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Original Article

# Study, Docking, *in silico* ADME and Predicted Acute Toxicity of Novel Hetero-Aromatic Imidazolidine Analogues as Potential Anti-Epileptic Agents

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## ABSTRACT

**Background:** In the present work, molecular docking analysis was conducted on proposed protein derivatives from the protein data bank using the Auto Dock for Docking programme. study on protein binding affinity using 1-acetyl-3-(2-aminophenyl)-5,5-diphenylimidazolidine-2,4-dione derivatives and the GABA receptor. Even if a number of innovative anticonvulsants have been created in India, some types of seizures are still not adequately controlled by smaller side effects even after the use of modern and revolutionary treatments. **Materials and Methods:** Target-oriented virtual screening of ligands under investigation with adaptable molecular docking techniques. We can choose the most promising compounds for further study of various derivatives by evaluating the ligands' affinity to the GABAA active sites. Via the inhibitor GABAergic route, a number of 5,5-diphenylimidazolidine derivatives were designed and investigated *in silico*. **Results:** Using the AutoDock 4.2 programme, a number of molecules associated with 5,5-diphenylimidazolidine were investigated for molecular docking, acute prediction, and ADMET analysis. According to docking research, these molecules have at least one hydrogen bond stabilising them. The proposed composites were all investigated for Gamma Aminobutyric Acid (GABA) inhibitory exertion and all shown good *in silico* ADME and molecular docking results. **Conclusion:** One of the essential enzymes for biosynthesis in many natural ecosystems, Gamma Aminobutyric Acid (GABA) is present in both humans and animals. By meticulously replicating the prior pharmacological experiment's circumstances, we are able to compare the outcomes and talk about certain commonalities in how molecule fragments affect anticonvulsant action. Docking score, ADMET analysis, acute toxicity prediction, and structural location of ligands in the active GABAA site enzyme were found to positively correlate, supporting the viability of target-based virtual screening as a way to expedite pharmacological screening.

**Keywords:** Gamma aminobutyric acid, Molecular Docking, Structure-Based Drug Design, and 3D QSAR.

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## INTRODUCTION

The World Health Organisation (WHO) estimates that 65 million people worldwide suffer from epilepsy. Eighty percent of them are said to live in low- and middle-income countries. Nevertheless, epilepsy is an uncontrollable, neurological seizure.[1-3] It occurs seven times more advanced than the typical state of all chronic illnesses.[4-7] An earlier investigation found that the US spends around $15.5 billion a year on medical expenses, including seizures. Due to the high incidence of epilepsy in the US and India, more effective and safer anticonvulsants must be developed in order to lower the cost of treating epilepsy. Several different countries have put a lot of effort into finding novel, safe, and effective epilepsy medications. Epilepsy can take many different forms, such as absence seizures, clonic seizures, focal or generalised seizures, etc. Modern research has yielded novel anticonvulsants that are used to treat focal seizures. Current and newer medicines cannot cure all forms of epilepsy.[8-12] Uncontrolled storms and an overabundance of transitory neuronal discharges were the causes of epilepsy.[13,14] League Against Epilepsy (LAE), can be listed as two unprovoked seizures occurring during the following decade, followed by single unprovoked (or reflex) seizure and a

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chance of further seizures proportional to the overall recurrence risk (at least 60%). Potassium bromide, the first anticonvulsant medication, was initially described in the middle of the 1800s. Since then, a number of Antiepileptic medications (AEDs) have been authorised by medical professionals and scientists and are accessible as the first line of treatment for individuals with epilepsy.[15,16] A significant part of the medication development process for a more recent class of drugs with anticonvulsant action involves these derivatives or group. Roughly forty derivatives have been demonstrated to possess anticonvulsant characteristics.[17-19] Presynaptic GABAergic neurons synthesise GABA (Gamma-Aminobutyric Acid) from glutamate. GABA is a key neurotransmitter in the brain that regulates the balance between excitement and inhibition. These presynaptic neurons depolarize, which causes the release of GABA for neurotransmission. GABA can bind to either of the two main GABA receptors on postsynaptic neurons-GABAA or GABAB receptors-when it is released into the synaptic cleft. The principal chloride ion channel in GABAA receptors opens as a result of GABA binding allosterically to those receptors. This ultimately causes the neuronal membrane to become hyperpolarized, which lowers cell excitability and increases neural inhibition. As metabotropic receptors, GABAB receptors are activated by GABA, which causes the corresponding potassium channels to open through G-protein coupled receptors. Hyperpolarization and neural inhibition follow, which are comparable to the actions of GABAA receptors.

