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AN *IN SILICO* EVALUATION OF NOVEL 1,2,4-TRIAZOLE SCHIFF BASE DERIVATIVES AS POTENTIAL GABA-A RECEPTOR MODULATORS USING MOLECULAR DOCKING AND ADMET ANALYSIS

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ABSTRACT

The present study focuses on the computational assessment of novel 1,2,4 – Triazole Schiff base compounds as possible ligands targeting the GABA-A receptor for anticonvulsant activity. A series of 20 structurally diverse 1,2,4 – Triazole Schiff bases (Z)-4-[(substitutedmethylene)amino]-5-phenyl-4H-1,2,4-triazole-3-thiols **(AKS – 1 – AKS – 20)** were designed and subjected to molecular docking using Auto Dock Tools 1.5.7 against the GABA-A receptor (PDB ID: 6X3Z), indicating strong binding affinities for compounds 4-(2-chloro-4-methylbenzylideneamino)-5-phenyl-4H-1,2,4-triazole-3-thiol **(AKS – 1)**, 4-(3-chloro-4-methoxybenzylideneamino)-5-phenyl-4H-1,2,4-triazole-3-thiol **(AKS – 3)** and 4-(2-chloro-3-hydroxy-4-methoxybenzylideneamino)-5-phenyl-4H-1,2,4-triazole-3-thiol **(AKS – 7)**, with docking scores of -9.4, -10.1 and -9.1 kcal/mol, respectively. These three active compounds were also subjected to ADMET analysis to evaluate their pharmacokinetic behaviour, and drug-likeness properties. Molecular docking studies against the GABA-A receptor revealed significant interactions of the synthesized derivatives contains important residues of amino acids within the site that is active, indicating favourable receptor affinity and possible agonistic activity. ADMET prediction and Lipinski's rule analysis demonstrated that compounds AKS - 1, AKS - 3, and AKS – 7 possess acceptable pharmacokinetic profiles, good oral bioavailability, and low toxicity. Among the evaluated derivatives, compounds AKS - 1, AKS - 3, and AKS – 7 exhibited stable intermolecular connections and nearly same X, Y, Z coordinates to the reference ligand (phenytoin) of GABA-A receptor (PDB ID: 6X3Z), suggesting their potential as promising anticonvulsant agents.

KEYWORDS: GABA-A Receptor, 1,2,4-Triazole, Schiff Base, ADMET, Anticonvulsant activity, Epilepsy, Lipinski's rule.

1. INTRODUCTION

Medicinal chemistry continues to place a strong emphasis on the control of the central nervous system (CNS) through ligand-receptor interactions, especially for the treatment of neurological conditions like insomnia, anxiety, and epilepsy. A key component of inhibitory neurotransmission in the brain is the GABA-A receptor, a ligand-gated chloride ion channel. One important therapeutic target for the management of disorders of the central nervous system (CNS), including epilepsy, anxiety, and insomnia, is the gamma-aminobutyric acid type A (GABA-A) receptor [1]. Neurons become hyperpolarized and less excitable when this receptor is activated by gamma-aminobutyric acid, the main inhibitory neurotransmitter. As a result, GABA-A receptor modulators, such as barbiturates and benzodiazepines, have been widely used in clinical practice; nevertheless, their side effects, which include drowsiness, tolerance, and dependency, call for the creation of safer and more targeted substitutes [2, 3].

Heterocyclic compounds structural diversity and pharmacological adaptability have made them useful scaffolds in drug creation. Among them, the 1,2,4-triazole nucleus has garnered significant interest due to its wide range of biological actions, which include anti-inflammatory, anticonvulsant, anxiolytic, and antibacterial qualities [4, 5]. Additionally, it is known that Schiff bases, which are distinguished by the presence of an azomethine (–C=N–) linkage, increase biological activity by improving molecular flexibility and binding affinity [6]. The development of CNS-active medicines has demonstrated encouraging potential when Schiff base functionality is included into triazole compounds [7, 8].

Molecular docking is widely employed to predict the preferred binding orientation of a ligand within a receptor binding site and to estimate the relative strength of ligand–target interactions [9, 10]. In the present context, docking studies of novel 1,2,4-triazole Schiff-base derivatives against the GABA-A receptor can provide information regarding their binding poses, interacting amino-acid residues, hydrogen bonds, hydrophobic

contacts, and other non-covalent interactions. Such information may help explain the structure–activity relationship of the synthesized or proposed derivatives and identify structural features that could contribute to GABA-A receptor modulation.

However, strong predicted receptor binding alone is insufficient to establish the drug-likeness of a candidate molecule. A compound intended for central nervous system activity must possess appropriate physicochemical and pharmacokinetic characteristics, including adequate absorption, distribution, metabolic stability, and elimination properties [11, 12].

ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis is therefore an important complementary component of early drug discovery. Computational prediction of properties such as gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 interactions, metabolic liability, aqueous solubility, hepatotoxicity, and potential toxicity can help prioritize promising compounds and identify undesirable characteristics at an early stage [13, 14].

