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

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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 GABAergic 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, antispsychotic, 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-diarylpyridine (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

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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 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 anti-convulsant 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 anti-convulsant 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) [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.

Results

Docking Study: Molecular docking approach was utilize 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 Phenytin 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 benzothiazepine. Generally we have drawn the three series for the synthesis of 1,5 benzothiazepine 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
Simta et al. Silico design of potential 1,5-benzothiazepine derivatives as an anti-convulsant agent.

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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  | CH3 |
| 2             | H   | OCH3| H   | 52            | I   | Cl  | CH3 |
| 3             | H   | Cl  | H   | 53            | I   | NO2 | CH3 |
| 4             | H   | F   | H   | 54            | I   | NH2 | CH3 |
| 5             | H   | Br  | H   | 55            | I   | NH2 | CH3 |
| 6             | OH  | Br  | H   | 56            | I   | NH2 | F   |
| 7             | OH  | Br  | OH  | 57            | I   | NH2 | Br  |
| 8             | H   | NO2 | H   | 58            | I   | NH2 | NO2 |
| 9             | Cl  | H   | H   | 59            | I   | NH2 | NH2 |
| 10            | F   | H   | H   | 60            | F   | NH2 | F   |
| 11            | Br  | H   | H   | 61            | F   | NO2 | 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-CH3 | F   |
| 16            | H   | NO2 | H   | 66            | I   | NH-CH3 | F   |
| 17            | Br  | NO2 | H   | 67            | Br  | NH-CH3 | F   |
| 18            | F   | NO2 | H   | 68            | H   | NH-CH3 | F   |
| 19            | NO2 | NO2 | H   | 69            | H   | NH-CH3 | H   |
| 20            | OH  | NO2 | H   | 70            | H   | NH-CH3 | OH  |
| 21            | OH  | NO2 | Cl  | 71            | H   | NH-CH3 | CH3 |
| 22            | OH  | NO2 | F   | 72            | H   | NH-CH3 | I   |
| 23            | OH  | NO2 | Br  | 73            | H   | NH-CH3 | Cl  |
| 24            | OH  | NO2 | NO2 | 74            | H   | NH-CH3 | Br  |
| 25            | OH  | NO2 | I   | 75            | NO2 | NH-CH3 | Br  |
| 26            | OH  | H   | H   | 76            | NO2 | NH-CH3 | F   |
| 27            | H   | H   | H   | 77            | NO2 | CH2-CH3 | CH3 |
| 28            | OH  | CH3 | CH3 | 78            | NH2 | CH2-CH3 | CH3 |
| 29            | CH3 | H   | H   | 79            | F   | CH2-CH3 | CH3 |
| 30            | CH3 | H   | Br  | 80            | I   | CH2-CH3 | CH3 |
| 31            | CH3 | H   | F   | 81            | I   | NO2 | CH3 |
| 32            | CH3 | H   | Cl  | 82            | Cl  | -H-CH3 | CH3 |
| 33            | CH3 | H   | CH3 | 83            | NO2 | -H-CH3 | CH3 |
| 34            | CH3 | Cl  | CH3 | 84            | NH2 | -H-CH3 | CH3 |
| 35            | CH3 | Br  | CH3 | 85            | NH2 | -H-CH3 | F   |
| 36            | CH3 | F   | CH3 | 86            | NH2 | -H-CH3 | CH3 |
| 37            | CH3 | NO2 | CH3 | 87            | Cl  | C=O | H   |
| 38            | CH3 | NO2 | H   | 88            | H   | C=O | H   |
| 39            | CH3 | NO2 | Cl  | 89            | Br  | C=O | H   |
| 40            | CH3 | NO2 | F   | 90            | OH  | C=O | H   |
| 41            | CH3 | NO2 | Br  | 91            | I   | C=O | H   |
| 42            | CH3 | CH3 | H   | 92            | NO2 | C=O | H   |
| 43            | CH3 | CH3 | CH3 | 93            | F   | C=O | H   |
| 44            | Cl  | CH3 | CH3 | 94            | NH2 | C=O | H   |
| 45            | Br  | CH3 | CH3 | 95            | NH2 | -H-CH3 | I   |
| 46            | F   | CH3 | CH3 | 96            | NH2 | -H-CH3 | NO2 |
| 47            | NO2 | CH3 | CH3 | 97            | NO2 | -H-CH3 | I   |
| 48            | I   | CH3 | CH3 | 98            | NO2 | -H-CH3 | Br  |
| 49            | I   | I   | CH3 | 99            | NO2 | -H-CH3 | NH2 |
| 50            | I   | F   | CH3 | 100           | NO2 | -H-CH3 | NO2 |
Table 2. Proposed chemical structure (101-200) for docking study