## MATERIALS AND METHODS

### Receptors and Ligands Collections

Wang and his fellow researchers' efforts produced a collection of trustworthy experimental anti-epilepsy data sets and their characteristics, comprising nine strong chemicals. It was demonstrated in the literature that these particular experimental AEDs had superior activity to co-compounds. Chemdraw software was utilized to create 2D structural forms from the dependable data sets, which were then stored in cdx format. The Spartan 14 software's DFT (density functional theory) method was used to geometrically optimise the drawn structures in order to make the atoms of the compounds energetically stable and seem realistic.

### Molecular Docking Simulation

In this investigation, docking simulations were carried out using the Pyrx multifunctional simulation software's Autoduck vina docking tool. Adequate preparation was done for both the receptor and the ligands, which were then saved in PDF format using the Discovery Studio programme, uploaded into Pyrx, and converted to PSDT format. The autoduck vina feature of the programme was activated when the GABA receptor and the ligands (Table 1) were moved to the X, Y, and Z grid of the Pyrx software interface. The docked posture with the best orientation binding energy was chosen, examined, and recorded following several minutes of selective ligand poses on the Gamma-Aminobutyric Acid (GABA)A receptor binding site.

### Preparation of Ligands

MarvinSketch 18.23 was used to obtain structures, which were then saved in mol format. stored as pdb files and optimised by Chem3D using the molecular-mechanical MM2 method. Protein preparation The crystal was treated with Discovery Studio Visualizer 2017 / R2 to exclude ligand molecules and water. PDB files were used to store protein structures. Native ligands have grid boxes placed on them. For docking, AutoDock Vina was employed. The acquired docking result was visualised and evaluated using Discovery Studio V17.2.0.16349 (Table 1).

## RESULTS

To evaluate the physiochemical properties of each synthesised molecule (sb1-sb5), *in silico* evaluations were performed using Lipinski's rule (Table 2). The Lipinski rule states that an epileptic

**Table 1: Ligand used for Docking.**

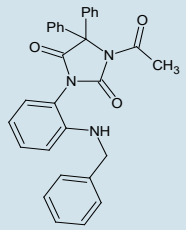
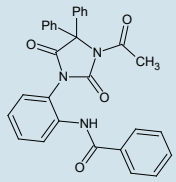
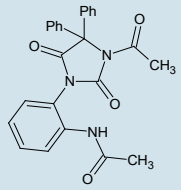
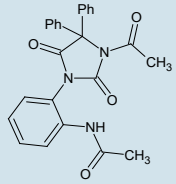
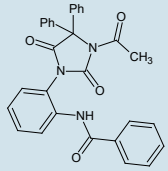
| Label | Structure |
|---|---|
| Sa1 |  |
| Sa2 |  |
| Sa3 |  |
| Sa4 |  |
| Sa5 |  |

**Table 2:** Lipinski rule of five.

| Compound Codes | Lipinski rule of five | | | | | Veber's rule | |
|---|---|---|---|---|---|---|---|
| | M Log P | Mol. Wt. (g/mol) | HBA | HBD | Violations | Total polar surface area (Å²) | No. of rotatable bonds |
| Sa1 | 1.93 | 458.47 | 5 | 3 | 0 | 130.83 | 8 |
| Sa2 | 2.33 | 459.45 | 6 | 2 | 0 | 128.03 | 8 |
| Sa3 | 3.23 | 492.53 | 4 | 3 | 0 | 113.76 | 8 |
| Sa4 | 2.41 | 537.52 | 6 | 3 | 2 | 159.58 | 9 |
| Sa5 | 3.39 | 521.52 | 6 | 2 | 1 | 128.03 | 9 |

