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# GABA-AT INHIBITORY ACTIVITY OF BENZOTHIAZOLE – GABA ANALOGS: *IN-SILICO* APPROACH FOR ANTIEPILEPTIC PROFILE

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**Keywords:**

GABA – AT, Antiepileptic agents, Benzothiazole – GABA, Docking study

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**ABSTRACT:** Estimation of binding affinity of receptor – ligand complex in docking study of small molecules plays an Important role in structure based drug development process. The γ-amino-butyric acid amino-transferase (GABA-AT) exhibits a catalytic role in regulating γ-amino -butyric acid (GABA) level in brain and responsible for many physiological and pathological changes. Here, *in* – silico study of benzothiazoles – GABA analogs as γ-amino-butyric acid amino-transferase inhibitors for antiepileptic activity was done. Docking study was completed by AutoDock Vina 1.1.2 (MGI Tools 1.5.6) and PyMol 1.7. We derived energy optimized pharmacophoric features for eighty five ligands and; compared with carbamazepine and vigabatrine. Docking results reveal that most of the ligands showed more affinity (-10.6 to -6.2 kcal/ mol) towards GABA – AT as compared to carbamazepine (-6.7 kcal/ mol) and vigabatrine (-5.0 kcal/ mol). Derivative with serial number 68 was found to possess the best binding affinity for GABA-AT with scoring energy as 10.6 kcal/ mol. Different descriptors were derived and analyzed for any violation of Lipinsky's rule of five (Ro5) of the designed derivatives.

**INTRODUCTION:** Epilepsy is a common neurological disorder characterized by recurrent seizures. In epilepsy, seizures tend to recur, and have no specific underlying symptom or cause [1]. Catalytic degradation of γ-amino-butyric acid involves enzyme γ-amino-butyric acid amino-transferase, and regulates GABA level in nervous tissues. In literature, GABA – AT was used frequently as protein (PDB ID: 1OHV and 4ZSW) for virtual screening and designing of new molecules for anti-epileptic activity and other neurological disorders [2-6].

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Decrease in GABA level may cause serious central nervous system (CNS) disorders [7] such as epilepsy [8], Alzheimer's disease [9], Parkinson's disease [10] etc. Benzothiazoles derivative were proved many times in literature as scaffolds for antiepileptic activity [11]. Riluzole was documented as neurologically active molecule for biochemical change in CNS disorders [12, 13]. Some well known GABA analogs commonly used for pharmacotherapy in relation to epilepsy; such as, vigabatrin, tiagabine, gabapentin and pregabalin[14]. Acetamide moiety is the most frequently used for development of antiepileptic agents [15].

In study presented in this paper, we were combined the structural features of benzothiazoles, GABA and acetamide moieties for designing of ligands with expectation that the hypothesized molecules may result in better antiepileptic activity.

The novel designed pharmacophore **Fig. 1** is a reflection of commonly used drugs like acetazolamide, riluzole and retigabine. The novel designed ligands **Table 1** evaluated experimentally for GABA – AT inhibitory activity. Each docking experiment was done carefully for accurate observation. All the designed derivatives were further processed as required for calculation of descriptors for any violation from Lipinsky's rule of five (Ro5).

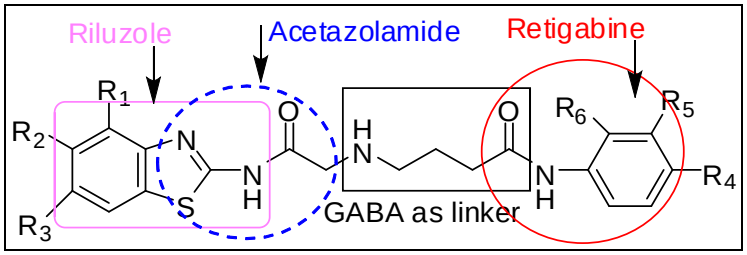



**FIG. 1: BENZOTHAZOLE – GABA PHARMACOPHORE DESIGNING**

**TABLE 1: STRUCTURAL FEATURE, BINDING AFFINITY AS OBTAINED FROM AUTODOCK VINA AND OTHER PARAMETERS DERIVED FROM MARVIN SKETCH OF DESIGNED LIGANDS**

