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Original Article

# Molecular Docking Studies and ADME Prediction of Benzimidazole Derivatives on Anti-convulsant Activity by Inhibiting Voltage-Gated Sodium Channel (NavMs)-5HVX

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## ABSTRACT

**Background:** Epilepsy was described as utmost common be habitual brain complaint. A typical symptom of epilepsy is unbridled storms due to transient neuronal discharges. Despite the fact that numerous novel anti-convulsants have been developed in the Indian request but after treatment of new and current curatives; certain kinds of seizures are still not sufficiently controlled by smaller side goods. **Materials and Methods:** The exploration reported on concentrated work on molecular docking and ADME of the relations that do between the chlorinated benzimidazole derivations and the sodium (Nav) voltage-gated channels. A series of the benzimidazole derivations were planned and studied *in silico* was performed by through a sodium channel inhibitor GABAergic pathway. The medicine- likeness parcels of the designed composites were prognosticated. **Results:** All the designed composites showed good *in silico* ADME and molecular docking parcels and delved for Voltage-gated Sodium Channel (NavMs)-5HVX inhibitory exertion. According to molecular docking studies, all composites showed better commerce with target protein and could be the potent asset of sodium channels via a GABAergic pathway. The designed benzimidazole derivations analogues may be more effective anticonvulsant drugs that are also safer. **Conclusion:** Voltage-gated Sodium Channel (NavMs)-5HVX is one of the crucial enzymes of GABAergic pathway biosynthesis in different natural fiefdoms and is set up in beast and also in humans. Voltage-gated Sodium Channel (NavMs)-5HVX proteins belong to the class of superfamily. It's the most conserved protein. Unlike other enzymes, Voltage-gated Sodium Channel (NavMs)-5HVX also gives strong particularity.

**Keywords:** Voltage-Gated Sodium Channels, Molecular Docking, Anticonvulsant, Structure-Based Drug Design, 3D QSAR.

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## INTRODUCTION

One of the most prevalent neurological problems is epilepsy or seizures, which is set up in all periods. According to World Health Association (WHO), 65 million persons globally are estimated affected by epilepsy.[1-3] It was observed that 80% of them reside in developing or middle-income nations. Still, Epilepsy is a neurological and unbridled seizure. It happens seven times advanced than normal for all habitual diseases.[4-7] Former exploration said that the expenditures of United States on health care including seizures are roughly $15.5 billion annually. The prevalence of epilepsy in the US and India is significant, necessitating the development of safer and more potent anticonvulsants to reduce the expense of treating epilepsy. Numerous efforts have been made by diverse nations in the search for innovative, secure, and efficient epilepsy treatments. There are various or numerous forms of epilepsy like focal or generalized seizures; absence seizure and clonic seizures. Nowadays; new anti-convulsants have been discovered and they're used for focal seizures. Different types of Epilepsy cannot be cure with newer and currenttherapies.[8-12] In epilepsy; it was linked by unbridled storms and it was brought on by excessive transient neuronal discharges. The broad etiology of epilepsy or seizures pattern, important substantiation suggests that more than one medium may be responsible for the colorful convulsions. It was shown by in highly excitable cells; the action eventuality is in the depolarization phase. The initial inward current during the depolarization stage of the action eventuality in cells is produced by voltage-gated sodium (Nav) channels. The diminution of GABAergic transmission is likewise correlated with the voltage-gated sodium (Nav) channels; as excessive glutamatergic neurotransmission increase the physiological abnormalities. So that cases suffering from epileptic seizures. Recently, several structurally various anticonvulsant active stereoisomers have been synthesized, and our lab has been researching them for