The integration of molecular docking with ADMET prediction provides a more comprehensive computational strategy for the preliminary evaluation of novel bioactive molecules. Docking can provide a structural rationale for target engagement, whereas ADMET analysis can assess whether the compounds possess physicochemical and pharmacokinetic characteristics compatible with their intended biological application [15, 16]. Therefore, the present study is aimed at the in computational investigation of novel 1,2,4-triazole Schiff-base derivatives as potential modulators of the GABA-A receptor using molecular docking and ADMET analysis.

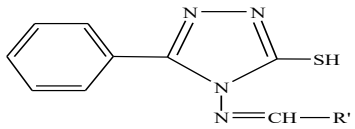


Figure 1: General structure of selected series of 1,2,4-Triazole Schiff bases.

2. MATERIAL AND METHODS

2.1 Molecular Docking

2.1.1. Ligand Preparation

The 1,2,4-Triazole Schiff bases were initially sketched using Chem Draw Pro 8.0 and ChemSketch. After these 2D structures were converted into 3D conformations using PyMOL and Avogadro, stable geometries suitable for docking were found by energy minimization. After saving the optimized ligands in PDB format they were converted to PDBQT format using ScienceCodons. To enable flexible docking, rotatable bonds were defined and Gasteiger charges were assigned [17, 18].

2.1.2. Receptor Preparation

The Protein Data Bank provided the crystal structure of the GABA-A receptor (PDB ID: 6X3Z). By using Auto Dock 1.5.7 and Biovia Discovery Studio 2025, polar hydrogens were added, water molecules and ligands were eliminated, and the receptor's Gasteiger and Kollman charges were calculated. A grid box was built to contain the leftovers from the active site and to allow adequate ligand interaction. The receptor was saved in PDBQT format for use in the docking simulation [19, 20].

2.1.3. Docking Parameters:

AutoDock Vina (combined with AutoDock Tools) was used for molecular docking. Explicit coordinates and dimensions (X, Y, Z centers and box sizes) were optimized for each protein in order to build docking grid boxes around the active site residues. The maximum number of binding modes was fixed at 10, the energy range was set at 4, and the exhaustiveness was set at 8. Binding affinity, represented as binding energy (kcal/mol), was assessed using the AutoDock Vina scoring tool [21, 22].

2.1.4. Validation of Molecular Docking

The co-crystallized (reference) ligand from the GABA-A receptor structure was re-docked into its binding site using the same grid and docking parameters in order to verify the docking procedure. The docked pose's root-mean-square deviation (RMSD) from the original ligand position was calculated. An RMSD value of 0.759 Å (less than 2.0 Å) confirmed the accuracy and reliability of the docking setup [23]. To ensure that the docking data were biologically relevant, Biovia Discovery Studio 2025 was also used to evaluate and validate important chemical interactions, including as hydrophobic contacts and hydrogen bonding. Molecular Docking is also validated that compounds AKS - 1, AKS - 3, and AKS – 7 exhibited nearly same X, Y, Z coordinates to the co-crystallized (reference) ligand of GABA-A receptor, suggesting their potential as promising anticonvulsant agents.

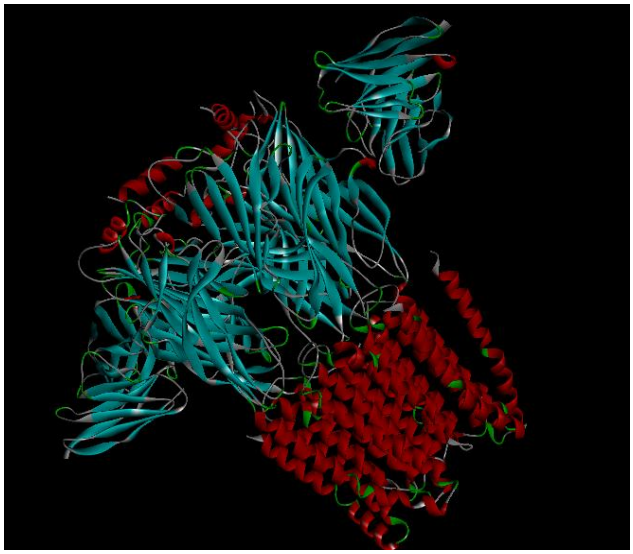


Figure 2: PDBID: 6X3Z

2.2 Drug likeness studies and ADME prediction

For compounds (AKS - 1, AKS - 3 and AKS - 7), molecular characteristics and drug-likeness parameters were calculated. Because it finds compounds that meet the criteria for being similar to medications, the drug-likeness study is significant. The pharmacokinetic characteristics of medicinal drugs, such as their oral bioavailability, cell penetration, metabolism, and elimination, make it imperative to look into ADME qualities. Lipinski's rule of five and other physicochemical factors like molecular refractivity, GI absorption, water solubility, and the number of rotatable bonds were predicted using Swiss ADME methodology. Lipinski's Rule of Five provides a widely accepted criterion for predicting oral bioavailability based on molecular weight (MW $<$ 500 g/mol), lipophilicity (Log P $\leq$ 5), hydrogen bond donors (HBD $\leq$ 5), and hydrogen bond acceptors (HBA $\leq$ 10). This study employed a number of software programs to guaranty precise forecasts and thorough analysis. Predictions for Absorption, Distribution, Metabolism, and Excretion (ADME) were developed using Swiss ADME, which offered vital information on the pharmacokinetic characteristics of the drugs. To evaluate the compounds toxicity profiles and guaranty their safety for additional research, ProTox II (version 3.0) was utilized. The table 6 and 7 summarizes the predicted physicochemical and pharmacokinetic properties of the synthesized derivatives when compared to the reference medication phenytoin [24, 25].