| Ligand no. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | Affinity (kcal/mol) | logP | HBD | HBA | PSA | MR | Mol. Wt. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | H | H | H | H | H | H | -8.2 | 3.13 | 3 | 4 | 83.12 | 103.42 | 368.45 |
| 2. | H | H | H | Br | H | H | -6.9 | 3.92 | 3 | 4 | 83.12 | 111.04 | 447.35 |
| 3. | H | H | H | H | Br | H | -7.6 | 3.92 | 3 | 4 | 83.12 | 111.04 | 447.35 |
| 4. | H | H | H | H | H | Br | -8.3 | 3.92 | 3 | 4 | 83.12 | 111.04 | 447.35 |
| 5. | H | H | H | Cl | H | H | -6.7 | 3.85 | 3 | 4 | 83.12 | 108.22 | 402.9 |
| 6. | H | H | H | H | H | Cl | -8.3 | 3.85 | 3 | 4 | 83.12 | 108.22 | 402.9 |
| 7. | H | H | H | Cl | H | Cl | -7.1 | 4.16 | 3 | 4 | 83.12 | 113.03 | 437.34 |
| 8. | H | H | H | Cl | Cl | H | -7.6 | 4.16 | 3 | 4 | 83.12 | 113.03 | 437.34 |
| 9. | H | H | H | H | $CH_3$ | H | -6.5 | 3.59 | 3 | 4 | 83.12 | 108.46 | 382.48 |
| 10. | H | H | H | $CH_3$ | H | $CH_3$ | -7.6 | 4.06 | 3 | 4 | 83.12 | 113.5 | 396.51 |
| 11. | H | H | H | $NO_2$ | H | H | -10.3 | 3.08 | 3 | 6 | 126.26 | 109.74 | 413.45 |
| 12. | H | H | H | H | $NO_2$ | H | -8.1 | 3.08 | 3 | 6 | 126.26 | 109.74 | 413.45 |
| 13. | H | H | H | H | H | $NO_2$ | -8.5 | 3.08 | 3 | 6 | 126.26 | 109.74 | 413.45 |
| 14. | H | H | H | $NO_2$ | H | $NO_2$ | -6.7 | 3.03 | 3 | 8 | 169.4 | 116.06 | 458.45 |
| 15. | H | H | H | $OCH_3$ | H | H | -7.2 | 2.87 | 3 | 5 | 92.35 | 109.88 | 398.48 |
| 16. | H | H | H | H | $OCH_3$ | H | -7.9 | 2.87 | 3 | 5 | 92.35 | 109.88 | 398.48 |
| 17. | H | H | H | H | H | $OCH_3$ | -6.7 | 2.87 | 3 | 5 | 92.35 | 109.88 | 398.48 |
| 18. | $OCH_3$ | H | H | H | H | H | -8.1 | 2.87 | 3 | 5 | 92.35 | 109.88 | 398.48 |
| 19. | $OCH_3$ | H | H | Br | H | H | -7.5 | 3.67 | 3 | 5 | 92.35 | 117.5 | 477.37 |
| 20. | $OCH_3$ | H | H | H | Br | H | -6.3 | 3.67 | 3 | 5 | 92.35 | 117.5 | 477.37 |
| 21. | $OCH_3$ | H | H | H | H | Br | -6.8 | 3.67 | 3 | 5 | 92.35 | 117.5 | 477.37 |
| 22. | $OCH_3$ | H | H | Cl | H | H | -9.6 | 3.39 | 3 | 5 | 92.35 | 114.68 | 432.92 |
| 23. | $OCH_3$ | H | H | H | H | Cl | -8.5 | 3.39 | 3 | 5 | 92.35 | 114.68 | 432.92 |
| 24. | $OCH_3$ | H | H | Cl | H | Cl | -6.9 | 3.91 | 3 | 5 | 92.35 | 117.5 | 467.37 |
| 25. | $OCH_3$ | H | H | Cl | Cl | H | -6.4 | 3.91 | 3 | 5 | 92.35 | 117.5 | 467.37 |
| 26. | $OCH_3$ | H | H | H | $CH_3$ | H | -6.8 | 3.34 | 3 | 5 | 92.35 | 114.68 | 412.51 |
| 27. | $OCH_3$ | H | H | $CH_3$ | H | $CH_3$ | -8.3 | 3.81 | 3 | 5 | 92.35 | 119.49 | 426.54 |
| 28. | $OCH_3$ | H | H | $NO_2$ | H | H | -8.1 | 2.83 | 3 | 6 | 135.49 | 116.2 | 443.48 |
| 29. | $OCH_3$ | H | H | H | $NO_2$ | H | -6.8 | 2.83 | 3 | 6 | 135.49 | 116.2 | 443.48 |
| 30. | $OCH_3$ | H | H | H | H | $NO_2$ | -7.1 | 2.83 | 3 | 6 | 135.49 | 116.2 | 443.48 |
| 31. | $OCH_3$ | H | H | $NO_2$ | H | $NO_2$ | -7.6 | 2.78 | 3 | 7 | 178.63 | 122.52 | 488.48 |
| 32. | $OCH_3$ | H | H | $OCH_3$ | H | H | -8.1 | 2.62 | 3 | 6 | 101.58 | 116.34 | 428.51 |
| 33. | $OCH_3$ | H | H | H | $OCH_3$ | H | -6.9 | 2.62 | 3 | 6 | 101.58 | 116.34 | 428.51 |
| 34. | $OCH_3$ | H | H | H | H | $OCH_3$ | -9.8 | 2.62 | 3 | 6 | 101.58 | 116.34 | 428.51 |
| 35. | H | Br | H | H | H | H | -9.6 | 3.92 | 3 | 4 | 83.12 | 111.04 | 446.04 |
| 36. | H | Br | H | Br | H | H | -7.2 | 4.71 | 3 | 4 | 83.12 | 117.83 | 524.95 |
| 37. | H | Br | H | H | Br | H | -6.4 | 4.71 | 3 | 4 | 83.12 | 117.83 | 524.95 |
| 38. | H | Br | H | H | H | Br | -8.3 | 4.71 | 3 | 4 | 83.12 | 117.83 | 524.95 |
| 39. | H | Br | H | Cl | H | H | -7.3 | 4.44 | 3 | 4 | 83.12 | 115.84 | 480.49 |
| 40. | H | Br | H | H | H | Cl | -8.2 | 4.44 | 3 | 4 | 83.12 | 115.84 | 480.49 |
| 41. | H | Br | H | Cl | H | Cl | -7.3 | 4.96 | 3 | 4 | 83.12 | 117.83 | 514.94 |
| 42. | H | Br | H | Cl | Cl | H | -8.1 | 4.96 | 3 | 4 | 83.12 | 117.83 | 514.94 |
| 43. | H | Br | H | H | $CH_3$ | H | -7.5 | 4.39 | 3 | 4 | 83.12 | 115.84 | 460.07 |
