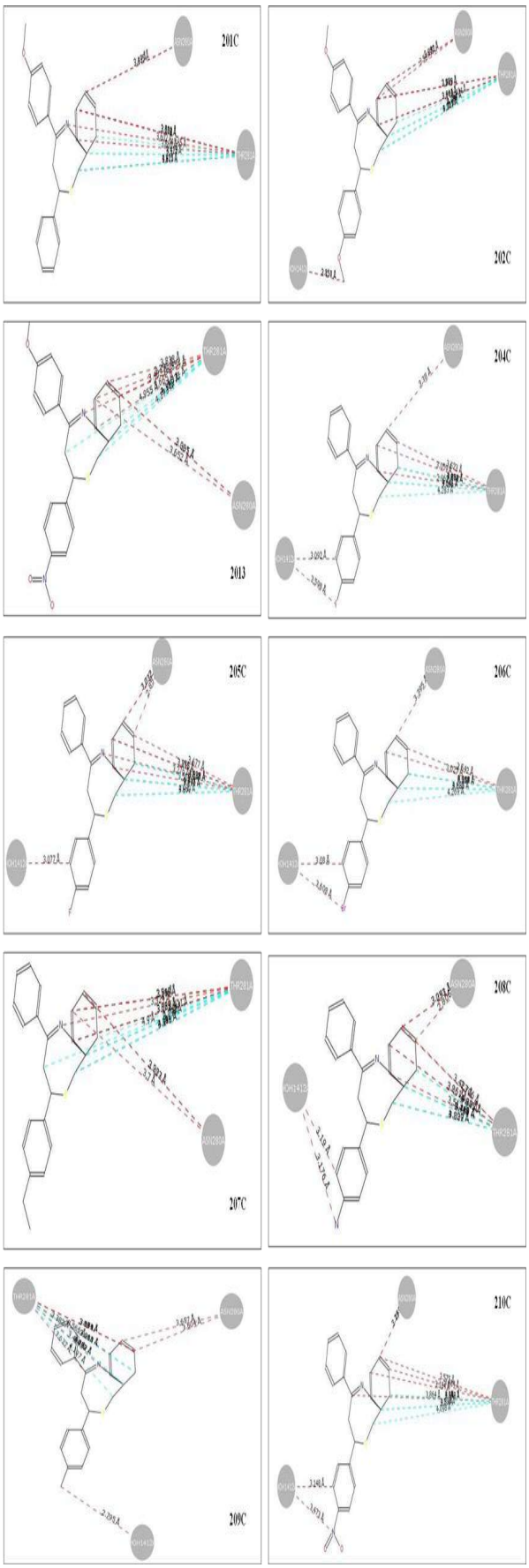


Fig 5. 2D images of 201C-210C bonding with 3IP9 protein

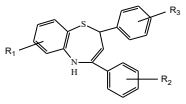
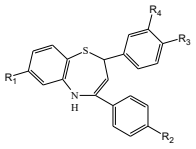