2.3 Boiled-EGG analysis

The BOILED-Egg model was used to assess the gastrointestinal absorption and blood–brain barrier permeability of the chosen medications [26, 27]. The study was carried out using the Swiss ADME digital platform (Figure 16).

2.4 Toxicity studies

A toxicity study was carried out to assess the synthetic compounds safety profile. ProTox-II (version 3.0), an in silico prediction platform, was used to evaluate acute toxicity, toxicity class, and organ-specific toxicities such as hepatotoxicity, mutagenicity, and carcinogenicity [28, 29]. Based on SMILES input, it enables efficient early-stage screening of potential harmful effects using machine learning and molecular similarity algorithms [30] (Table 6).

3. RESULT AND DISCUSSION

3.1 Docking Study

Binding energies ranging from –5.6 to –10.1 kcal/mol were found when 1,2,4-triazole Schiff bases were docked with the GABA-A receptor (PDB ID: 6X3Z). Compounds AKS-1, AKS-3, and AKS-7 showed the strongest binding, with docking scores of –9.4, –10.1, and –9.1 kcal/mol, respectively. These compounds demonstrated favorable interactions with key amino acid residues in the receptor's active region, primarily by hydrophobic contacts and stable hydrogen bonding. The ligands ideal accommodation within the GABA-A receptor binding pocket was confirmed by additional examination using Discovery Studio, demonstrating their stable and advantageous binding conformations.

Table 1. Docking score of 20 triazole Schiff base derivative with GABA-A receptor

S. No.	Compound	Binding Score (kcal/mol)
1	AKS-1	-9.4
2	AKS-2	-7.6
3	AKS-3	-10.1
4	AKS-4	-7.9
5	AKS-5	-8.1
6	AKS-6	-7.8
7	AKS-7	-9.1
8	AKS-8	-8.2
9	AKS-9	-7.7
10	AKS-10	-6.5
11	AKS-11	-8.8
12	AKS-12	-7.1
13	AKS-13	-6.9
14	AKS-14	-6.8
15	AKS-15	-5.6
16	AKS-16	-7.2
17	AKS-17	-5.8
18	AKS-18	-6.1
19	AKS-19	-6.7
20	AKS-20	-8.3
21	Standard (Phenytoin)	-12.6

3.2 Selection of top three compounds (AKS - 1–AKS – 3 and AKS - 7)

A shortlisting method was used to find the most promising candidates for additional validation out of the 20 compounds. Several computational filters served as the foundation for the selection criteria: (i) Docking affinity for all three protein targets; (ii) Interaction with catalytically significant residues; (iii) Adherence to ADME and drug-likeness regulations; (iv) Predicted toxicity class; and (v) Blood-brain barrier penetration. Compounds that matched these multi-parameter criteria were selected for comparison analysis. On the basis of binding score the top score compounds were AKS – 1, AKS – 3 and AKS – 7.

3.3 Visualization of the selected compounds (AKS – 1, AKS – 3 and AKS - 7)

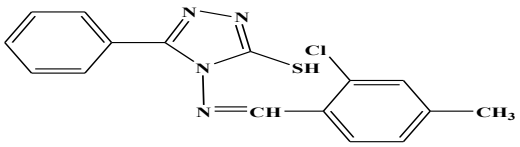


Figure 3: 4-(2-chloro-4-methylbenzylideneamino)-5-phenyl-4H-1,2,4-triazole-3-thiol (AKS – 1)