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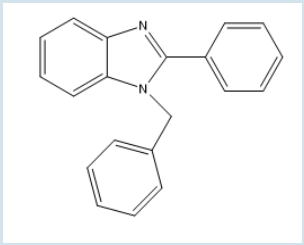
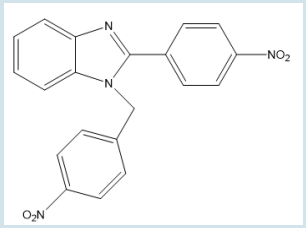
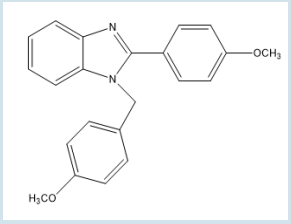
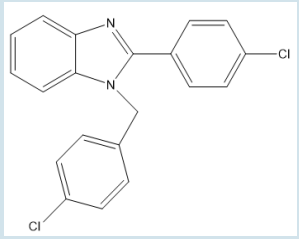
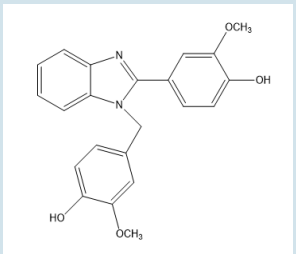
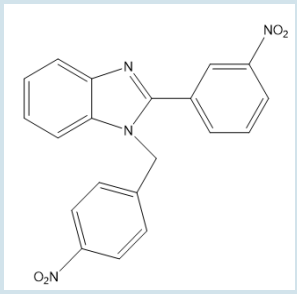
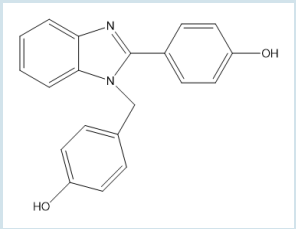
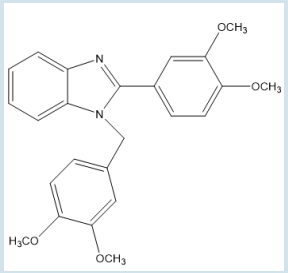
more than 20 years. In addition to providing good to moderate protection against the Minimal Electroshock Seizure (MES) test and via subcutaneous delivery, these derivations have produced a diverse range of structural variation with pentylenetetrazole i.e., PTZ test. A 3D QSAR model was utilized for prognosticate particular structural and electronic futures that are crucial for understanding the origins of active stereoisomers and their relations with implicit Nav channels and prokaryotic Nav channelstargets.[13-15] The original results from organic conflation, *in vivo* natural exertion Studies using ligand-based 3D QSAR have showed promise in the creation of novel anti-convulsant drugs by exercising colorful reagents. There's some substantiation that the anti-convulsant conditioning of these derivations gives action via two mechanisms of a GABAergic route and actions like sodium channel inhibition. Recent research in physiology suggests and demonstrates that the depolarization phase of the action eventuality in hyper excitable cells[16,17] is caused by a set of recently synthesized 6Hz Nav channels. Our ability to observe Nav channel inhibition in relation to the study's stereoisomers will be improved by the deployment of this high-resolution, full-length Nav channel demitasse. To ascertain the active list point of the stereoisomers derivations to the Nav channels, molecular docking experiments will be used. Understanding the relationships between the stereoisomers' derivations and the open form Nav channel[18,19] will be possible thanks to molecular docking investigations. Understanding the mechanisms of Nav channel blockage by chlorinated N-benzimidazole compounds will be aided by our results.

## MATERIALS AND METHODS

### *In silico* ADME (Absorption, Distribution, Metabolism and Excretion Studies)

The pharmacokinetics of the motes inside an organism's body are described by ADME or IDME. The ADME assesses the

**Table 1: Derivatives of designed compound of benzimidazole.**

| Label | Structure | Label | Structure |
|---|---|---|---|
| A1 |  | A5 |  |
| A2 |  | A6 |  |
| A3 |  | A7 |  |
| A4 |  | A8 |  |

danger of administering a pharmaceutical emulsion to a mortal body or other living things. Using an online tool comparable to, new derivations of benzimidazole pharmacokinetic packages are linked *in silico* Swiss ADME (http//www.swissadme.ch/). We study Lipinski's rule. According to Lipinski's rule of 5, two or further violation makes the motes orally inactive. It includes hydrophobicity, electronic distribution, and the presence of several pharmocophore features.

## Molecular docking Study

To prognosticate the list commerce of designed benzimidazole derivations molecular docking was carried out with the targeted protein. The Voltage-gated Sodium Channel (NavMs)-5HVX is the targeted protein. We study molecular docking with software i.e., Autodock Vina software. The protein is downloaded from PDB and the unwanted tittles like hetero tittles unwanted chains, cofactors and water motes are removed and also protein get ready for commerce. The designed benzimidazole derivations are optimized by using 3D software and 2D software. The designed benzimidazole nucleus derivations are given Figure 1.