Table 1. Proposed chemical structure (1-100) for docking study

Compound Code	R1	R2	R3	Compound Code	R1	R2	R3
1	H	OH	H	51	I	Br	CH_3
2	H	OCH_3	H	52	I	Cl	CH_3
3	H	Cl	H	53	I	NO_2	CH_3
4	H	F	H	54	I	NH_2	CH_3
5	H	Br	H	55	I	NH_2	I
6	OH	Br	H	56	I	NH_2	F
7	OH	Br	OH	57	I	NH_2	Br
8	H	NO_2	H	58	I	NH_2	NO_2
9	Cl	H	H	59	I	NH_2	NH_2
10	F	H	H	60	F	NH_2	F
11	Br	H	H	61	F	NO_2	F
12	OH	H	H	62	F	I	F
13	OH	I	H	63	F	Cl	F
14	OH	Cl	H	64	F	Br	F
15	OH	F	H	65	F	$NH\text{-}CH_3$	F
16	H	NO_2	H	66	I	$NH\text{-}CH_3$	F
17	Br	NO_2	H	67	Br	$NH\text{-}CH_3$	F
18	F	NO_2	H	68	H	$NH\text{-}CH_3$	F
19	NO_2	NO_2	H	69	H	$NH\text{-}CH_3$	H
20	OH	NO_2	H	70	H	$NH\text{-}CH_3$	OH
21	OH	NO_2	Cl	71	H	$NH\text{-}CH_3$	CH_3
22	OH	NO_2	F	72	H	$NH\text{-}CH_3$	I
23	OH	NO_2	Br	73	H	$NH\text{-}CH_3$	Cl
24	OH	NO_2	NO_2	74	H	$NH\text{-}CH_3$	Br
25	OH	NO_2	I	75	NO_2	$NH\text{-}CH_3$	Br
26	OH	H	H	76	NO_2	$NH\text{-}CH_3$	F
27	H	H	H	77	NO_2	$CH_2\text{-}CH_3$	CH_3
28	OH	CH_3	CH_3	78	NH_2	$CH_2\text{-}CH_3$	CH_3
29	CH_3	H	H	79	F	$CH_2\text{-}CH_3$	CH_3
30	CH_3	H	Br	80	I	$CH_2\text{-}CH_3$	CH_3
31	CH_3	H	F	81	I	$-HC(CH_3)_2$	CH_3
32	CH_3	H	Cl	82	Cl	$-HC(CH_3)_2$	CH_3
33	CH_3	H	CH_3	83	NO_2	$-HC(CH_3)_2$	CH_3
34	CH_3	Cl	CH_3	84	NH_2	$-HC(CH_3)_2$	CH_3
35	CH_3	Br	CH_3	85	NH_2	$-HC(CH_3)_2$	F
36	CH_3	F	CH_3	86	NH_2	$-HC(CH_3)_2$	Br
37	CH_3	NO_2	CH_3	87	Cl	C=O	H
38	CH_3	NO_2	H	88	H	C=O	H
39	CH_3	NO_2	Cl	89	Br	C=O	H
40	CH_3	NO_2	F	90	OH	C=O	H
41	CH_3	NO_2	Br	91	I	C=O	H
42	CH_3	CH_3	H	92	NO_2	C=O	H
43	CH_3	CH_3	CH_3	93	F	C=O	H
44	Cl	CH_3	CH_3	94	NH_2	C=O	H
45	Br	CH_3	CH_3	95	NH_2	$-HC(CH_3)_2$	I
46	F	CH_3	CH_3	96	NH_2	$-HC(CH_3)_2$	NO_2
47	NO_2	CH_3	CH_3	97	NO_2	$-HC(CH_3)_2$	I
48	I	CH_3	CH_3	98	NO_2	$-HC(CH_3)_2$	Br
49	I	I	CH_3	99	NO_2	$-HC(CH_3)_2$	NH_2
50	I	F	CH_3	100	NO_2	$-HC(CH_3)_2$	NO_2