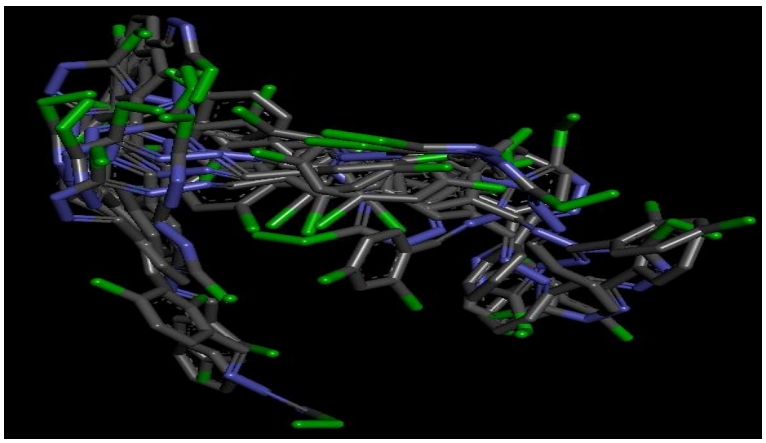


Figure 4: Various Docking Pose of AKS -1

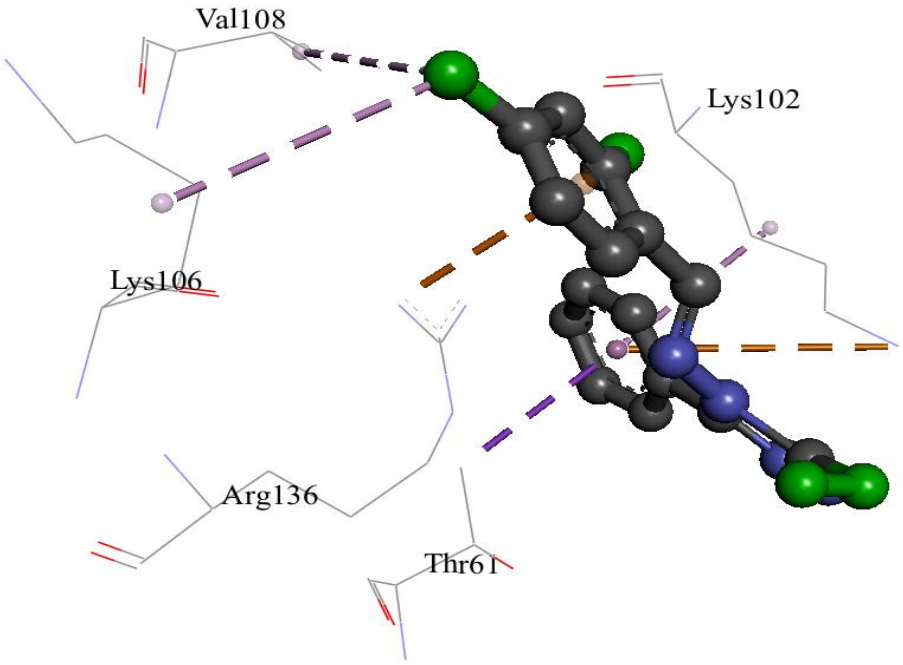


Figure 5: 3D Representation of compound AKS - 1 with PDBID: 6X3Z

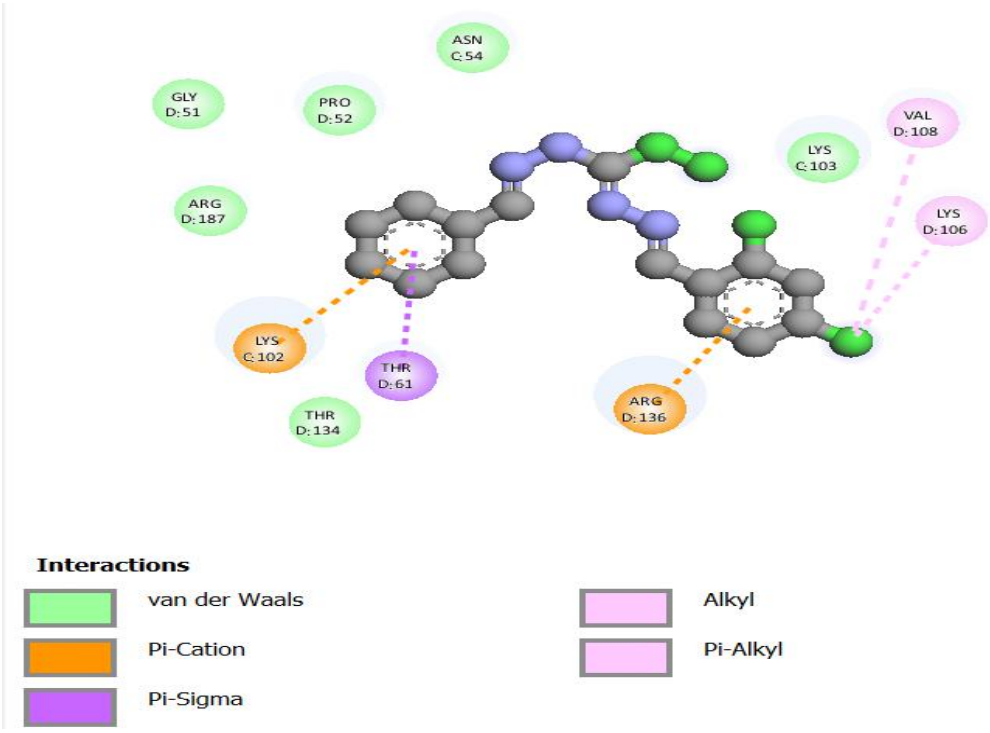


Figure 6: 2D Representation of compound AKS - 1 with PDBID: 6X3Z

Table 2: Docking interaction of receptor (6X3Z) with compound AKS-1

S. No.	Residual atom	Distance	Category	Type of interaction
1	LYS102	4.96147	Electrostatic	Pi-Cation
2	ARG136	3.5035	Electrostatic	Pi-Cation
3	THR61	3.65665	Hydrophobic	Pi-Sigma
4	LYS106	4.70527	Hydrophobic	Alkyl
5	VAL108	5.12537	Hydrophobic	Alkyl
6	LYS102	4.0314	Hydrophobic	Pi-Alkyl