| Compound Code | R1   | R2   | R3   | R4 | Compound Code | R1   | R2   | R3   | R4 |
|---------------|------|------|------|----|---------------|------|------|------|----|
| 101           | H    | OH   | OH   |    | 151           | H    | F    | CH₃  | NH₂ |
| 102           | H    | OCH₃ | OH   |    | 152           | H    | Cl   | CH₃  | NH₂ |
| 103           | H    | Cl   | OH   |    | 153           | H    | Br   | CH₂  | NH₂ |
| 104           | H    | I    | OH   |    | 154           | H    | NO₂  | CH₂  | NH₂ |
| 105           | H    | F    | OH   |    | 155           | H    | NH₂  | CH₂  | NH₂ |
| 106           | H    | -CH₂-CH₃ | OH | 156 | H    | CH₃  | CH₂  | NH₂ |
| 107           | H    | Br   | OH   |    | 157           | H    | CH₂-CH₃ | CH₂ | NH₂ |
| 108           | H    | NO₂  | OH   |    | 158           | OH   | NH-CH₂ | CH₂ | NH₂ |
| 109           | H    | NH₂  | OH   |    | 159           | H    | NH-CH₂ | CH₂ | NH₂ |
| 110           | H    | CH₃  | OH   |    | 160           | OH   | NH-I  | CH₂ | NH₂ |
| 111           | OH   | Cl   | OH   |    | 161           | OH   | NH-F  | CH₂ | NH₂ |
| 112           | H    | CH₂  | Br   |    | 162           | OH   | NH-Br | CH₂ | NH₂ |
| 113           | H    | NH₂  | Br   | NH₂ | 163           | OH   | I    | NH₂ | NH₂ |
| 114           | H    | NO₂  | Br   | NH₂ | 164           | OH   | F    | NH₂ | NH₂ |
| 115           | H    | Br   | Br   | NH₂ | 165           | OH   | Cl   | NH₂ | NH₂ |
| 116           | H    | Cl   | Br   | NH₂ | 166           | OH   | Br   | NH₂ | NH₂ |
| 117           | H    | F    | Br   | NH₂ | 167           | OH   | CH₂  | NH₂ | NH₂ |
| 118           | H    | I    | Br   | NH₂ | 168           | OH   | NO₂  | NH₂ | NH₂ |
| 119           | H    | I    | NO₂  | NH₂ | 169           | OH   | NH₂  | NH₂ | NO₂ |
| 120           | H    | F    | NO₂  | NH₂ | 170           | OH   | NH-CH₂ | NH₂ | NO₂ |
| 121           | H    | Cl   | NO₂  | NH₂ | 171           | OH   | NH-CH₂ | NO₂ | NO₂ |
| 122           | H    | Br   | NO₂  | NH₂ | 172           | OH   | CH₂-CH₂ | NO₂ | NO₂ |
| 123           | H    | CH₃  | Cl   | NH₂ | 173           | OH   | CH₂  | NH₂ | NO₂ |
| 124           | H    | NH₂  | Cl   | NH₂ | 174           | OH   | NH₂  | NO₂ | NO₂ |
| 125           | H    | NO₂  | Cl   | NH₂ | 175           | OH   | NO₂  | NO₂ | NO₂ |