| 44. | H | Br | H | $CH_3$ | H | $CH_3$ | -7.9 | 4.85 | 3 | 4 | 83.12 | 121.12 | 474.12 |
| 45. | H | Br | H | $NO_2$ | H | H | -6.9 | 3.87 | 3 | 5 | 126.26 | 117.36 | 491.04 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 46. | H | Br | H | H | $NO_2$ | H | -6.4 | 3.87 | 3 | 5 | 126.26 | 117.36 | 491.04 |
| 47. | H | Br | H | H | H | $NO_2$ | -6.8 | 3.87 | 3 | 5 | 126.26 | 117.36 | 491.04 |
| 48. | H | Br | H | $NO_2$ | H | $NO_2$ | -6.2 | 3.83 | 3 | 6 | 169.4 | 123.68 | 536.04 |
| 49. | H | Br | H | $OCH_3$ | H | H | -8.1 | 3.67 | 3 | 5 | 92.35 | 117.5 | 476.07 |
| 50. | H | Br | H | H | $OCH_3$ | H | -7.2 | 3.67 | 3 | 5 | 92.35 | 117.5 | 476.07 |
| 51. | H | Br | H | H | H | $OCH_3$ | -6.8 | 3.67 | 3 | 5 | 92.35 | 117.5 | 476.07 |
| 52. | H | H | $OCH_3$ | H | H | H | -8.1 | 2.87 | 3 | 5 | 92.35 | 109.88 | 398.14 |
| 53. | H | H | $OCH_3$ | Br | H | H | -7.2 | 3.67 | 3 | 5 | 92.35 | 117.5 | 477.04 |
| 54. | H | H | $OCH_3$ | H | Br | H | -6.8 | 3.67 | 3 | 5 | 92.35 | 117.5 | 477.04 |
| 55. | H | H | $OCH_3$ | H | H | Br | -6.4 | 3.67 | 3 | 5 | 92.35 | 117.5 | 477.04 |
| 56. | H | H | $OCH_3$ | Cl | H | H | -6.1 | 3.39 | 3 | 5 | 92.35 | 114.68 | 432.59 |
| 57. | H | H | $OCH_3$ | H | H | Cl | -7.5 | 3.39 | 3 | 5 | 92.35 | 114.68 | 432.59 |
| 58. | H | H | $OCH_3$ | Cl | H | Cl | -7.1 | 3.91 | 3 | 5 | 92.35 | 119.49 | 467.03 |
| 59. | H | H | $OCH_3$ | Cl | Cl | H | -8 | 3.91 | 3 | 5 | 92.35 | 119.49 | 467.03 |
| 60. | H | H | $OCH_3$ | H | $CH_3$ | H | -9.6 | 3.34 | 3 | 5 | 92.35 | 114.92 | 412.17 |
| 61. | H | H | $OCH_3$ | $CH_3$ | H | $CH_3$ | -8.5 | 3.81 | 3 | 5 | 92.35 | 119.96 | 426.18 |
| 62. | H | H | $OCH_3$ | $NO_2$ | H | H | -6.9 | 2.83 | 3 | 7 | 135.49 | 116.2 | 443.14 |
| 63. | H | H | $OCH_3$ | H | $NO_2$ | H | -8.1 | 2.83 | 3 | 7 | 135.49 | 116.2 | 443.14 |
| 64. | H | H | $OCH_3$ | H | H | $NO_2$ | -7.4 | 2.83 | 3 | 7 | 135.49 | 116.2 | 443.14 |
| 65. | H | H | $OCH_3$ | $NO_2$ | H | $NO_2$ | -8.5 | 2.78 | 3 | 8 | 178.63 | 122.52 | 488.15 |
| 66. | H | H | $OCH_3$ | $OCH_3$ | H | H | -8.3 | 2.62 | 3 | 6 | 101.58 | 116.34 | 428.16 |
| 67. | H | H | $OCH_3$ | H | $OCH_3$ | H | -7.6 | 2.62 | 3 | 6 | 101.58 | 116.34 | 428.16 |
| 68. | H | H | $OCH_3$ | H | H | $OCH_3$ | -10.6 | 2.62 | 3 | 6 | 101.58 | 116.34 | 428.16 |
| 69. | H | H | Cl | H | H | H | -9.7 | 3.65 | 3 | 4 | 83.12 | 108.22 | 402.09 |
| 70. | H | H | Cl | Br | H | H | -8.2 | 4.44 | 3 | 4 | 83.12 | 115.84 | 481.79 |
| 71. | H | H | Cl | H | Br | H | -7.1 | 4.44 | 3 | 4 | 83.12 | 115.84 | 481.79 |
| 72. | H | H | Cl | H | H | Br | -8.6 | 4.44 | 3 | 4 | 83.12 | 115.84 | 481.79 |
| 73. | H | H | Cl | Cl | H | H | -7.6 | 4.16 | 3 | 4 | 83.12 | 113.03 | 436.05 |
| 74. | H | H | Cl | H | H | Cl | -9.4 | 4.16 | 3 | 4 | 83.12 | 113.03 | 436.05 |
| 75. | H | H | Cl | Cl | H | Cl | -6.9 | 4.68 | 3 | 4 | 83.12 | 117.83 | 471.42 |
| 76. | H | H | Cl | Cl | Cl | H | -6.3 | 4.68 | 3 | 4 | 83.12 | 117.83 | 471.42 |
| 77. | H | H | Cl | H | $CH_3$ | H | -6.9 | 4.11 | 3 | 4 | 83.12 | 113.26 | 416.24 |
| 78. | H | H | Cl | $CH_3$ | H | $CH_3$ | -8.8 | 4.58 | 3 | 4 | 83.12 | 118.3 | 430.18 |
| 79. | H | H | Cl | $NO_2$ | H | H | -7.5 | 3.6 | 3 | 6 | 126.26 | 114.54 | 447.21 |
| 80. | H | H | Cl | H | $NO_2$ | H | -8.2 | 3.6 | 3 | 6 | 126.26 | 114.54 | 447.21 |
| 81. | H | H | Cl | H | H | $NO_2$ | -8.2 | 3.6 | 3 | 6 | 126.26 | 114.54 | 447.21 |
| 82. | H | H | Cl | $NO_2$ | H | $NO_2$ | -7.4 | 3.55 | 3 | 8 | 169.4 | 120.86 | 492.23 |
| 83. | H | H | Cl | $OCH_3$ | H | H | -10.2 | 3.39 | 3 | 5 | 92.35 | 114.68 | 432.14 |
| 84. | H | H | Cl | H | $OCH_3$ | H | -6.2 | 3.39 | 3 | 5 | 92.35 | 114.68 | 432.14 |
| 85. | H | H | Cl | H | H | $OCH_3$ | -10.1 | 3.39 | 3 | 5 | 92.35 | 114.68 | 432.14 |
| Carbamazepine | | | | | | | -6.7 | 3.22 | 1 | 1 | 46.33 | 71.89 | 236.27 |
| Vigabatrin | | | | | | | -5 | 0.17 | 2 | 3 | 63.32 | 34.29 | 129.16 |