# RESULTS AND DISCUSSION

New derivations of benzimidazole are designed which was given in (Table 1) for its anti convulsant exertion. The general criteria for new successful drug are medicine or chemical have high natural exertion at low attention with low toxin or low side effect. Benzimidazole heterocylic cynosures are reported extensively for treatment of upheaval complaint. New derivations of Benzimidazole are design for its anti upheaval exertion. It uses a GABAergic route and targets sodium channel inhibition. All the designed composites are given in Table 1. It was set up that the designed emulsion shows sodium channel inhibition and GABAergic pathway with a minimum adverse medicine response.

## Molecular docking results

A fascinating method for predicting the major list mode of a ligand with a target protein with a known three-dimensional structure is molecular docking. It's a crucial tool in the design of structure-based, computer-supported medicine. The intended benzimidazole derivations bind successfully with the target protein's active site Voltage-gated Sodium Channel (NavMs)-5HVX by using Autodock software. The designed emulsion A4, A6, A8 shows good list via hydrophobic and hydrogen bonds, respectively, to the target protein, whereas A1, A2, A3, A5, A7shows hydrophobic cling. The relations introduced by the active derivations within 5 Å compass to the list point of sodium

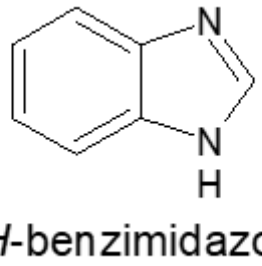



**Figure 1:** Designed benzimidazole derivatives.

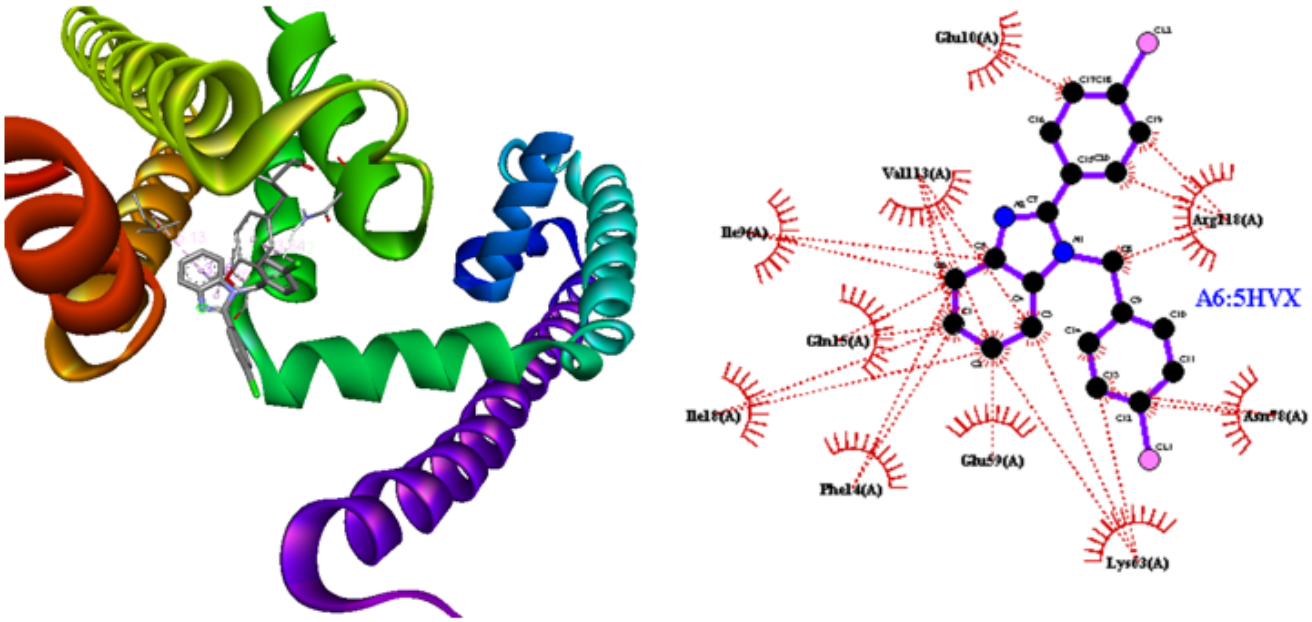



**Figure 2:** 2D and 3D Structure Designed Benzimidazole derivatives of A6.

**Table 2: Druglikeness analysis of derivatives of designed compound of benzimidazole.**

| Comp. | Molecular weight (g/mol) | CMC rule violation | Lipinski's rule violation | Mol Log P | H bond donor | H bond acceptor | No. of Rotatable bonds | TPSA (Å2) |
|---|---|---|---|---|---|---|---|---|
| A1 | 432.86 g/mol | 0 | Yes | 2.95 | 1 | 4 | 6 | 83.55 Å² |
| A2 | 412.44 g/mol | 0 | Yes | 2.68 | 1 | 4 | 6 | 83.55 Å² |
| A3 | 443.41g/mol | 0 | Yes | 2.40 | 1 | 6 | 7 | 129.37 Å² |
| A4 | 426.46 g/mol | 0 | Yes | 2.88 | 1 | 4 | 7 | 83.55 Å² |
| A5 | 477.31 g/mol | 0 | Yes | 3.05 | 1 | 4 | 6 | 83.55 Å² |
| A6 | 449.48 g/mol | 0 | Yes | 3.15 | 1 | 4 | 6 | 83.55 Å² |
| A7 | 428.44g/mol | 0 | Yes | 2.15 | 1 | 5 | 7 | 92.78 Å² |
| A8 | 398.41g/mol | 0 | Yes | 2.47 | 1 | 4 | 6 | 83.55 Å² |
| A9 | 416.40g/mol | 0 | Yes | 2.84 | 1 | 5 | 6 | 83.55 Å² |
| A10 | 423.42 g/mol | 0 | Yes | 1.81 | 1 | 5 | 6 | 107.34 Å² |

