

In silico SAR-Guided Discovery of Imidazole-Based Anticonvulsants with Optimized ADMET Profiles

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ABSTRACT

Background: Epilepsy is a chronic neurological disorder characterized by recurrent seizures caused by abnormal electrical activity in the brain. The development of novel anticonvulsant agents with improved efficacy and safety remains a significant therapeutic challenge. This study aimed to evaluate imidazole derivatives as potential anticonvulsant candidates through comprehensive *in silico* ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis. **Materials and Methods:** A total of 29 imidazole derivatives were evaluated using SwissADME for physicochemical and drug-likeness properties. Based on favorable characteristics, the top eight compounds were selected for detailed pharmacokinetic and toxicity assessment using pkCSM and admetSAR. The clinically approved antiepileptic drug phenytoin was included as a reference compound for comparative analysis. Structure-Activity Relationship (SAR) and target prediction analyses were also performed to investigate the relationship between structural features and anticonvulsant activity. **Results:** All compounds complied with Lipinski's rule of five, with molecular weights ranging from 217 to 438 Da. The selected compounds exhibited favorable Log *p* values (1.35-2.36) and Topological Polar Surface Area (TPSA) values (44.12-70.42 Å²), indicating good drug-likeness and excellent intestinal absorption (99.8-100%). Compound A21 demonstrated the highest Blood-Brain Barrier (BBB) permeability (log BB= 0.182) and Central Nervous System (CNS) penetration (log PS= -1.3). Compound A20 exhibited moderate BBB permeability (log BB = -0.898), a higher clearance rate (0.887 log mL/min/kg), lower predicted neurotoxicity (18.15%) than A21 (44.45%), and acceptable acute toxicity (LD₅₀=2.461 mol/kg). SAR analysis suggested that the imidazole core and ester substitutions contribute to enhanced BBB permeability and reduced neurotoxicity. Target prediction identified GABA-A receptors, GRM4/GRM5, and ADORA1/ADORA2A as potential molecular targets, indicating modulation of inhibitory and excitatory neurotransmission. **Conclusion:** Among the evaluated compounds, A20 demonstrated the most balanced pharmacokinetic and safety profile, highlighting its potential as a promising anticonvulsant candidate. These findings support further *in vitro* and *in vivo* investigations to validate its therapeutic efficacy and safety.

Keywords: ADMET, admetSAR, Anticonvulsants, Blood-brain barrier, Imidazole derivatives, Neurotoxicity, pkCSM, STOPTOX, SwissADME.

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Received: 02-04-2026;

Revised: 21-06-2026;

Accepted: 13-08-2026.

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures caused by abnormal electrical activity in the brain and affects millions of individuals worldwide (Nagaraj *et al.*, 2026). It results from an imbalance between excitatory glutamate transmission and decreased inhibitory Gamma-Aminobutyric Acid (GABA) activity, leading to neuronal hyperexcitability. Neurons fire uncontrollably, resulting in seizure propagation due to disrupted neurotransmitter balance and abnormalities

in sodium, calcium, and potassium ion channels. Seizures are broadly classified into two types: focal types that begin in one particular brain area and generalized types that start by affecting both brain hemispheres. Many antiepileptic drugs act through pathways modulation, yet their use leads to incomplete seizure control and are associated with adverse effects. Therefore, there is a need to develop safer and effective therapies targeting multiple mechanisms (Engel *et al.*, 2022; Ghosh *et al.*, 2021).

Heterocyclic compounds are important scaffolds in CNS drug discovery. Among them, imidazole has become a subject of interest because its structural flexibility enables it to produce various biological effects. Imidazole derivatives have shown promising anticonvulsant properties through modulation of GABA pathways, ion channels and excitatory neurotransmitter systems. Their physicochemical properties enable them to enter the CNS, thus increasing their effectiveness as epilepsy treatment (Burlacu



DOI: 10.5530/ijpi.20270083

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et al., 2026; Marzouk *et al.*, 2020). Imidazole, first synthesized by Heinrich Debus in 1858, through the reaction of glyoxal, formaldehyde, and ammonia. Five-membered heterocyclic compound known as 1,3-diazole (Figure 1). It contains two nitrogen atoms that enables interactions with biological targets, making it an important in medicinal chemistry and drug design (Tolomeu and Fraga, 2023; Yadav and Jain, 2025).

