Journal of Computational Methods in Molecular Design, 2016, 6 (3):47-54

ISSN : 2231- 3176
CODEN (USA): JCMMDA

Molecular Docking Study of 6-substituted 2-aminobenzothiazole derivatives as anticonvulsant agents.

Love Kumar Soni* and Bhagat Singh Chouhan

School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Parisar, Khandwa Road, Indore 452001, India

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ABSTRACT

Molecular docking studies were carried out against γ-amino butyric acid (GABA) molecular target using Molegro Virtual Docker v 5.0 to accomplish preliminary confirmation of the observed in-vivo anticonvulsant activity. Docking studies have shown that the title compound interact and bind efficiently with 1OHY subunits of γ-amino butyric acid (GABA) enzyme which resulted in anticonvulsant activity. The quantitative assessment after docking procedure was made on the basis of Mol dock scores, re rank scores and hydrogen bond. Compound BSC-05 (6-methyl-[3-(3,4-dihydroxyphenyl)-prop-2-eneamido] benzothiazole) showed good binding interaction with mol dock score -84.236, re rank score -54.993 and hydrogen bond -8.414 which was close to the reference drug phenytoin.

Keywords: 6-substituted 2-aminobenzothiazole**,** Anticonvulsant activity**,** Molecular Docking

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INTRODUCTION

Epilepsy is a common neurological disorder [1], which is characterized by an enduring predisposition to generate seizures and by its neurobiological, cognitive, psychological, and social consequences [2]. World Health Organization (WHO) reports 50 million people with epilepsy worldwide, out of which 80% people reside in developing countries [3]. In India about 10 million people are affected with epilepsy (prevalence of about 1%) [4], this being higher in the rural (1.9%) as compared with the urban counterpart (0.6%) [5-7]. Main strategy for epilepsy treatment is pharmacotherapy with antiepileptic or anticonvulsant drugs [8]. A number of anti-epileptic drugs (AEDs) such as topiramate [9], lamotrigine [10], tiagabine [11], felbamate [12], vigabatrin [13], and zonisamide [14] have been introduced to treat epilepsy diseases. However, 20-30% of patients are failed to control seizures by current medications. Aminobenzothiazole and its derivatives have been reported as precursors for pharmacological agents. Their biological activities reported as anti-allergic agents [15], antibacterial [16], p56 lck enzyme inhibitor [17], b-glucuronidase [18] and neuroprotective agents [19-20]. The substituted 2-aminobenzothiazole derivatives are reported as powerful anticonvulsant agents and chosen for clinical evaluation [21]. It has been proposed that the GABA like pharmacophore on the benzothiazole nucleus might bind sufficiently with the receptors and the resultant molecules will have a synergistic anticonvulsant effect due to increased lipophilicity. The presence of an amide group as hydrogen bonding domain (HBD) is an optimal anticonvulsant pharmacophoric feature in the title compound. The additional features include benzothiazolyl hydrophobic-domain (A), S atom as electron donor system (D) with distal phenyl residue (R), which influences the blood brain barrier (BBB) diffusion and pharmacokinetic properties of the anticonvulsants (Fig.1) [22]. Docking studies gave valuable insights assessing lipophilicity and steric hindrance as main molecular determinants most likely affecting the newly synthesized 2-aminobenzothiazole derivatives in their anticonvulsant activity. Mol dock score forms the basis of predicting the

experimental binding affinity of a protein - ligand complex while the rerank score in molecular docking provides estimation of the strength of the interaction.

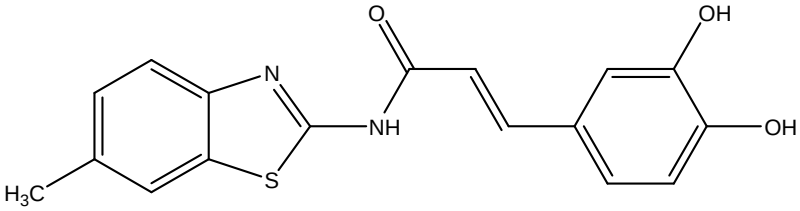

Fig 1. Titled compound for the present study

MATERIALS AND METHODS

2.1. Molecular Docking Study

The amino acid primary sequence of 1OHY subunit of γ-amino butyric acid was retrieved from the Protein Data Bank [23]. The docking studies were carried out using the Molegro Virtual Docker (MVD) [24-26], a program for predicting the most likely conformation of how a ligand will bind to a macromolecule. The active site exploited in docking studies was defined through the calculated cavity. The interaction modes of each ligand with the 1OHY active site were determined as the highest protein-ligand complex energy (mol dock and rerank) score used during docking.