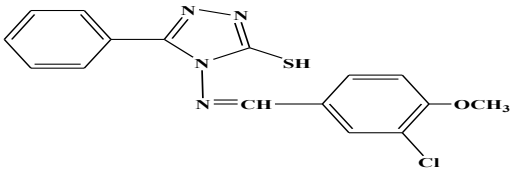


Figure 7: 4-(3-chloro-4-methoxybenzylideneamino)-5-phenyl-4H-1,2,4-triazole-3-thiol (AKS – 3)

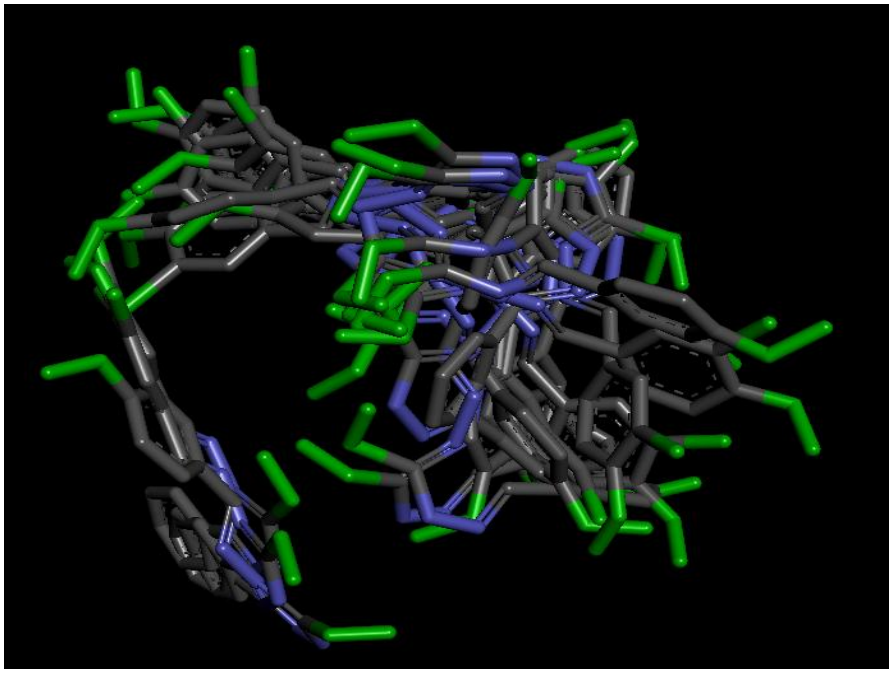


Figure 8: Various Docking Pose of AKS -3

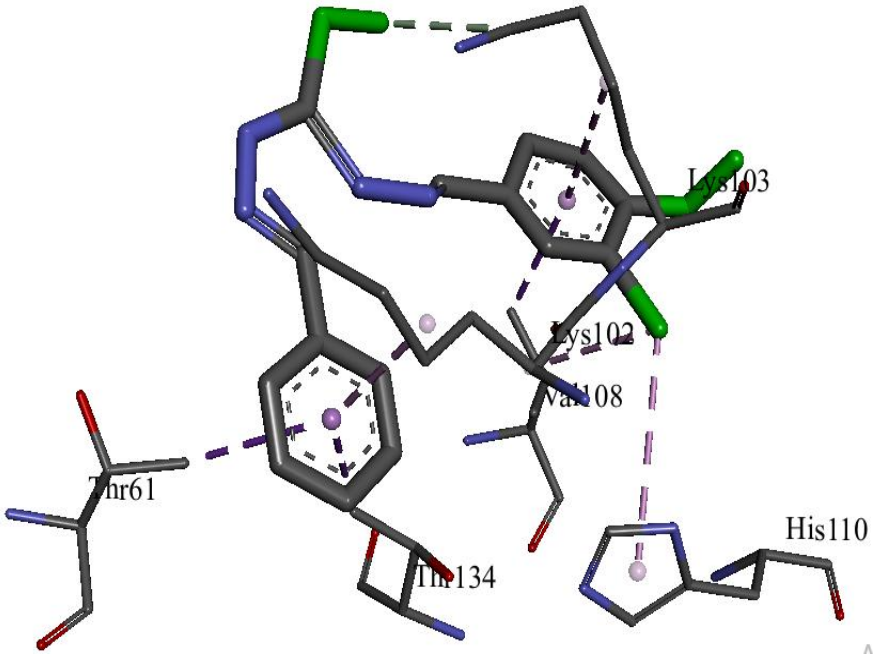


Figure 9: 2D Representation of compound AKS - 3 with PDBID: 6X3Z

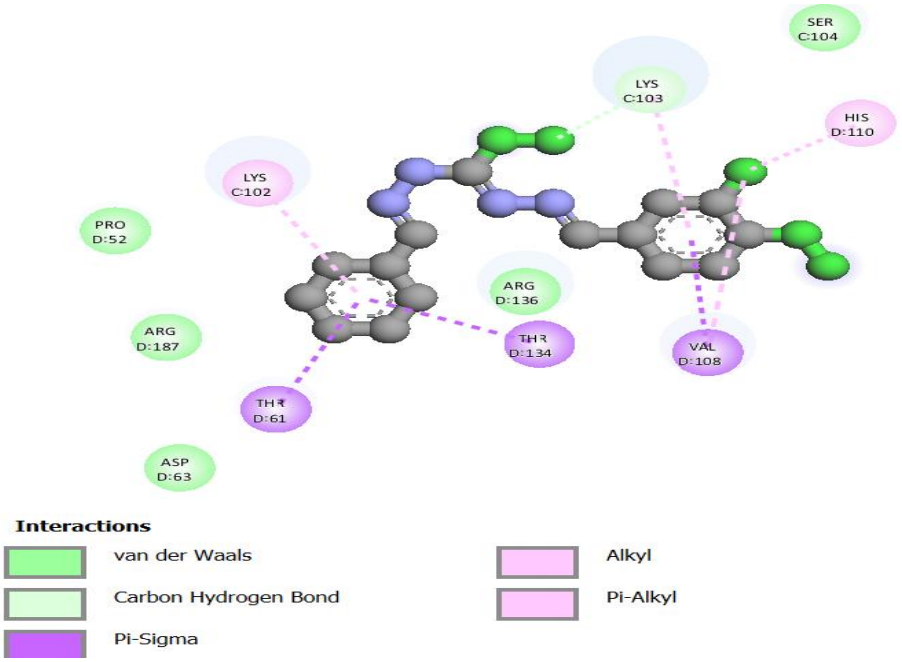


Figure 10: 2D Representation of compound AKS - 3 with PDBID: 6X3Z

Table 3: Docking interaction of receptor (6X3Z) with compound AKS-3

S. No.	Residual atom	Distance	Category	Type of interaction
1	LYS103	3.55457	Hydrogen Bond	Carbon Hydrogen Bond
2	THR61	3.90137	Hydrophobic	Pi-Sigma
3	VAL108	3.59659	Hydrophobic	Pi-Sigma
4	THR134	3.87702	Hydrophobic	Pi-Sigma
5	VAL108	4.0295	Hydrophobic	Alkyl
6	HIS110	4.40165	Hydrophobic	Pi-Alkyl
7	LYS102	3.95683	Hydrophobic	Pi-Alkyl
8	LYS103	4.79293	Hydrophobic	Pi-Alkyl

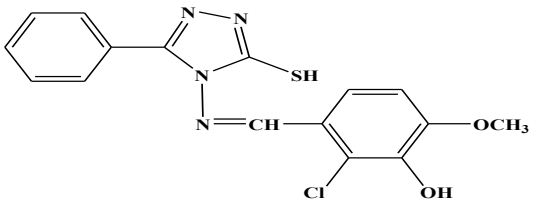


Figure 11: 4-(2-chloro-3-hydroxy-4-methoxybenzylideneamino)-5-phenyl-4H-1,2,4-triazole-3-thiol (AKS – 7)