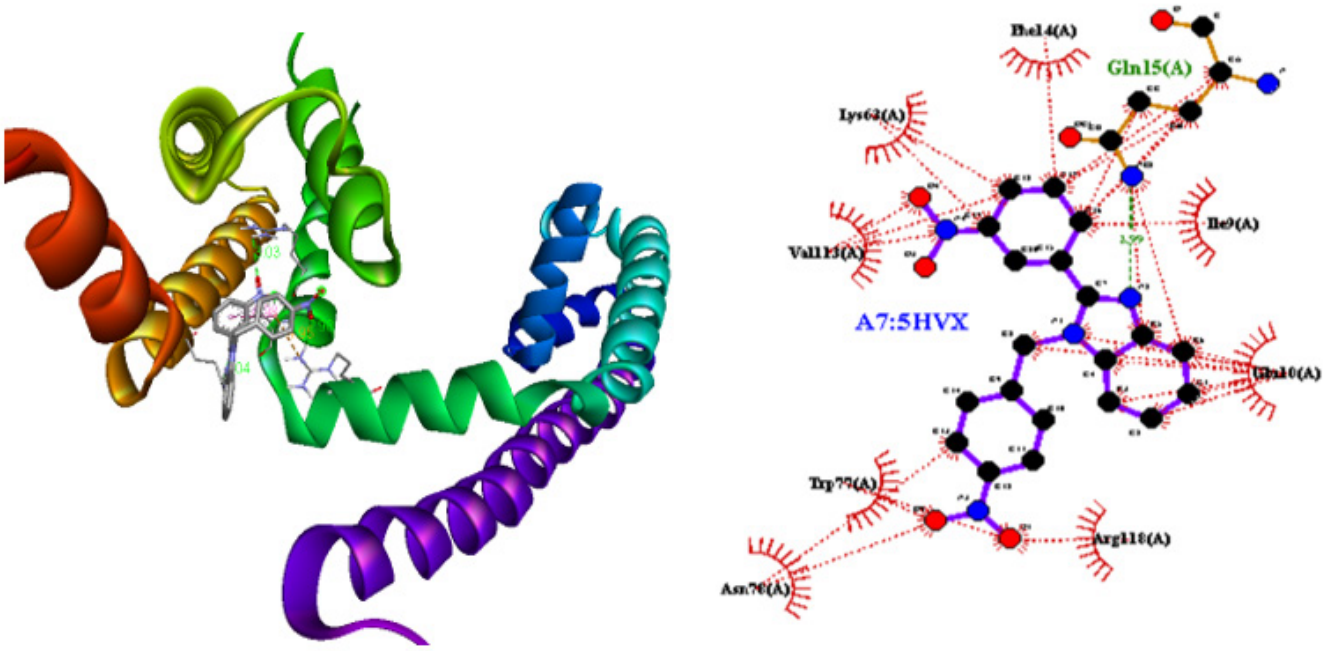



**Figure 3:** 2 D and 3 D Structure Designed Benzimidazole derivatives of A7.

channels and via a GABAergic pathway. In this exploration; all composites are active and A6 and A7 is the most active emulsion with minimal list affinity are named as potent impediments. Hydrophobic commerce of A8 and A7 with LEU168; LEU168; PHE142; LEU168; LEU138; MET175; PHE142; PHE172; LEU168; LEU138 a distinct group. The hydrogen bond conformation between the motes PHE and LEU is another factor is completely honored as indicated which have observed Tables 2 and 3. Docking investigations showed that the planned emulsion and target protein were the list mode of the most active composites. 2D and 3D Structure of designed benzimidazole derivations of A6; A7 and A8 are given (Figures 2, 3, 4).

**Table 3:** **The active amino residues, bond length, bond category, bond type, ligand energies, and docking scores of benzimidazole.**

| Active Amino acid | Bond length | Bond Type | Bond Category | Ligand Energy | Docking score |
|---|---|---|---|---|---|
| **A1** | | | | | |
| LEU168 | 3.36354 | Hydrogen Bond | Carbon Hydrogen Bond | 22.9420 kcal/mol | -8.1 |
| LEU168 | 3.55906 | Hydrophobic | Pi-Sigma | | |
| LEU168 | 3.86165 | Hydrophobic | Pi-Sigma | | |
| PHE142 | 3.80812 | Hydrophobic | Pi-Pi Stacked | | |
| PHE172 | 4.06452 | Hydrophobic | Pi-Pi Stacked | | |
| LEU138 | 5.32262 | Hydrophobic | Pi-Alkyl | | |
| **A2** | | | | | |