2.1.1. Structure drawing and energy minimization:

CS Chem Office 8.0 was used for the sketching of molecules with the help of drawing tools of Chem Draw. 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 (Molecular Orbital Package) until the RMS gradient attained a value smaller than 0.0001 kcal/mol Å.

2.1.2. Docking Procedure:

Protein (PDB code: 1OHY) [23] was downloaded from the Protein Data Bank. Protein model of *GABA-AT*. All designed ligands and reference ligand, phenytoin were imported in the work space area of Molegro Virtual Docker (Ver.5.0), and necessary bonds, bond orders, hybridizations, hydrogen atoms and charges were assigned. Protein ligand docking studies were carried out based on the basis of crystal structure of protein Pdb 1OHY and ligand binding.

All solvents molecule, cofactor and co-crystallized ligands were removed from structures. The parameter selected in the docking studies were mol dock optimizer, number of runs 10, population size 50, cross over rate 0.90 and max iteration 2000 and cavity selected is user define. The selection of the ligands from the docking wizard was done on the basis of the scoring function (Mol Dock score and rerank score).

The Mol dock scoring function (Mol Dock Score), Escore is defined by the following energy terms:

$$Escore = Einter + Eintra$$

Where

E intra is the inter energy of the ligand; E inter is the ligand –protein interaction energy.

Table 1 Mol Dock score, Re rank score and H-bond energy of title and reference compound

S. No.	Ligand	Mol Dock Score	Re rank Score	H-Bond
1.	Title Comp	-84.236	-54.993	-8.414
2.	Phenytoin	-75.398	-58.617	-2.813

Docking studies shows that Phe-401, Pro-417, Asp-415, Thr-416, Ile-444, Ser-403, Lys-442, present in the protein structure of GABAA are highly conserved and might play a major role in substrate binding. Standard drug phenytoin is also found to be bind to these amino acids. The interactions of both were compared and the score

tabulated and studied. The docking energies of the ligands were negative which shows the stable binding interaction between the receptor and the ligands.

Table 2 Common types of interactions between protein structures of GABAA with title compound and phenytoin

S. No.	Interaction	Residue
1.	Hydrogen Bond Interaction	Thr-416
2.	Electrostatic Interaction	Phe-401, Pro-417, Ser-403, Ile-402, Lys-442, Arg-422, Asp-415