**Table 3:** Pharmacokinetics and drug-likeness properties of compounds.

| Compound codes | Pharmacokinetics | | | | | | | | | Drug-likeness | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GI abs. | BBB pen. | P-gp sub. | CYP1A2 | CYP2C19 | CYP2C9 | CYP2D6 | CYP3A4 | Log $K_p$ (skin permeation, cm/s) | Ghose | Egan | Muegge | Bioavailability Score |
| | | | | inhibitors | | | | | | | | | |
| Sa1 | High | No | Yes | No | No | Yes | No | No | -7.47 | Yes | Yes | Yes | 0.55 |
| Sa2 | High | No | No | No | Yes | Yes | No | Yes | -7.06 | Yes | Yes | Yes | 0.55 |
| Sa3 | High | No | No | No | Yes | Yes | No | Yes | -6.00 | Yes | Yes | Yes | 0.55 |
| Sa4 | Low | No | No | No | Yes | Yes | No | Yes | -6.00 | No | No | No | 0.17 |
| Sa5 | High | No | No | No | Yes | Yes | No | No | -6.27 | No | Yes | Yes | 0.55 |

**Table 4: Predicted acute toxicity of molecules.**

| Compound codes | Parameters | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $LD_{50}$ (mg/kg) | Toxicity class | Prediction accuracy (%) | Hepatotoxicity (Probability) | Carcinogenicity | Immunotoxicity | Mutagenicity | Cytotoxicity |
| Sa1 | 1190 | 4 | 100 | A (0.69) | I (0.62) | A (0.96) | I (0.97) | I (0.93) |
| Sa2 | 5000 | 5 | 67.38 | A (0.62) | I (0.56) | I (0.79) | I (0.73) | I (0.71) |
| Sa3 | 5000 | 5 | 67.38 | A (0.52) | I (0.51) | A (0.69) | I (0.72) | I (0.69) |
| Sa4 | 5000 | 5 | 54.26 | A (0.56) | A (0.55) | A (0.95) | A (0.76) | I (0.62) |
| Sa5 | 5000 | 5 | 54.26 | A (0.64) | I (0.52) | A (0.82) | I (0.83) | I (0.70) |

drug's physicochemical properties, directly correlate with how well it is absorbed. Every functional variation possesses hydrogen bond donor and acceptor domains, as per Lipinski's criterion. The superior lipophilicity of the generated compounds leads to an increase in bioavailability in the end. The aforementioned statement was supported by an analysis of the VDss is similar to that of traditional medications. The estimated maximum total clearance values for each compound were comparable, according to the total clearance values (Table 3).

## Predicted Acute Toxicity of Molecules

The goal of acute toxicity studies is to identify the amount that, whether administered once or over a few administrations, will result in death or major toxicological consequences. They also function as a source of knowledge on dosages that ought to be used in later research. These investigations offer an additional chance to ascertain compound-induced effects as shown by clinical chemistry, morphology, or other assessments. Additionally, acute investigations may provide an early indicator of the potential target organ or organs. This is a section of the acute toxicity studies. The median Lethal Dose ($LD_{50}$) is defined as the dosage at which 50% of exposed animals die. This discovery has been useful in comparing the acute toxicity of different substances and served as the basis for the environmental and industrial toxicant categorization. Pharmaceutical development used to begin with a formal $LD_{50}$ evaluation. Experience showed that the $LD_{50}$ (Table 4) used much too many animals and provided little useful information for the creation of pharmacological products.

## *In silico* Docking Studies

Molecular docking study was done to identify the many binding interactions of synthetic molecules within the target pocket of well-known antiepileptic medications, such as GABA receptors. The development of the anticonvulsant activity of the investigated medications was also aided by the comparative investigation of interactions with different targets. Every synthetic molecule having antiepileptic efficacy *in vivo* has been selected for molecular docking investigations using a variety of targets *in silico* (Table 5). The binding energies of the conventional medications (phenytoin and phenobarbital) and active compounds (sa4, sa3, and sa5) with selected targets are listed in Table 5. The binding energies of all active molecules range from -11.7 to -9.7 kcal/mol, which is quite similar to the binding energies of phenytoin (-5.48 kcal/mol) of common pharmaceuticals.