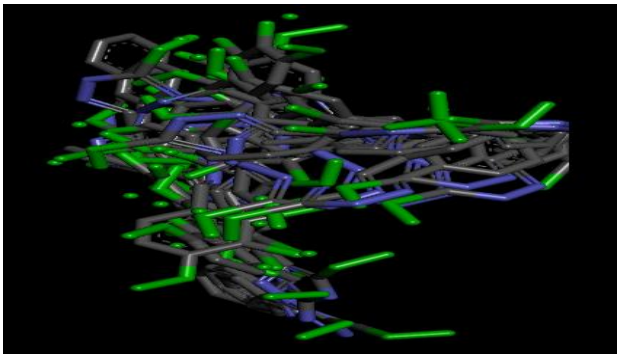


Figure 12: Various Docking Pose of AKS -7

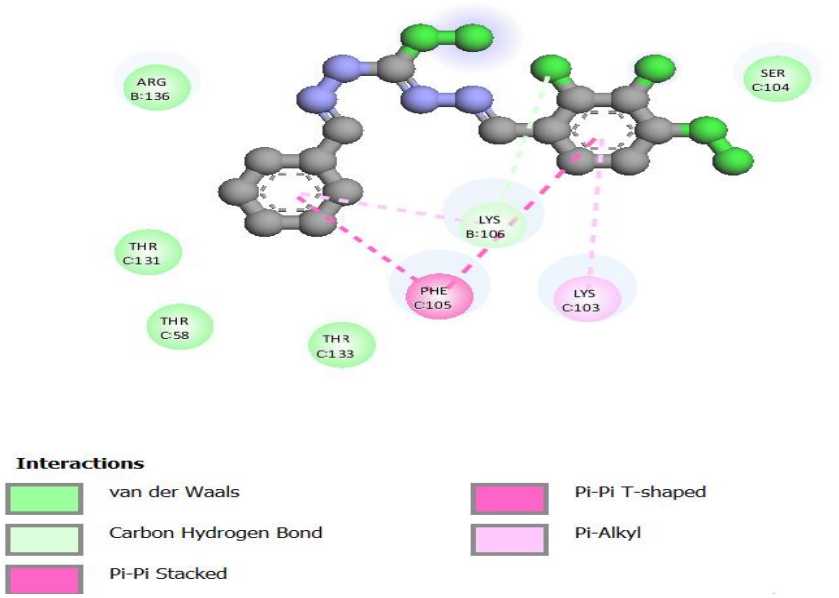


Figure 13: 2D Representation of compound AKS - 7 with PDBID: 6X3Z

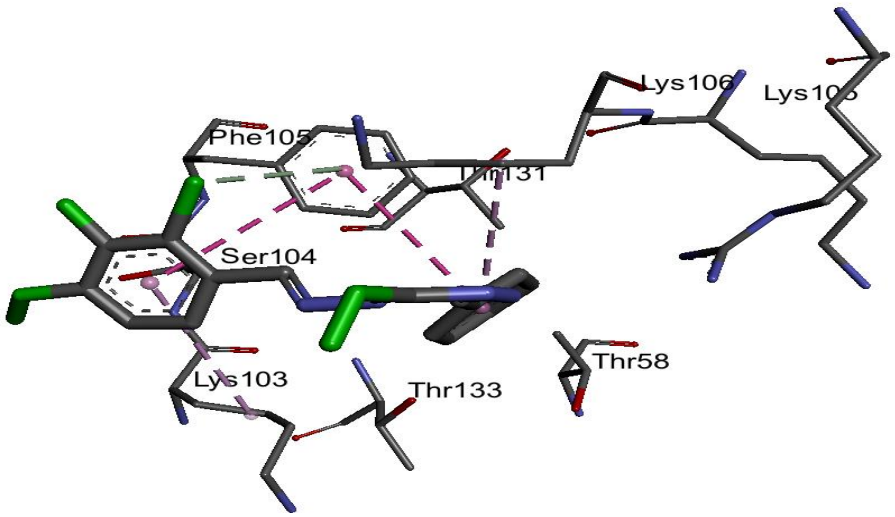


Figure 14: 3D Representation of compound AKS - 7 with PDBID: 6X3Z

Table 4: Docking interaction of receptor (6X3Z) with compound AKS-7

S. No.	Residual atom	Distance	Category	Type of interaction
1	LYS106	3.57879	Hydrogen Bond	H-Donor
2	PHE105	5.4314	Hydrophobic	Pi-Orbitals
3	PHE105	4.92265	Hydrophobic	Pi-Orbitals
4	LYS106	5.04972	Hydrophobic	Pi-Orbitals
5	LYS103	4.95604	Hydrophobic	Pi-Orbitals

3.4 Docking Validation by X, Y, Z coordinates of reference (phenytoin) ligand of GABA-A receptor

Table 5: X, Y, Z coordinates of AKS – 1, AKS – 2, AKS – 3 and Reference ligand

Ligands	X, Y, Z coordinates	X, Y, Z coordinates	X, Y, Z coordinates	X, Y, Z coordinates of reference ligand (Phenytoin)
AKS - 1	101.67	120.68	108.43	112.92, 131.18 111.78
AKS - 3	106.98	121.33	106.77	

AKS - 7	100.65	124.31	101.54	

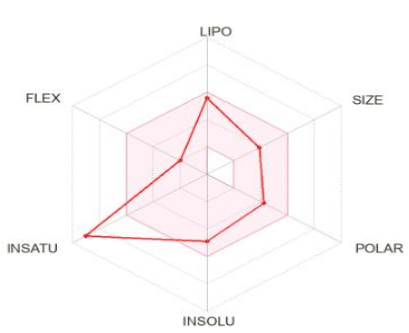