| 126           | H    | Br   | Cl   | NH₂ | 176           | OH   | CH₂  | H   |    |
| 127           | H    | Cl   | Cl   | NH₂ | 177           | OH   | H    |    |    |
| 128           | H    | F    | Cl   | NH₂ | 178           | OH   | -CH₂-CH₃ | H   |    |
| 129           | H    | I    | Cl   | NH₂ | 179           | OH   | -CH₂-NH₂ | H   |    |
| 130           | H    | I    | F    | NH₂ | 180           | OH   | NH-CH₂ | NH₂ |    |
| 131           | H    | F    | F    | NH₂ | 181           | OH   | NH₂  | H   |    |
| 132           | H    | Cl   | F    | NH₂ | 182           | OH   | Br   | H   |    |
| 133           | H    | Br   | F    | NH₂ | 183           | OH   | Cl   | H   |    |
| 134           | H    | NO₂  | F    | NH₂ | 184           | OH   | F    | H   |    |
| 135           | H    | NH₂  | F    | NH₂ | 185           | OH   | I    | H   |    |
| 136           | H    | CH₃  | F    | NH₂ | 186           | OH   | I    | NH₂ |    |
| 137           | H    | -CH₂-CH₃ | I | NH₂ | 187           | NH₂  | I    | H   | H   |
| 138           | H    | CH₃  | I    | NH₂ | 188           | NH₂  | F    | H   | H   |
| 139           | H    | NO₂  | I    | NH₂ | 189           | NH₂  | NH₂  | H   |    |
| 140           | H    | NH₂  | I    | NH₂ | 190           | H    | NH-CH₂ | NH₂ |    |
| 141           | H    | Br   | I    | NH₂ | 191           | CH₂  | NH₂  | NH₂ |    |
| 142           | H    | Cl   | I    | NH₂ | 192           | CH₂  | NH-CH₂ | H   | NH₂ |
| 143           | H    | F    | I    | NH₂ | 193           | CH₂  | NH-CH₂ | CH₂ | NH₂ |
| 144           | H    | CH₂I | I    | NH₂ | 194           | CH₂  | NH-CH₂ | CH₂Cl | NH₂ |
| 145           | H    | CH₂I | OH   |    | 195           | CH₂  | NH-CH₂ | CH₂Br | NH₂ |
| 146           | H    | CH₂F | OH   |    | 196           | CH₂  | NH-CH₂ | CH₂F | NH₂ |
| 147           | H    | CH₂Cl | OH  |    | 197           | CH₂  | NH-CH₂ | CH₂NH₂ | NH₂ |
| 148           | H    | CH₂Br | OH  |    | 198           | CH₂  | NH-CH₂ | CH₂NO₂ | NH₂ |
| 149           | H    | CH₂NO₂ | OH | NH₂ | 199           | Cl   | NH₂  | H   | NH₂ |
| 150           | H    | CH₂NH₂ | OH | NH₂ | 200           | Cl   | NH-NH₂ | CH₂ | NH₂ |
Table 3. Proposed chemical structure (201-300) for docking study