**MATERIALS AND METHODS:** Receptor protein and related database were obtained from National Centre for Biotechnology Information's (NCBI) and Protein Data Base (PDB) websites. Pig brain GABA – AT (PDB ID: 4ZSW, resolution 1.7 angstroms, residue count: 1844) [16] inactivated by [RW2] (1S)-4-[(3 - hydroxy -2- methyl -5- [(cyclophosphonooxy) methyl]pyridine -4- yl) amino]cyclopent -3- ene -1,3- dicarboxylic acid (RW2), 4FE – 2S- o hybrid cluster (FSF), glycerol and acetate ion in different chains, was used as protein. Autodock Vina [17] Version 1.1.2 (MGI Tools 1.5.6), PyMOL(TM) [18] 1.7 Edu - Educational Product, Chem Draw Ultra 10.0 and Chem3D Ultra 10.0 [19] were used as software tools for drawing structures, calculating parameters and virtual screening. The chemical structure of the benzothiazoles - GABA analogs was drawn using Chem Draw Ultra 10.0

and energy minimization to its lowest energy state to attain highest stability of each derivative was achieved with Chem3D Ultra 10.0. The energy minimized 3D configuration of ligands was then converted to protein data bank format. The ".pdb" files were further subjected to MGI Tools 1.5.6 (AutoDock Tools) for facilitating autodock properties like hydrogen addition, charge dispersion etc. to the ligands. Now the designed ligands ready for autodock study.