# DISCUSSION

Molecular docking experiments have been utilized to determine how conventional medicines interact with ligands on proteins. The goal of the molecular docking study was to access and comprehend the interaction binding energy dynamics of a few strong anti-epilepsy drugs that were produced experimentally on the Gamma-Aminobutyric Acid (GABA) A receptor. Table

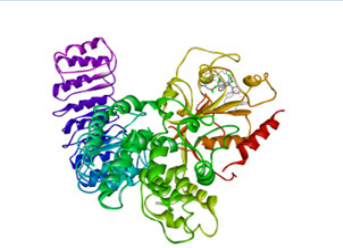
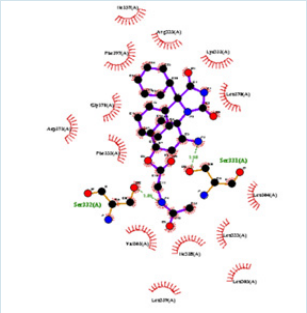
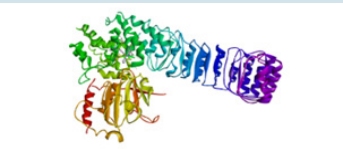
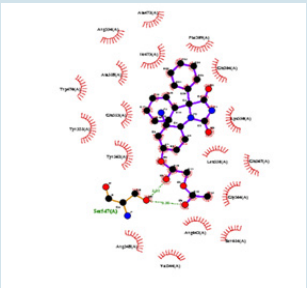
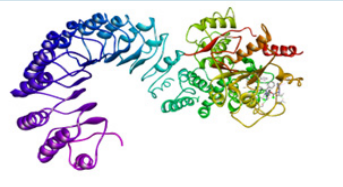
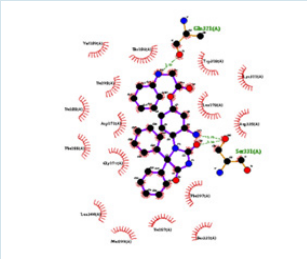
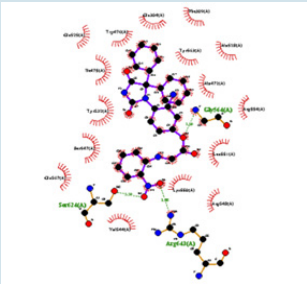
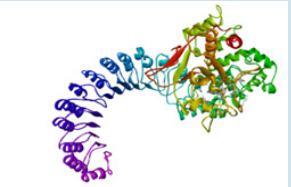
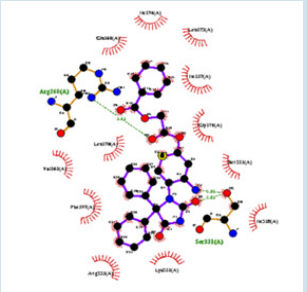
**Table 5:** **The active amino residues, bond length, bond category, bond type, ligand energies, and docking scores.**