3.5 Result of Drug Likeness Studies and ADME Prediction

Table 6: Screening of Drug-likeness Parameters

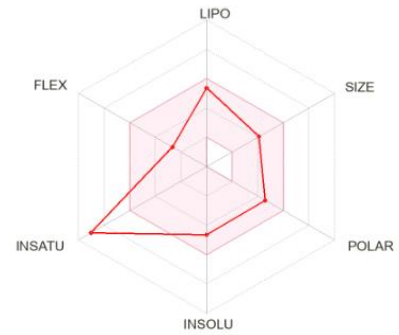
S. No.	Ligands	MF	Lipinski's Rule of 5				Lipinski's Violation	Lipinski's Rule
			MW (g/mol)	logP	HBA	HBD		
1	AKS - 1	C16H13ClN4S	328.82	1.81	1	3	0	Yes
2	AKS -3	C16H13ClN4OS	344.82	1.69	0	4	0	Yes
3	AKS -7	C16H13ClN4O2S	360.82	1.59	2	4	0	Yes
4	Standard (Phenytoin	$C_{15}H_{12}N_2O_2$	252.27	1.65	2	2	0	Yes

Table 7: Evaluation of computational ADMET Parameters

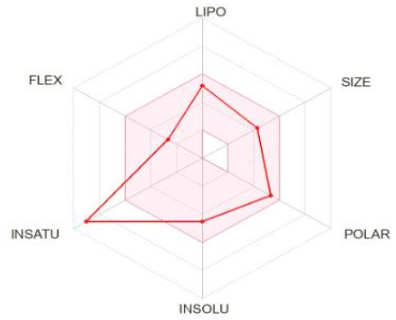
Ligands	Docking Score (kcal/mol)	Computational ADMET							
		Absorption	Distribution	Metabolism					Toxicity (ProTox-II) Class
		Water Solubility (logS)	BBB Permeability	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Class
AKS - 1	-9.4	-2.89 Moderately Soluble	Yes	No	No	No	No	No	Class IV
AKS - 3	-10.1	-3.64 Moderately Soluble	Yes	No	No	No	No	No	Class IV
AKS - 7	-9.1	-3.50 Moderately Soluble	Yes	No	No	No	No	No	Class IV
Phenytoin (Standard)	-12.9	-3.3 Moderately Soluble	Yes	No	No	No	No	No	Class V