| THR139 | 2.49397 | Hydrogen Bond | Conventional Hydrogen Bond | 34.4955 kcal/mol | -7.8 |
| LEU168 | 3.42119 | Hydrophobic | Pi-Sigma | | |
| PHE172 | 4.16443 | Hydrophobic | Pi-Pi Stacked | | |
| PHE172 | 4.26798 | Hydrophobic | Pi-Pi Stacked | | |
| PHE142 | 4.96145 | Hydrophobic | Pi-Pi T-shaped | | |
| ALA135 | 4.3971 | Hydrophobic | Alkyl | | |
| LEU138 | 4.32799 | Hydrophobic | Alkyl | | |
| TYR143 | 5.25675 | Hydrophobic | Pi-Alkyl | | |
| LEU138 | 5.3909 | Hydrophobic | Pi-Alkyl | | |
| **A3** | | | | | |
| LEU168 | 3.79525 | Hydrogen Bond | Carbon Hydrogen Bond | 21.0582 kcal/mol | -8.3 |
| THR139 | 3.50541 | Hydrogen Bond | Carbon Hydrogen Bond | | |
| LEU168 | 3.81015 | Hydrophobic | Pi-Sigma | | |
| LEU168 | 3.58694 | Hydrophobic | Pi-Sigma | | |
| PHE172 | 4.16592 | Hydrophobic | Pi-Pi Stacked | | |
| PHE172 | 4.2107 | Hydrophobic | Pi-Pi Stacked | | |
| UNL1 | 4.87253 | Hydrophobic | Pi-Pi Stacked | | |
| PHE142 | 4.77548 | Hydrophobic | Pi-Pi T-shaped | | |
| LEU168 | 4.94469 | Hydrophobic | Alkyl | | |
| LEU138 | 5.35849 | Hydrophobic | Pi-Alkyl | | |
| **A4** | | | | | |
| THR139 | 2.32321 | Hydrogen Bond | Conventional Hydrogen Bond | 20.5745 kcal/mol | -7.9 |
| LEU168 | 3.5664 | Hydrophobic | Pi-Sigma | | |
| PHE172 | 4.09765 | Hydrophobic | Pi-Pi Stacked | | |
| PHE172 | 4.33962 | Hydrophobic | Pi-Pi Stacked | | |
| UNL1 | 4.26071 | Hydrophobic | Pi-Pi Stacked | | |
| PHE142 | 4.83269 | Hydrophobic | Pi-Pi T-shaped | | |
| LEU138 | 5.26085 | Hydrophobic | Pi-Alkyl | | |