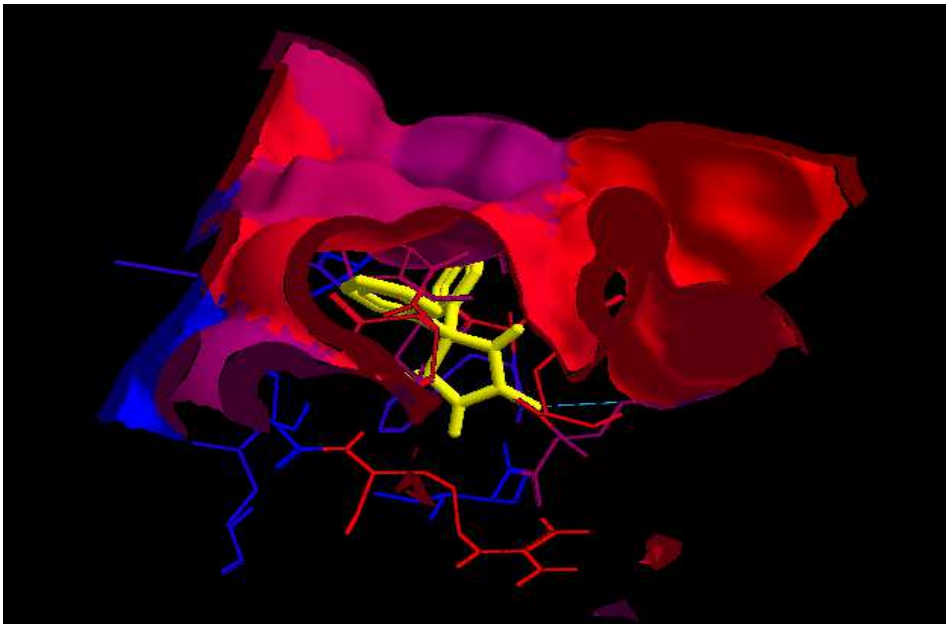

Fig. 2 Hydrophobic interaction of phenytoin with protein (1OHY)

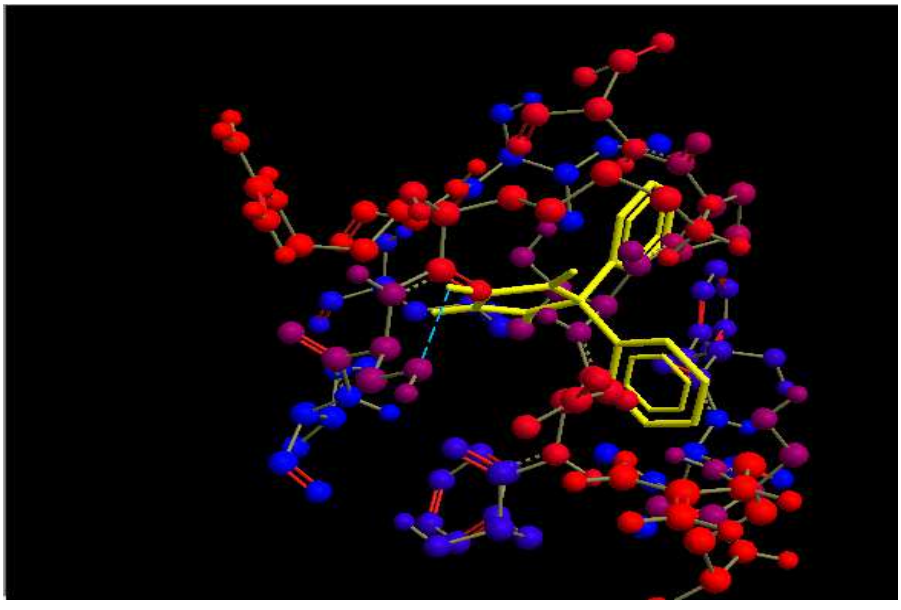

Fig. 3 Hydrogen bond interaction of phenytoin with protein (1OHY)