AKS - 1



AKS - 3



AKS - 7

Figure 15: Radar plots showing ADME properties (LIPO, SIZE, POLAR, INSOLU, INSATU, FLEX) of top three 1,2,4 - triazole Schiff base compounds (AKS – 1, AKS – 3 and AKS - 7)

3.6 Result of Boiled-EGG analysis

The study found that whereas substances in the yellow zone were predicted to have greater permeability across the blood–brain barrier, those in the white region were associated with better intestinal absorption capacity.

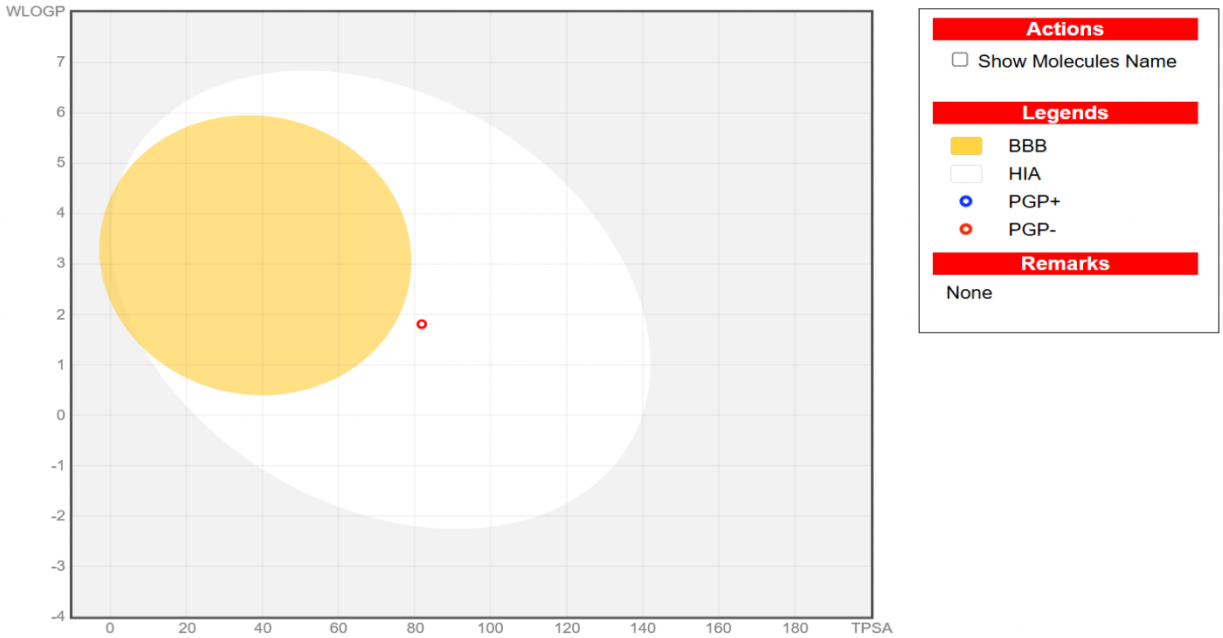


Figure 16: Boiled egg model for compound AKS – 1

4. CONCLUSION

Three new 1,2,4 - triazole-based Schiff base compounds, AKS-1, AKS-3, and AKS-7, have a promising affinity for the GABA-A receptor and may be useful as anticonvulsant drugs, according to the current computational analysis. The synthesized derivatives favorable binding contacts with important amino acid residues in the receptors active region were identified by molecular docking studies, suggesting their possible modulatory activity. According to Lipinski's rule analysis and ADMET, the assessed compounds also showed adequate pharmacokinetic and drug-likeness characteristics, indicating acceptable safety profiles and bioavailability. It was discovered that structural electron-donating and electron-withdrawing substituents have a major impact on

the stability of ligand-receptor interactions and the effectiveness of receptor binding. Out of 20 derivatives under investigation three derivatives (AKS-1, AKS-3, and AKS-7) showed superior docking scores and interaction patterns that were comparable with conventional anticonvulsant medications, indicating their potential as lead molecules for future research. Compounds AKS - 1, AKS - 3, and AKS – 7 also exhibited nearly same X, Y, Z coordinates to the reference ligand (Phenytoin) of GABA-A receptor (PDB ID: 6X3Z), suggesting their potential as promising anticonvulsant agents. Overall, the results of this study support further production, in vitro testing, and in vivo evaluation to develop therapeutic compounds that successfully treat epilepsy and other neurological disorders. They also offer important theoretical insight into the design of novel 1,2,4 - triazole Schiff base derivatives.

5. ACKNOWLEDGEMENT

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