Table 2. Proposed chemical structure (101-200) for docking study



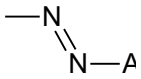
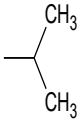
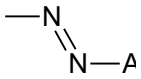
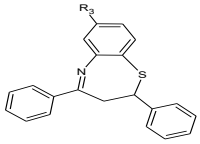
Com-pound Code	R1	R2	R3	R4	Compound Code	R1	R2	R3	R4
101	H	OH	OH		151	H	F	CH_3	NH_2
102	H	OCH_3	OH		152	H	Cl	CH_3	NH_2
103	H	Cl	OH		153	H	Br	CH_3	NH_2
104	H	I	OH		154	H	NO_2	CH_3	NH_2
105	H	F	OH		155	H	NH_2	CH_3	NH_2
106	H	$-CH_2-CH_3$	OH		156	H	CH_3	CH_3	NH_2
107	H	Br	OH		157	H	CH_2-CH_3	CH_3	NH_2
108	H	NO_2	OH		158	OH	$NH-CH_3$	CH_3	NH_2
109	H	NH_2	OH		159	H	$NH-CH_3$	CH_3	NH_2
110	H	CH_3	OH		160	OH	NH-I	CH_3	NH_2
111	OH	Cl	OH		161	OH	NH-F	CH_3	NH_2
112	H	CH_3	Br		162	OH	NH-Br	CH_3	NH_2
113	H	NH_2	Br	NH_2	163	OH	I	NH_2	NH_2
114	H	NO_2	Br	NH_2	164	OH	F	NH_2	NH_2
115	H	Br	Br	NH_2	165	OH	Cl	NH_2	NH_2
116	H	Cl	Br	NH_2	166	OH	Br	NH_2	NH_2
117	H	F	Br	NH_2	167	OH	CH_3	NH_2	NH_2
118	H	I	Br	NH_2	168	OH	NO_2	NH_2	NH_2
119	H	I	NO_2	NH_2	169	OH	NH_2	NH_2	NO_2
120	H	F	NO_2	NH_2	170	OH	$NH-CH_3$	NH_2	NO_2
121	H	Cl	NO_2	NH_2	171	OH	$NH-CH_3$	NO_2	NO_2
122	H	Br	NO_2	NH_2	172	OH	CH_2-CH_3	NO_2	NO_2
123	H	CH_3	Cl	NH_2	173	OH	CH_3	NO_2	NO_2
124	H	NH_2	Cl	NH_2	174	OH	NH_2	NO_2	NO_2
125	H	NO_2	Cl	NH_2	175	OH	NO_2	NO_2	NO_2
126	H	Br	Cl	NH_2	176	OH	CH_3		H
127	H	Cl	Cl	NH_2	177	OH			H
128	H	F	Cl	NH_2	178	OH	$-CH_2-CH_3$		H
129	H	I	Cl	NH_2	179	OH	$-CH_2-NH_2$		H
130	H	I	F	NH_2	180	OH	$NH-CH_3$		NH_2
131	H	F	F	NH_2	181	OH	NH_2		H
132	H	Cl	F	NH_2	182	OH	Br		H
133	H	Br	F	NH_2	183	OH	Cl		H
134	H	NO_2	F	NH_2	184	OH	F		H
135	H	NH_2	F	NH_2	185	OH	I		H
136	H	CH_3	F	NH_2	186	OH	I		NH_2
137	H	$-CH_2-CH_3$	I	NH_2	187	NH_2	I	H	H
138	H	CH_3	I	NH_2	188	NH_2	F	H	H
139	H	NO_2	I	NH_2	189	NH_2	NH_2		H
140	H	NH_2	I	NH_2	190	H	$NH-CH_3$		NH_2
141	H	Br	I	NH_2	191	CH_3	NH_2		NH_2
142	H	Cl	I	NH_2	192	CH_3	$NH-CH_3$	H	NH_2
143	H	F	I	NH_2	193	CH_3	$NH-CH_3$	CH_3	NH_2
144	H	CH_2I	I		194	CH_3	$NH-CH_3$	CH_2Cl	NH_2
145	H	CH_2I	OH		195	CH_3	$NH-CH_3$	CH_2Br	NH_2
146	H	CH_2F	OH		196	CH_3	$NH-CH_3$	CH_2I	NH_2
147	H	CH_2Cl	OH		197	CH_3	$NH-CH_3$	CH_2NH_2	NH_2
148	H	CH_2Br	OH		198	CH_3	$NH-CH_3$	CH_2NO_2	NH_2
149	H	$CH_2 NO_2$	OH	NH_2	199	Cl	NH_2	H	NH_2
150	H	CH_2NH_2	OH	NH_2	200	Cl	$NH-NH_2$	CH_{-2}	NH_2