| Active Amino acid | Bond length | Bond Type | Bond Category | Ligand Energy | Docking score |
|---|---|---|---|---|---|
| **A5** | | | | | |
| THR139 | 2.27351 | Hydrogen Bond | Conventional Hydrogen Bond | 15.7829 kcal/mol | -8.5 |
| LEU168 | 3.76897 | Hydrogen Bond | Carbon Hydrogen Bond | | |
| LEU168 | 3.48472 | Hydrophobic | Pi-Sigma | | |
| PHE142 | 5.76341 | Hydrophobic | Pi-Pi Stacked | | |
| PHE172 | 4.31901 | Hydrophobic | Pi-Pi Stacked | | |
| PHE172 | 4.18386 | Hydrophobic | Pi-Pi Stacked | | |
| PHE142 | 5.27218 | Hydrophobic | Pi-Pi T-shaped | | |
| **A6** | | | | | |
| LEU168 | 3.94059 | Hydrophobic | Pi-Sigma | 23.7210 kcal/mol | -8.1 |
| LEU168 | 3.58577 | Hydrophobic | Pi-Sigma | | |
| PHE142 | 3.75521 | Hydrophobic | Pi-Pi Stacked | | |
| LEU168 | 5.38106 | Hydrophobic | Alkyl | | |
| LEU138 | 4.31334 | Hydrophobic | Alkyl | | |
| MET175 | 4.66181 | Hydrophobic | Alkyl | | |
| PHE142 | 4.45107 | Hydrophobic | Pi-Alkyl | | |
| PHE172 | 5.21336 | Hydrophobic | Pi-Alkyl | | |
| LEU168 | 4.04581 | Hydrophobic | Pi-Alkyl | | |
| LEU138 | 5.41196 | Hydrophobic | Pi-Alkyl | | |
| **A7** | | | | | |
| THR139 | 2.27153 | Hydrogen Bond | Conventional Hydrogen Bond | 26.7202 kcal/mol | -8.7 |
| LEU168 | 3.7803 | Hydrogen Bond | Carbon Hydrogen Bond | | |
| THR139 | 3.48539 | Hydrogen Bond | Carbon Hydrogen Bond | | |
| ALA135 | 3.35577 | Hydrogen Bond | Carbon Hydrogen Bond | | |
| UNL1 | 3.72372 | Hydrogen Bond | Carbon Hydrogen Bond | | |
| LEU168 | 3.81841 | Hydrophobic | Pi-Sigma | | |
| LEU168 | 3.59081 | Hydrophobic | Pi-Sigma | | |
| PHE172 | 4.22858 | Hydrophobic | Pi-Pi Stacked | | |
| PHE172 | 4.19296 | Hydrophobic | Pi-Pi Stacked | | |
| UNL1 | 4.84604 | Hydrophobic | Pi-Pi Stacked | | |
| LEU168 | 4.96597 | Hydrophobic | Alkyl | | |
| LEU168 | 4.92852 | Hydrophobic | Alkyl | | |
| LEU138 | 4.06661 | Hydrophobic | Alkyl | | |

| Active Amino acid | Bond length | Bond Type | Bond Category | Ligand Energy | Docking score |
|---|---|---|---|---|---|
| | | | A8 | | |
| THR139 | 2.30219 | Hydrogen Bond | Conventional Hydrogen Bond | 44.7859 kcal/mol | -7.8 |
| THR13 | 3.5655 | Hydrogen Bond | Carbon Hydrogen Bond | | |
| ALA135 | 3.34208 | Hydrogen Bond | Carbon Hydrogen Bond | | |
| LEU168 | 3.80109 | Hydrophobic | Pi-Sigma | | |
| LEU168 | 3.60123 | Hydrophobic | Pi-Sigma | | |
| PHE172 | 4.25657 | Hydrophobic | Pi-Pi Stacked | | |
| PHE172 | 4.21428 | Hydrophobic | Pi-Pi Stacked | | |
| UNL1 | 4.90046 | Hydrophobic | Pi-Pi Stacked | | |
| LEU168 | 4.98171 | Hydrophobic | Alkyl | | |
| LEU168 | 4.89463 | Hydrophobic | Alkyl | | |
| LEU138 | 4.06486 | Hydrophobic | Alkyl | | |