| Active Amino acid | Bond length | Bond Type | Bond Category | Docking score |
|---|---|---|---|---|
| **Compound: Sa1** | | | | |
| SER331 | 2.1288 | Conventional Hydrogen Bond | Hydrogen Bond | -10.5 |
| ILE328 | 3.02982 | Conventional Hydrogen Bond | Hydrogen Bond | |
| SER332 | 1.83542 | Conventional Hydrogen Bond | Hydrogen Bond | |
| UNL1 | 3.12931 | Pi-Donor Hydrogen Bond | Hydrogen Bond | |
| PHE297 | 4.35718 | Pi-Pi Stacked | Hydrophobic | |
| PHE297 | 3.86223 | Pi-Pi Stacked | Hydrophobic | |
| PHE255 | 5.22747 | Pi-Pi T-shaped | Hydrophobic | |
| ILE328 | 5.40136 | Pi-Alkyl | Hydrophobic | |
| ARG335 | 5.19041 | Pi-Alkyl | Hydrophobic | |
| **Compound: Sa2** | | | | |
| SER547 | 3.02173 | Conventional Hydrogen Bond | Hydrogen Bond | -9.7 |
| SER547 | 3.3004 | Conventional Hydrogen Bond | Hydrogen Bond | |
| LEU551 | 2.83608 | Conventional Hydrogen Bond | Hydrogen Bond | |
| UNL1 | 2.65348 | Conventional Hydrogen Bond | Hydrogen Bond | |
| ILE475 | 3.45533 | Pi-Sigma | Hydrophobic | |
| TYR563 | 3.41608 | Pi-Sigma | Hydrophobic | |
| TYR532 | 4.85189 | Pi-Pi Stacked | Hydrophobic | |
| ILE475 | 4.43218 | Pi-Alkyl | Hydrophobic | |
| ARG554 | 4.37848 | Pi-Alkyl | Hydrophobic | |
| ALA472 | 4.9063 | Pi-Alkyl | Hydrophobic | |
| ALA528 | 4.4155 | Pi-Alkyl | Hydrophobic | |
| **Compound: Sa3** | | | | |
| SER331 | 3.16048 | Conventional Hydrogen Bond | Hydrogen Bond | -10.9 |
| ARG335 | 3.01627 | Conventional Hydrogen Bond | Hydrogen Bond | |
| SER331 | 2.51564 | Conventional Hydrogen Bond | Hydrogen Bond | |
| UNL1 | 1.90316 | Conventional Hydrogen Bond | Hydrogen Bond | |
| GLN321 | 2.45132 | Conventional Hydrogen Bond | Hydrogen Bond | |
| LEU270 | 3.34915 | Carbon Hydrogen Bond | Hydrogen Bond | |
| ILE285 | 3.64701 | Pi-Sigma | Hydrophobic | |
| MET299 | 4.93138 | Pi-Sulfur | Other | |
| PHE297 | 5.96706 | Pi-Pi T-shaped | Hydrophobic | |
| LYS322 | 4.28553 | Pi-Alkyl | Hydrophobic | |

| Active Amino acid | Bond length | Bond Type | Bond Category | Docking score |
|---|---|---|---|---|
| ARG335 | 4.28831 | Pi-Alkyl | Hydrophobic | |
| ILE257 | 4.55796 | Pi-Alkyl | Hydrophobic | |
| LEU270 | 5.1494 | Pi-Alkyl | Hydrophobic | |
| **Compound: Sa4** | | | | |
| SER624 | 3.299 | Conventional Hydrogen Bond | Hydrogen Bond | -11.7 |
| ARG643 | 2.8825 | Conventional Hydrogen Bond | Hydrogen Bond | |
| SER547 | 2.80776 | Carbon Hydrogen Bond | Hydrogen Bond | |
| GLU567 | 3.75048 | Pi-Anion | Electrostatic | |
| TYR532 | 3.83066 | Pi-Donor Hydrogen Bond | Hydrogen Bond | |
| SER547 | 3.35935 | Pi-Donor Hydrogen Bond | Hydrogen Bond | |
| ILE475 | 3.47636 | Pi-Sigma | Hydrophobic | |
| ILE475 | 3.60702 | Pi-Sigma | Hydrophobic | |
| TYR532 | 4.62253 | Pi-Pi Stacked | Hydrophobic | |
| LEU551 | 4.62429 | Pi-Alkyl | Hydrophobic | |
| ARG554 | 5.25732 | Pi-Alkyl | Hydrophobic | |
| ALA472 | 4.60765 | Pi-Alkyl | Hydrophobic | |
| ALA528 | 4.43503 | Pi-Alkyl | Hydrophobic | |
| VAL544 | 5.1625 | Pi-Alkyl | Hydrophobic | |
| **Compound: Sa5** | | | | |
| ARG268 | 3.03078 | Conventional Hydrogen Bond | Hydrogen Bond | -10.7 |
| SER331 | 2.82898 | Conventional Hydrogen Bond | Hydrogen Bond | |
| SER33 | 2.04784 | Conventional Hydrogen Bond | Hydrogen Bond | |
| UNL1 | 2.16101 | Conventional Hydrogen Bond | Hydrogen Bond | |
| ILE257 | 3.63488 | Carbon Hydrogen Bond | Hydrogen Bond | |
| GLY271 | 3.4741 | Carbon Hydrogen Bond | Hydrogen Bond | |
| GLY271 | 4.02217 | Pi-Donor Hydrogen Bond | Hydrogen Bond | |
| ILE274 | 3.57086 | Pi-Sigma | Hydrophobic | |
| ILE257 | 5.36084 | Pi-Alkyl | Hydrophobic | |
| ARG335 | 3.9779 | Pi-Alkyl | Hydrophobic | |
| LEU270 | 4.69216 | Pi-Alkyl | Hydrophobic | |
| VAL262 | 5.49931 | Pi-Alkyl | Hydrophobic | |