Table 3. Proposed chemical structure (201-300) for docking study



Compound Code	R1	R2	R3	Compound Code	R1	R2	R3
201	OCH_3	H	H	251	CH_3	H	NH_2
202	OCH_3	OCH_3	H	252	CH_3	H	CH_3
203	OCH_3	NO_2	H	253	CH_3	H	CH_2-CH_3
204	H	I	H	254	CH_3	H	CH_2-NO_2
205	H	F	H	255	CH_3	H	CH_2-NH_2
206	H	Br	H	256	CH_3	H	H
207	H	NO_2	H	257	CH_3	H	OH
208	H	NH_2	H	258	CH_3	H	NH_2
209	H	CH_3	H	259	H	H	CH_3
210	H	CH_2-CH_3	H	260	OH	H	CH_3
211	I	CH_2-CH_3	H	261	CH_3	NH_2	H
212	I	CH_3	H	262	CH_3	NO_2	H
213	I	NO_2	H	263	CH_3	Br	H
214	I	NH_2	H	264	CH_3	Cl	H
215	I	Br	H	265	CH_3	F	H
216	I	Cl	H	266	CH_3	I	H
217	I	F	H	267	CH_3	H	I
218	I	I	H	268	CH_3	H	Br
219	F	I	H	269	CH_3	H	F
220	F	F	H	270	CH_3	H	NO_2
221	F	Cl	H	271	NH_2	NO_2	H
222	F	Br	H	272	NH_2	NH_2	H
223	F	NO_2	H	273	NH_2	CH_3	H
224	F	NH_2	H	274	NH_2	CH_2-CH_3	H
225	F	CH_3	H	275	NH_2	CH_2-NH_2	H
226	F	CH_2-CH_3	H	276	NH_2	CH_2-NO_2	H
227	Cl	CH_2-CH_3	H	277	CH_3	CH_2-NO_2	H
228	Cl	CH_2-NH_2	H	278	CH_3	CH_2-NH_2	H
229	Cl	CH_3	H	279	CH_3	CH_2-CH_2-NH_2	H
230	Cl	NH_2	H	280	CH_3	CH_3	H
231	Cl	NO_2	H	281	NO_2	I	H
232	Cl	Br	H	282	NO_2	F	H
233	Cl	Cl	H	283	NO_2	Cl	H
234	Cl	F	H	284	NO_2	Br	H
235	Cl	I	H	285	NO_2	NH_2	H
236	Br	I	H	286	NO_2	NO_2	H
237	Br	F	H	287	NH_2	I	CH_3
238	Br	NH_2	H	288	NH_2	F	CH_3
239	Br	Cl	H	289	NH_2	Cl	CH_3
240	Br	Br	H	290	NH_2	Br	CH_3
241	Br	NO_2	H	291	Br	CH_2-NO_2	CH_3
242	Br	OCH_3	H	292	Br	CH_2-NH_2	CH_3
243	Br	CH_2-CH_3	H	293	NO_2	CH_2-NO_2	CH_3
244	OCH_3	CH_2-CH_3	H	294	NO_2	CH_2-NH_2	CH_3
245	OCH_3	NO_2	H	295	NO_2	CH_3	CH_3
246	OCH_3	CH_3	H	296	NO_2	CH_2-CH_2-NH_2	CH_3
247	OCH_3	F	H	297	Br	CH_2-CH_3	CH_3
248	OCH_3	I	H	298	Br	CH_3	CH_3
249	OCH_3	Cl	H	299	Br	NH_2	CH_3
250	OCH_3	H	H	300	Br	NO_2	CH_3

selected derivatives.

A conserved mechanism of GABA binding and antagonism is revealed by Structure-Function Analysis of the periplasmic binding protein Atu2422 [7]. Bacterial periplasmic binding proteins (PBPs) and eukaryotic PBP-like domains (also called as Venus flytrap modules) of G-protein-coupled receptors are involved in extracellular GABA perception (8). Gamma - Aminobutyric acids (GABA), the prime inhibitory neurotransmitter in the cerebral cortex, sustain the inhibitory tenor that counterbalance neuronal excitation