Read the GABA – AT, as it is retrieved from protein data bank, through PyMol to study the basic structural features. The α-chain of protein dimmer, water molecules and other crystals existed in protein were removed. Now, the refined protein

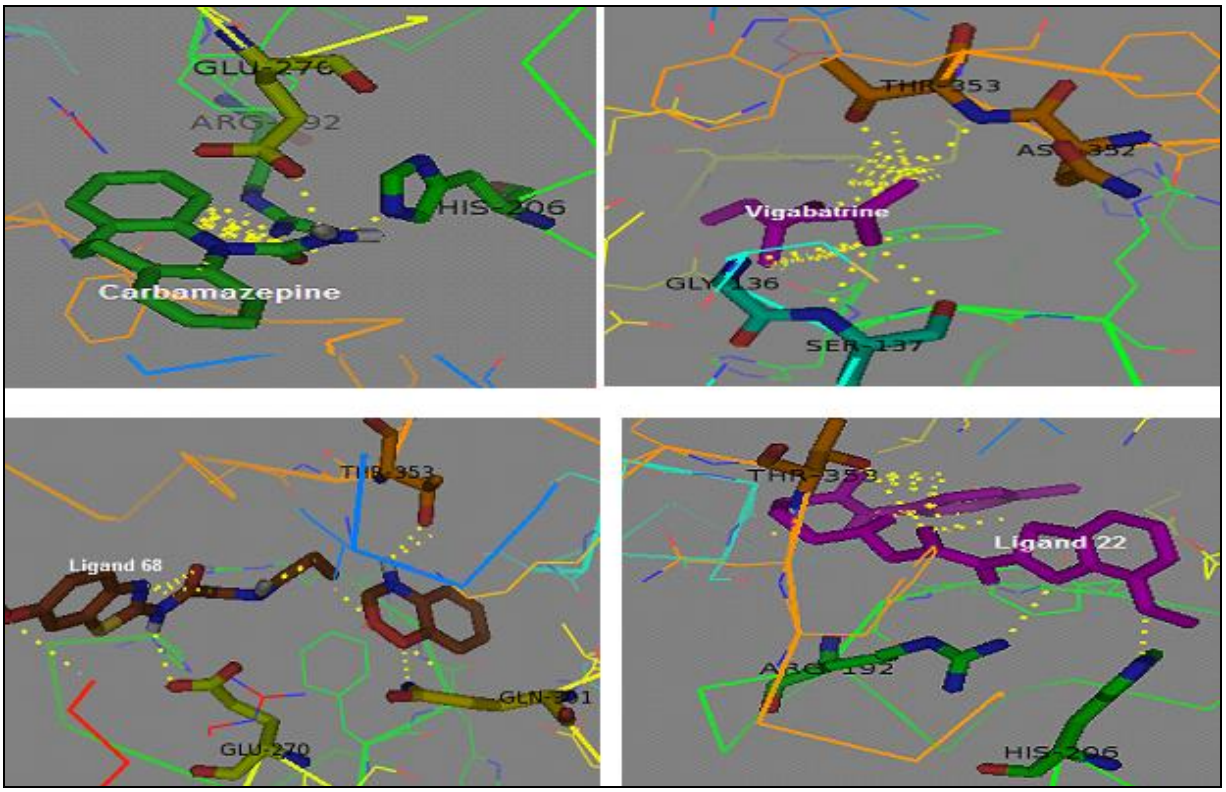
(PDB ID: 4ZSW) was subjected to docking analysis.