| Compound Code | R1   | R2   | R3   | Compound Code | R1   | R2   | R3   |
|---------------|------|------|------|---------------|------|------|------|
| 201           | OCH₁ | H    | H    | 251           | CH₁  | H    | NH₂  |
| 202           | OCH₁ | OCH₁ | H    | 252           | CH₁  | H    | CH₁  |
| 203           | OCH₁ | NO₂  | H    | 253           | CH₁  | H    | CH₂-NH₂ |
| 204           | H    | I    | H    | 254           | CH₁  | H    | CH₂-NO₂ |
| 205           | H    | F    | H    | 255           | CH₁  | H    | CH₂-NH₂ |
| 206           | H    | Br   | H    | 256           | CH₁  | H    | H    |
| 207           | H    | NO₂  | H    | 257           | CH₁  | H    | OH   |
| 208           | H    | NH₂  | H    | 258           | CH₁  | H    | NH₂  |
| 209           | H    | CH₁  | H    | 259           | H    | H    | CH₁  |
| 210           | H    | CH₂-C-H₁ | H | 260 | OH | H | CH₁ |
| 211           | I    | CH₃-C | H | 261 | CH₁ | H | NH₂ | H |
| 212           | I    | CH₁     | H | 262 | CH₁ | H | NO₂  | H |
| 213           | I    | NO₂     | H | 263 | CH₁ | H | Br   | H |
| 214           | I    | NH₂     | H | 264 | CH₁ | H | Cl   | H |
| 215           | I    | Br     | H | 265 | CH₁ | H | F    | H |
| 216           | I    | Cl     | H | 266 | CH₁ | H | I    | H |
| 217           | I    | F      | H | 267 | CH₁ | H | I   | H |
| 218           | I    | I      | H | 268 | CH₁ | H | Br   | H |
| 219           | F    | I      | H | 269 | CH₁ | H | F   | H |
| 220           | F    | F      | H | 270 | CH₁ | H | NO₂ | H |
| 221           | F    | Cl     | H | 271 | NH₂ | NO₂ | H |
| 222           | F    | Br     | H | 272 | NH₂ | NH₂ | H |
| 223           | F    | NO₂    | H | 273 | NH₂ | CH₁ | H |
| 224           | F    | NH₂    | H | 274 | NH₂ | CH₂-C-H₁ | H |
| 225           | F    | CH₁     | H | 275 | NH₂ | CH₂-NH₂ | H |
| 226           | F    | CH₂-C-H₁ | H | 276 | NH₂ | CH₂-NO₂ | H |
| 227           | Cl   | CH₂-C-H₁ | H | 277 | CH₁ | CH₂-NH₂ | H |
| 228           | Cl   | CH₂-NH₂ | H | 278 | CH₁ | CH₂-NH₂ | H |
| 229           | Cl   | CH₁     | H | 279 | CH₁ | CH₂-C-H₂-NH₂ | H |
| 230           | Cl   | NH₂    | H | 280 | CH₁ | CH₁ | H |
| 231           | Cl   | NO₂    | H | 281 | NO₂ | I | H |
| 232           | Cl   | Br     | H | 282 | NO₂ | F | H |
| 233           | Cl   | Cl     | H | 283 | NO₂ | Cl | H |
| 234           | Cl   | F      | H | 284 | NO₂ | Br | H |
| 235           | Cl   | I      | H | 285 | NO₂ | NH₂ | H |
| 236           | Br   | I      | H | 286 | NO₂ | NO₂ | H |
| 237           | Br   | F      | H | 287 | NH₂ | I | CH₁ |
| 238           | Br   | NH₂    | H | 288 | NH₂ | F | CH₁ |
| 239           | Br   | Cl     | H | 289 | NH₂ | Cl | CH₁ |
| 240           | Br   | Br     | H | 290 | NH₂ | Br | CH₁ |
| 241           | Br   | NO₂    | H | 291 | Br | CH₂-NO₂ | CH₁ |
| 242           | Br   | OCH₁   | H | 292 | Br | CH₂-NH₂ | CH₁ |
| 243           | Br   | CH₂-C-H₁ | H | 293 | NO₂ | CH₂-NO₂ | CH₁ |
| 244           | OCH₁ | CH₂-C-H₁ | H | 294 | NO₂ | CH₂-NH₂ | CH₁ |
| 245           | OCH₁ | NO₂    | H | 295 | NO₂ | CH₃ | CH₁ |
| 246           | OCH₁ | CH₁     | H | 296 | NO₂ | CH₂-C-H₂-NH₂ | CH₁ |
| 247           | OCH₁ | F      | H | 297 | Br | CH₂-C-H₁ | CH₁ |
| 248           | OCH₁ | I      | H | 298 | Br | CH₁ | CH₁ |
| 249           | OCH₁ | Cl     | H | 299 | Br | NH₂ | CH₁ |
| 250           | OCH₁ | H      | H | 300 | Br | NO₂ | CH₁ |
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.
Docking analysis was utilized to understand 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 standard 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, PHE287B, PHE420B (Figure 3). The series 2 compound showed hydrophobic 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 exhibited hydrophobic interaction with ALA549A (4.675), ASP593A (2.987), LYS647A (2.638) and Van der Waals interactions with SER528A (1.675), THR652A (3.293) and ASN555AA 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 100a, 101b, 102c to 300c and Sodium Phenytoin against 3IP9 in silico design of potential 1,5 benzothiazepine derivatives as an anti-convulsant agent.

**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 GABAergic mechanism.

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**Conflict of Interest:** Declared none

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