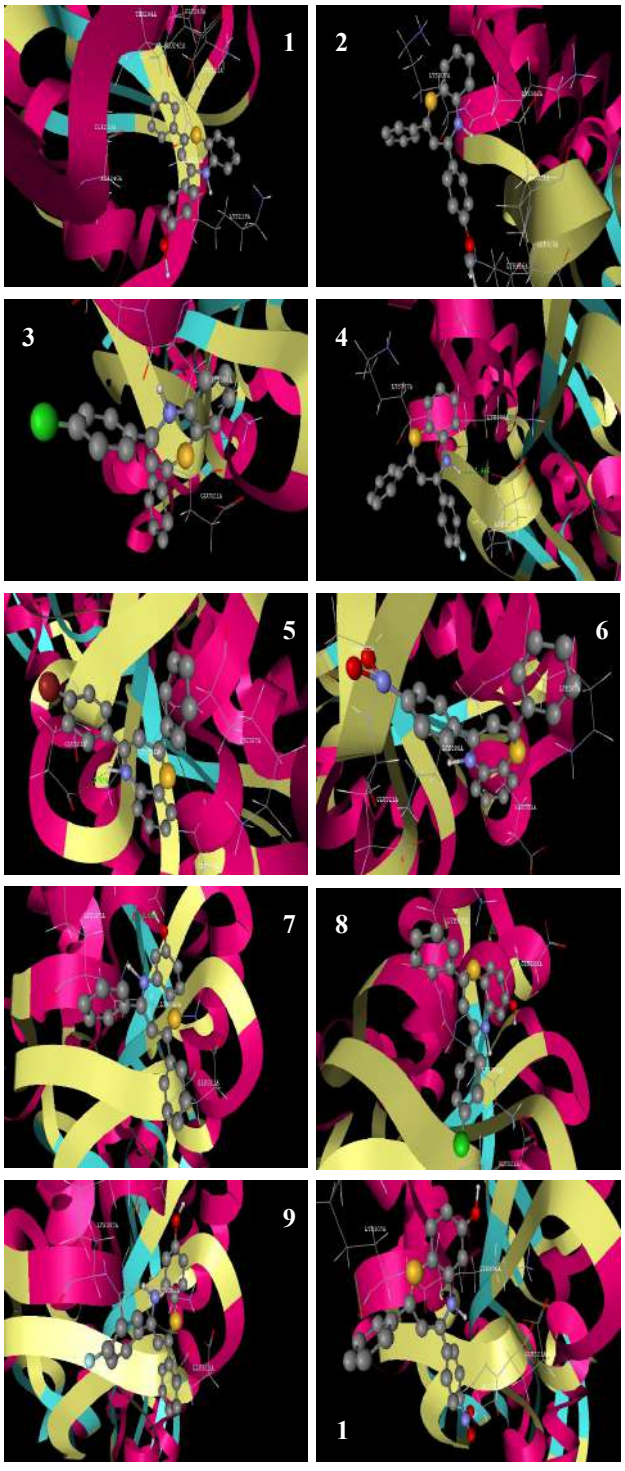


Fig 6. Docking 3D Images of 1A to 10A synthesized compounds

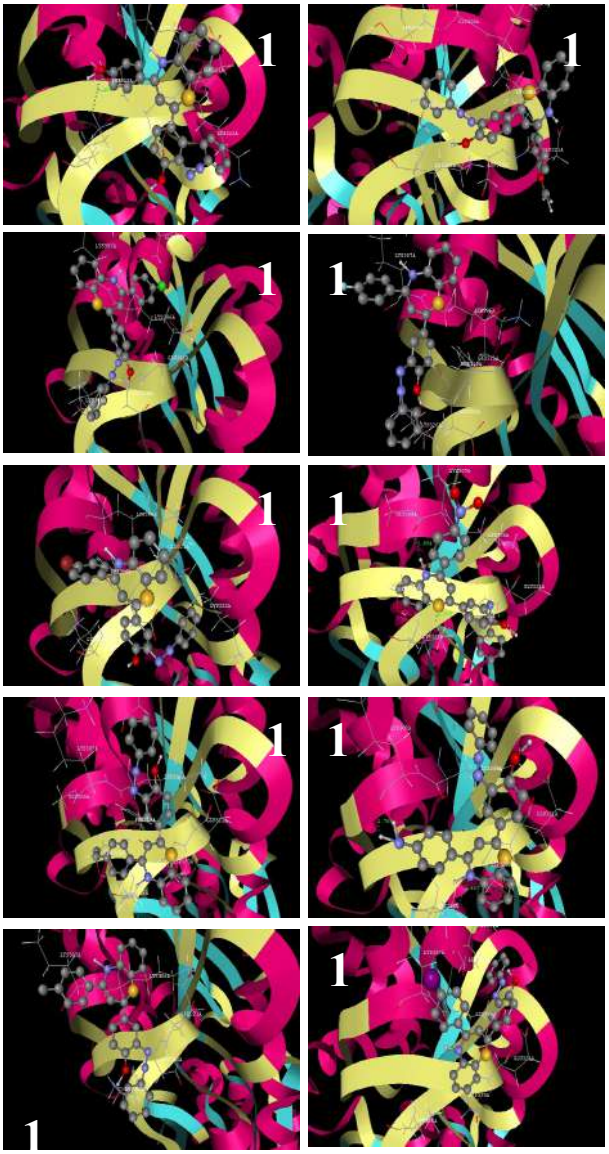


Fig 7. Docking 3D Images of 101B to 110B synthesized compounds

(9). Therefore we have targeted protein i.e 3IP9 (Structure of Atu2422-GABA receptor in complex with GABA) is particularly found in GABA receptor as per the report of Planamente et al., (2010) [7].

For checking binding interaction first open receptor in MDS followed by compound which saved as ligand dock file. From tool option click on merge molecule so that compound and receptoris merged together. From biopredicta tool edit this complex and select ligand and receptor structure afterward check its interaction. The said protein is correlates with anticonsulvant activity. To discuss the interaction details of ligands and protein, the docked conformations of the compounds were studied on 3IP9. The said proteins belong to the class of GABA receptor group of proteins, which exhibited structural stability to the gene and expression by epigenetic modification of DNA, plays significant role in epilepsy. It was noted that the docking score of 1a to 101a, 101b to 200b and 201c to 300c was almost same as that of selected standard sodium phenytoin. Protein showed hydrogen bonding with some of the compound from selected series with GABAnergic mechanism.