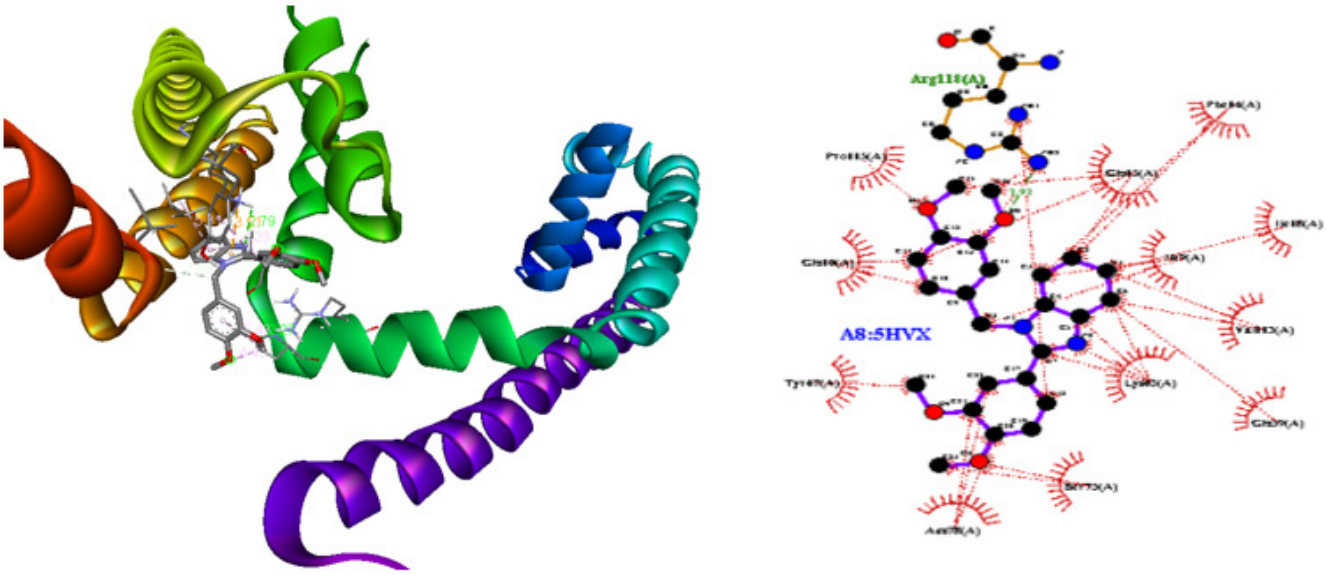



**Figure 4:** 2D and 3D Structure Designed Benzimidazole derivatives of A8.

## CONCLUSION

The benzimidazole derivatives were designed and their *in silico* parameter was studied. According to docking score, Druglikeness analysis of derivatives of designed compound of benzimidazole and ADME studies the designed mixes can be considered as super eminent molecules. Among the derivatives, A6, A7 and A8 show the most potent asset according to a molecular docking study. They interact with LEU168; LEU168; PHE142; LEU168; LEU138; MET175; PHE142; PHE172; LEU168; LEU138 to form hydrophobic commerce and with PHE and MET form hydrogen cleave. These mixes pass the ADME test, indicating that they are eligible for drug-likeness. These compounds have strong intestinal and PPB absorption capacities. Overall, the studies reveal that A8 mixes show potent impediments against target protein Voltage-gated Sodium Channel (NavMs)-5HVX.

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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; **gm:** Gram; **LEU:** Leucine; **THR:** Threonine; **ALA:** Alanine; **MET:** Methionine; **PHE:** Phenylalanine; **NavMs:** Voltage-gated Sodium Channel; **TPS:** Trehalose phosphate synthase; **WHO:** World Health Association; **Log P:** Partition coefficient.

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