2 revealed that the docking scores of the most powerful AED-selected anti-epilepsy medication candidates ranged from -5.1 to -6.8 kcal/mol. Consequently, the effective mechanism of 1-acetyl-3-(2-aminophenyl)-5,5-diphenylimidazolidine-2,4-dione might be through the inhibition of GABA (Gamma-Aminobutyric Acid) A receptor activity on the binding site. This is due to the fact that the strength of the docking scores strongly correlates with the ability to start ligand-protein interactions. A molecular docking analysis was done on each and every synthesised chemical. They were discovered to entirely occupy the active regions in the target protein, therefore potently inhibiting the Gamma-Aminobutyric Acid (GABA)A receptor. Compared to the typical anticonvulsant medication, some of the compounds had higher docking scores. Compound SA4, which had the highest docking score of (-6.33),

**Table 6: Docking Poses 2D and 3D.**

| 3D-docking poses | 2D-docking poses |
|---|---|
|  |  |
| Compound: Sa1 | |
|  |  |
| Compound: Sa2 | |
|  |  |
| Compound: Sa3 | |
|  |  |
| Compound: Sa4 | |
|  |  |
| Compound: Sa5 | |

was determined to be the most powerful of all the synthesised compounds. Due to hydrogen bonding, compound SA5's binding mode takes a favourable orientation (-0.85) as compared to the reference (-4.03 as Dock Score). Additionally, compounds SA4 and SA5 had strong docking scores of (-6.32) and H bonds (-0.85), respectively, which are higher than those of the commonly used medication. The studied chemicals' interactions with other targets, however, are not as significant. The most active compounds (sb4, sb3, and sb5) and reference medication (phenytoin) in 2D interaction images. Compound SA3's methoxy group joins forces with residues at SER A:678 and THR A:516 to create a standard hydrogen bond. Compound SB4's nitro group joins SER A:678 in a typical hydrogen bond. Compound SA5's hydroxyl group joins GLN A:485 in a typical hydrogen bond. The data shown above suggests that the tested drugs and targets interact well (Table 6). The facts presented above clearly demonstrated the good prospective antiepileptic properties of the synthesised compounds, which acted mainly through the mechanism of action of conventional medications like phenytoin. Additionally, it appears that the synthetic chemicals show strong anticonvulsant effects upon docking with the voltage-gated calcium channel receptor.

## CONCLUSION

Promising anticonvulsants, 1-acetyl-3-(2-aminophenyl)-5,5-diphenylimidazolidine-2,4-dione derivatives was synthesised as a structural homologue of phenytoin. These ligands were chosen for pharmacological screening based on how well they docked onto the GABAA receptor's active sites when compared to other substances. Acute toxicity and molecular docking ADMET analysis were seen in just 5 drugs. We might suggest the docking technology that has been given as a means of expediting screening because of the shown correlation between the active GABAA receptor sites and screening results.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**mg/kg:** Milligram/kilograms; **sec:** Seconds; **kcal:** Kilocalorie; **Mol. Wt:** Molecular Weight; **g:** Gram; **LEU:** Leucine; **THR:** Threonine; **ALA:** Alanine; **MET:** Methionine; **PHE:** Phenylalanine; **WHO:** World health association; **Log P:** Partition coefficient.

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