Docking analysis was utilized to predict the mechanism of action of the designed derivatives for anticonvulsant potential. All the molecules exhibited binding score in the range of -82.61 to -118.25 kcal/mol. Most active molecules from Series 1, 2 and 3 exhibited hydrogen bond interactions with LEU282B, LEU282B and LEU282B respectively. Also for the selected atandard sodium phenytoin showed the hydrogen bond interaction with LYS637A. The series 1 showed hydrophobic bonding interactions with VAL290B, VAL290B, GLY421B, LEU282B etc. and Vander Waals interactions with LEU282B, LEU282B, GLY283B, PHE 287B, PHE420B (**Figure 3**). The series 2 compound showed hyrdrophobic bond interactions with GLY421B, PHE420B, VAL 290B, LYS 309B and also Van der Waals interactions with LYS439B, PHE287B, GLY283B, LEU282B, GLY515B (**Figure 4**). The compound from series 3 showed hydrophobic interaction with VAL291B, VAL295B, GLY427B, LEU280B and Van der Waals interactions with LEU284B, LEU285B, GLY280B, PHE207B and PHE421B (**Figure 5**). Whereas standard sodium phenytoin exbited hydrophobic interaction with ALA549A (4.675), ASP593A (2.987), LYS647A (2.638) and Van der Waals interactions with SER528A (4.658), THR652A (1.675), GLU428A (3.293) and ASN55AA 2.105.