Using AutoDock tools, grid box was analyzed and prepared with dimensions X, Y and Z as 40, and center for grid box as x, y and z were 27.611, 54.444 and 64.750, respectively.

The designed ligands were analyzed and different descriptors like lipophilicity (logP), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), molar refractivity (MR) and molecular weight (Mol. wt.) were calculated by using Marvin Sketch version 15.9.21 [20].

**RESULT AND DISCUSSION:** Using PyMol, docking results were prepared by analyzing the different binding poses of ligands obtained from AutoDock Vina in comparison with receptor and ligand crystal interactions, previously prepared. The results showed that GLU-270, HIS-206, ARG-192, THR-353, SER-137 and GLY-136 could be the catalytic binding site residues present in the structure of GABA-AT protein **Fig. 2**. The results are comparable with the study by R. Wu *et. al.* [11] where ARG-192:A, THR-353:B, SER-137:A, ASP-298:A and GLN-301:A were reported as main active site for inhibition. The receptor – ligand interaction affinity was obtained from output of AutoDock Vina for best pose analyzed by using PyMol. The binding affinity for the best pose of benzothiazole-GABA analogs were tabulated in **Table 1** and were ranging from -10.6 to -6.2 kcal/ mol. Here negative sign reflected positive docking results and docking images has been displayed in **Fig. 3**.

Superimposability of vigabatrine and ligand 35 were analyzed over reference ligand i.e RW2, and RMS obtained 1.03 and 0.87, respectively **Fig. 3**. Most of the ligands obeyed Ro5, except some ligands like 14, 31, 48, 65 and 82 were found slight violation from normal range of polar surface area (PSA) i.e. 140. Ligands number 36, 37, 38, 41, 42 and 48 showed violation in mol. Wt. as compared to normal range i.e. below 500. But even then the binding affinities for different analogs showed better interaction with protein as compared to carbamazepine and vigabatrine. Although, the docked poses of benzothiazole-GABA analogs not superimposes on the reference ligand but nicely interact on receptor residues. The interaction may be allosteric inhibition type and could results in antiepileptic activity.