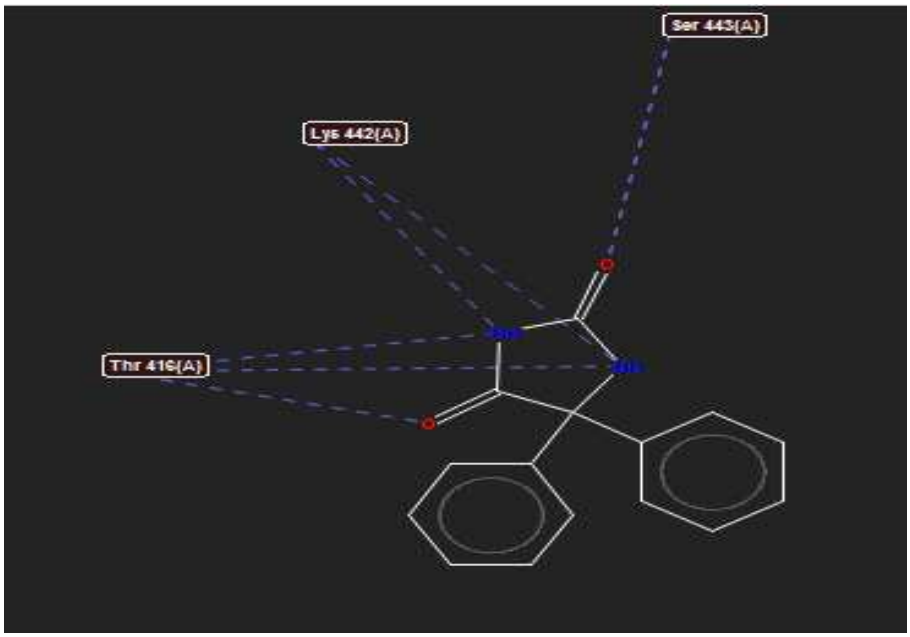

Fig. 4 Hydrogen bond interaction of phenytoin with protein (1OHY)

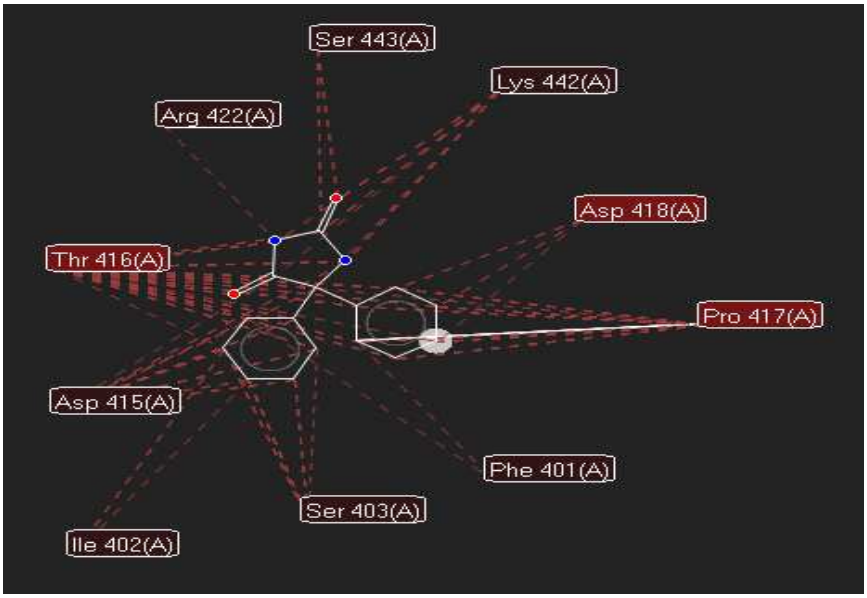

Fig. 5 Electrostatic interaction of phenytoin with protein (1OHY)

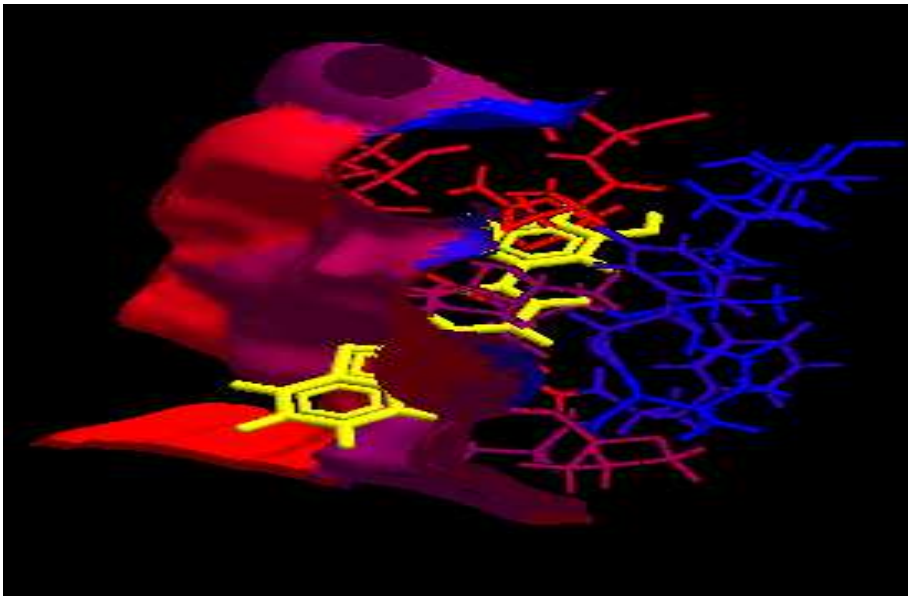

Fig. 6 Hydrophobic interaction of title compound with protein (1OHY)