From the series 1, ten derivatives are selected for the synthesis of 1,5 benzothiazepine class namely 1a to 10a. It was observed that the good docking score (**Table 4**). The docking posses with 3D picture are depicted in **Figure 5**. Whereas series 2 have also selected 10 derivative to synthesize the compounds namely 101b to 110b. 3D docking images are depicted in **Figure 6**. The best docking posses of the series 3 of 1, 5 benzothiazepine have been showed in the **Figure 7**. Total 30 compound are having good score which have been selected for the synthesis namely 1a-10a, 101b-110b and 201c to 210c. In the docking study their van. It was discovered that the potential of 1a-100a, 101b-200b, 201c-300c and Sodium Phenytoin against 3IP9 (Structure of Atu2422-GABA receptor in complex with GABA) was linked with the binding energy and the number of bonds formed at the catalytic site. It was noted that the hydrogen bond and hydrophobic interaction of 1a-100a, 101b-200b, 201c-300c and Sodium Phenytoin with proteins further stabilized the enzyme-inhibitor interaction. The 3IP9 had interaction with 1a-100a, 101b-200b, 201c-300c and Sodium Phenytoin through hydrogen bond, the hydrogen bond interaction of 1a-100a, Sodium Phenytoin with 3IP9 proteins further stabilized the enzyme-inhibitor interaction due to amino acid.

CONCLUSION

In this present investigation, it was found that all projected moiety were statistically significant, therefore from above 2D/3D models it could be concluded that 1,5 benzothiazepine derivatives are used to synthesize as anti-convulsant drugs. It was found that 1a-10a, 101b -110b and 201c-210c having good docking score for synthesizing the derivatives. It was noted that the docking score of 1a to 10a, 101b to 110b and 201c to 230c was almost same as that of selected standard sodium phenytoin. Protein showed hydrogen bonding with all synthesized compound showed potential against the epilepsy with GABAnergic mechanism.

Acknowledgment: The authors would like to thank the Director of the Diya Laboratory (Mumbai, India) for the tests of FT-IR, NMR, and Mass Spectra. We are also grateful to Pravara Institute of Medical Sciences-Deemed University (PIMS-Deemed university), Pravara Rural College of Pharmacy, Loni BK Tal. Rahata, District- Ahmednagar (India)-413736 & Dr.V.V.P.F's, college of Pharmacy, Vilad Ghat, Ahmednagar -414111 for providing research facilities and constant encouragement.

Conflict of Interest: Declared none

REFERENCES

[1] Kwan P, Brodie MJ. Effectiveness of First antiepileptic Drugs. Epilepsia. 2001;42(10): 1255-60

[2] Brodie MJ. Medical therapy of epilepsy: When to initiate treatment and when to combine? Journal of Neurology. 2005; 252:125-30

[3] Pandeya SN, Kumar D, Verma PK. Newer Applications of 1,5-Benzothiazepines & their anticonvulsant activity. Der Pharma Chemica. 2012;4(5):1853-5

[4] Sarro GD, Ferreri G, Gareri P, Russo E, Sarro AD, Gitto R, Chimirri A. Comparative anticonvulsant activity of some 2,3-benzodiazepine derivatives in rodents. Pharmacology Biochemistry and Behavior. 2003; 74(3):595-602

[5] Fukinaga M, Ishizawa K, Kamei C. Anticonvulsant properties of 1,4-benzodiazepine derivatives in amygdaloid-kindled seizures and their chemical structure-related anticonvulsant action. Pharmacology. 1998; 57(5): 233-41

[6] Planamente S, Vigouroux A, Mondy S, Nicaise M, Faure D, Morera S. A conserved mechanism of GABA binding and antagonism is revealed by structure-function analysis of the periplasmic binding protein Atu2422 in Agrobacterium tumefaciens. J.Biol.Chem. 2010; 285: 30294-303

[7] Laurie AT, Jackson RM. Q-SiteFinder: an energy-based method for the prediction of proteinligand binding sites. Bioinformatics. 2005; 21: 1908–16.

[8] Treiman DM. GABAergic mechanisms in epilepsy. Epilepsia. 2001; 42(3): 8-12.