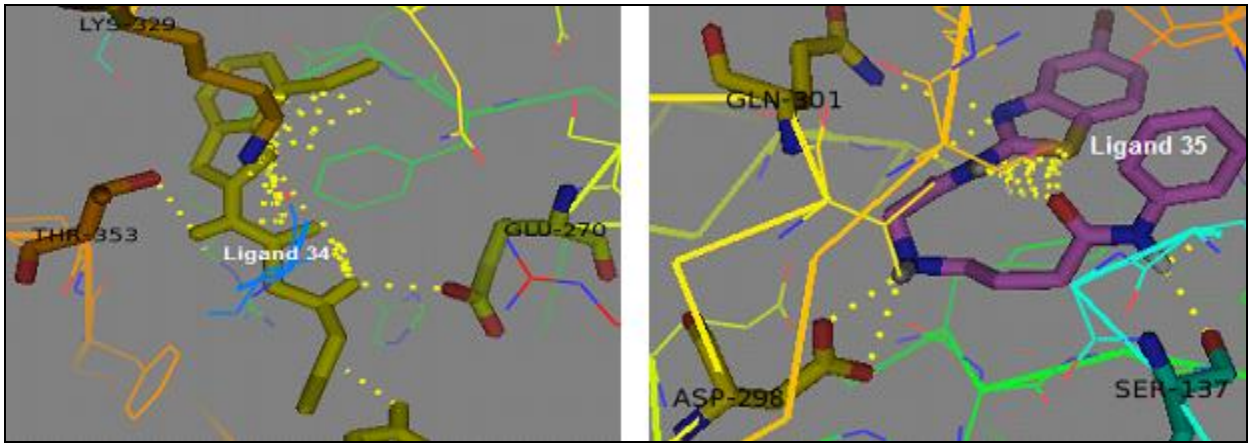



**FIG. 2: INTERACTING RESIDUES INVOLVED IN DOCKING OF CARBAMAZEPINE, VIGABATRINE AND OTHER LIGANDS AT ACTIVE SITE OF PIG BRAIN GABA – AT AND HYDROGEN BONDS ARE SHOWN WITH YELLOW DASHED LINE**

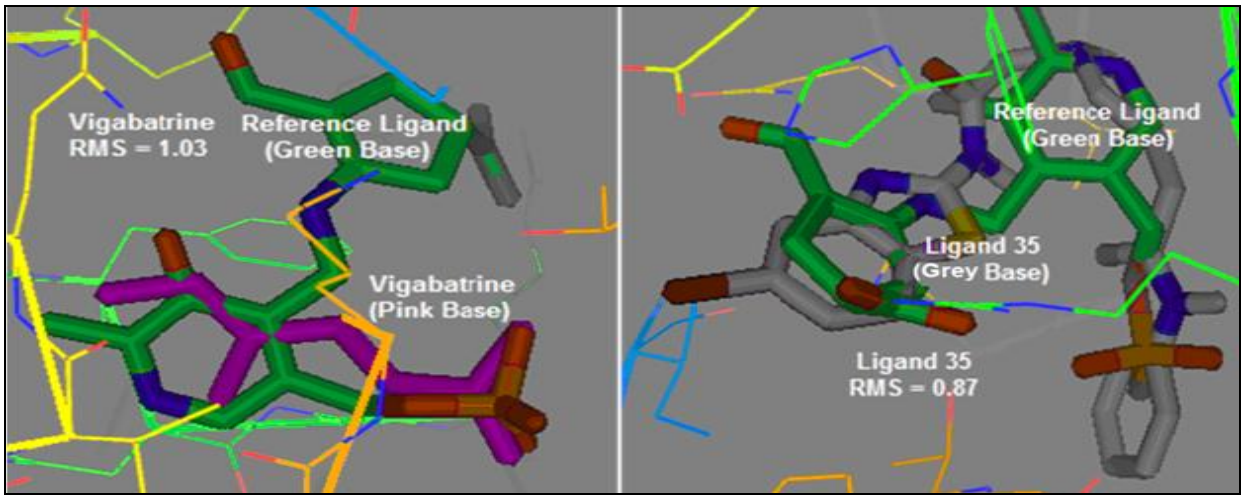



**FIG. 3: SUPER-IMPOSABLE IMAGES OF VIGABATRINE AND LIGAND 35 WITH REFERENCE LIGAND**

**CONCLUSION:** In present study, we concluded that the designed pharmacophore is strongly inhibiting the active site residues in same manner as it interact with vigabatrine and carbamazepine with high affinity and low binding energy. As most of the ligands showed in good agreement with Ro5, so it is expected that the molecules may have properties to cross blood brain barrier (BBB). The novel pharmacophore may be further evaluated for its potential as antiepileptic; the pharmacophore can be used in drug design for other diseases related to GABA-AT reduced level.

**COMPETING INTERESTS:** We declare that there are no any competing interests.

**AUTHORS' CONTRIBUTIONS:** Dr. Prabhakar Kumar Verma designed experimental protocol and help for the development of the manuscript. Jagbir Gagoria performed the experimental work and write manuscript. Both authors read and approved the final manuscript.

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