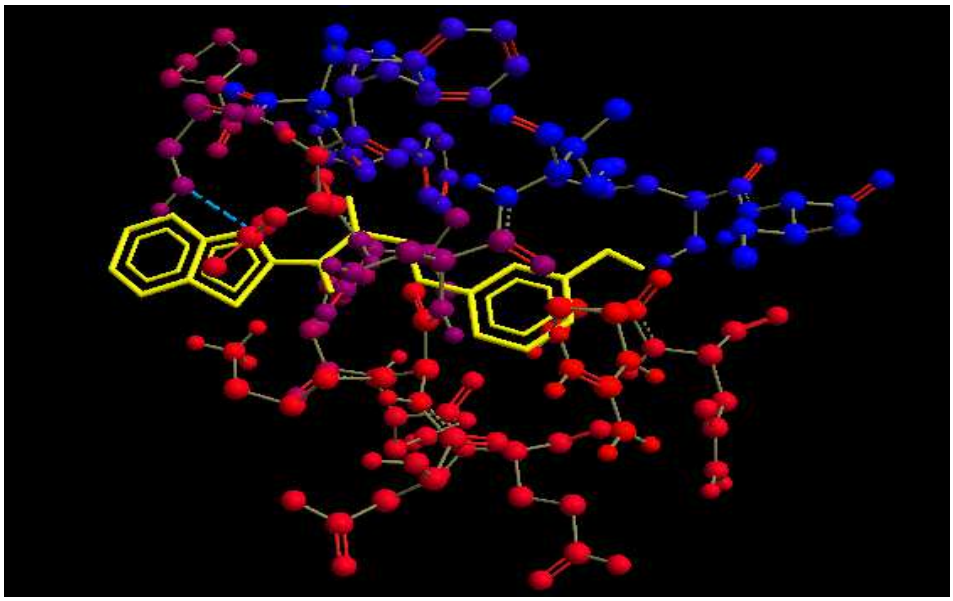

Fig. 7 Hydrogen bond interaction of title compound with protein (1OHY)

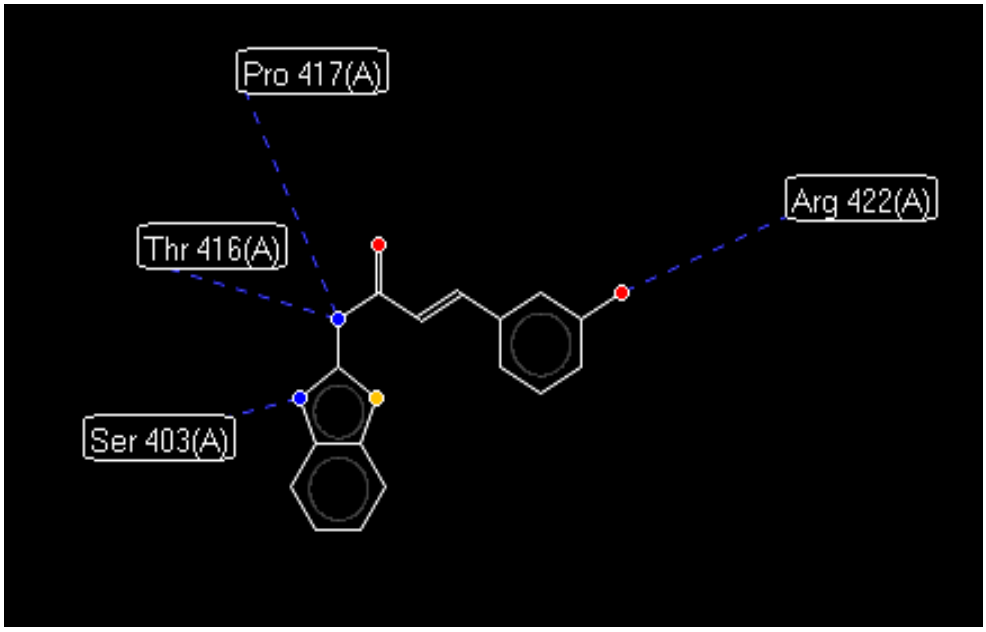

Fig. 8 Hydrogen bond interaction of title compound with protein (1OHY)

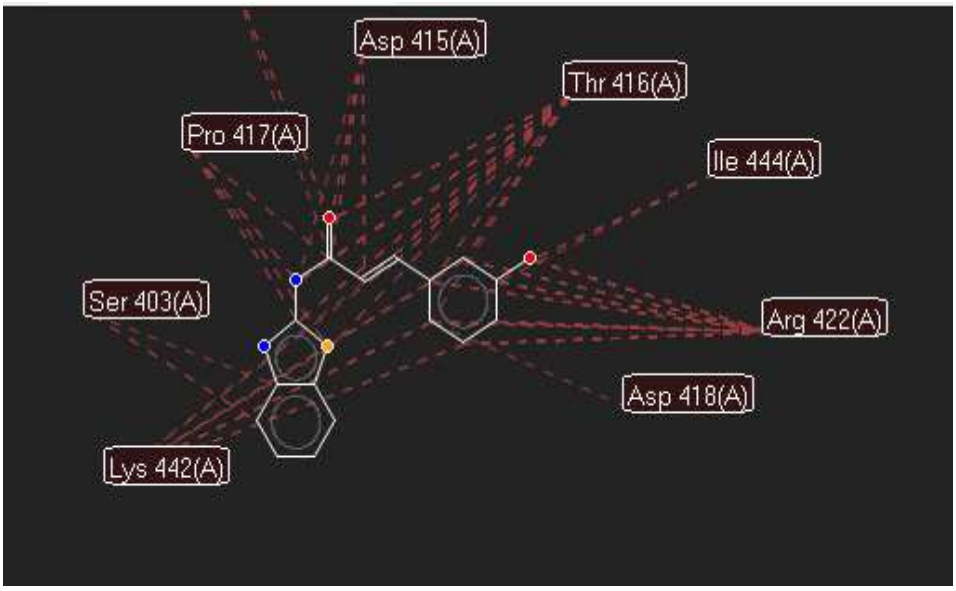

Fig. 9 Electrostatic interaction of title compound with protein (1OHY)

RESULTS AND DISCUSSION

The docked binding mode is used to establish a link between the mol dock scoring function, structural properties of the title compound and their biological activity against the 1OHY subunits of gamma amino butyric acid. Evaluation of the docking results was based on protein-ligand complementarity considering steric and electrostatic properties. On the analysis the hydrogen bond formed between the title compound and the 1OHY active site we observed that the title compound and phenytoin exhibited hydrogen bonds with Thr-416. On the analysis the electrostatic bond formed between the title compound and the 1OHY active site we observed that the title compound exhibited electrostatic bonds with Asp-415, Phe-401, Ile-402, Pro-417, Ser-403, Lys-442, Arg-422, Thr-416, Ser-443, Asp-418. Title compound 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. When the nitrogen atom is added close to the sulfur atom, the title compound interacts with Thr-416 through the hydrogen bond, stabilizing the ligand-protein complex.

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 1OHY subunit of $GABA_A$ as depicted in Table 1. According to these values, the title compound presented an estimated affinity to the 1OHY active site higher than the standard compound phenytoin and the most promising reference compound.

CONCLUSION

The scoring results reveal the higher negative mol dock score and rerank score of the title compound in comparison to phenytoin. It was also observed that the commercial drug phenytoin and the title compound binds to the specific binding sites and shows only one hydrogen bond interaction i.e. Thr-416. Here docking study provides an important insight in designing the structures of the most potent compound and subsequent construction of library of such derivatives.

Acknowledgements
The authors are thankful to the Head, School of Pharmacy, Devi Ahilya Vishwavidyalaya Indore, India for providing facility for research work.

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