The pharmacological potential of imidazole-based compounds has been extensively documented; however, their successful development depends on pharmacokinetic properties and their safety profiles. Many promising compounds fail during later drug development stages, due to poor absorption, low bioavailability, inadequate tissue distribution, metabolic instability, and toxicity. Therefore, early evaluation of ADMET properties is essential in drug design and discovery process (Çetiner *et al.*, 2023; Rahman *et al.*, 2021).

In silico techniques serve as efficient tools for the rapid and cost-effective evaluation of drug candidates. The methods use advance algorithms and curated datasets to predict drug properties and biological activities. SwissADME platform to measure physicochemical characteristics and lipophilicity and water solubility and gastrointestinal absorption and BBB permeability functions as vital factors in evaluating drugs for CNS treatment. The pkCSM platform predicts key pharmacokinetic parameters, including absorption, distribution, metabolism via cytochrome P450 enzymes and excretion and toxicity. STOPTOX provides comprehensive toxicity assessment, including acute oral toxicity, carcinogenicity, organ toxicity and skin sensitization using machine learning approaches (Kumar *et al.*, 2025; Orujova *et al.*, 2025).

The combination of these computational tools enables the identification and assessment of drug candidates. With favorable pharmacokinetic properties and safety profiles during the initial drug development process. CNS active agents require BBB permeability together with proper lipophilicity and low neurotoxicity to achieve their therapeutic efficacy. Therefore, this study aims to evaluate imidazole derivatives as potential anticonvulsant agents using integrated *in silico* ADMET and toxicity analysis (Mohan Kumar and Talwar, 2025). Although several studies have reported the synthesis and anticonvulsant activity of imidazole derivatives, comprehensive integration of SwissADME, pkCSM, admetSAR, STOPTOX, Swiss Target Prediction, and SAR analysis for prioritizing lead compounds has not been reported. The present study provides an integrated computational framework to identify imidazole derivatives with optimized pharmacokinetic properties and reduced neurotoxicity.

MATERIALS AND METHODS

Molecular Design and Structure Preparation

ChemSketch software was used to sketch the chemical structures of the imidazole derivatives. The optimized structures were subsequently converted into Simplified Molecular Input Line Entry System (SMILES) format, which was used as input for further computational analysis (Laxmi, 2017; Li *et al.*, 2004).

ADME Prediction using SwissADME

The pharmacokinetic properties of all designed compounds were evaluated using the SwissADME web server (www.swissadme.ch). Various physicochemical and drug-likeness parameters like MW, Log P and TPSA, Hydrogen Bond Donors (HBD), Hydrogen Bond Acceptors (HBA), and Lipinski's rule of five. Essential pharmacokinetic properties, including gastrointestinal absorption, BBB permeability, and water solubility were predicted to evaluate CNS drug-likeness (Daina *et al.*, 2017; Lipinski *et al.*, 2001b).

Selection of Lead Compounds

Based on SwissADME analysis, compounds with optimal properties were selected. Compounds possess drug-likeness and suitable physicochemical characteristics and optimal pharmacokinetic properties through their analysis. Among the initial set of compounds, the top eight candidates were selected for further analysis of their pharmacokinetic properties and toxic effects.

Pharmacokinetic Prediction using pkCSM

The selected compounds were further analyzed using pkCSM web server (<https://biosig.lab.uq.edu.au/pkcsml/>) to predict detailed pharmacokinetic parameters. Various physicochemical properties like absorption, volume of distribution at steady state (VDss), metabolism, excretion, and toxicity (Pires *et al.*, 2015).

Neurotoxicity Prediction using admetSAR

The admetSAR 3.0 web server (<https://lmmd.ecust.edu.cn/admet-sar2/>) was used to predict neurotoxicity for the selected imidazole derivatives. Neurotoxicity was predicted using admetSAR based on QSAR models that depend on molecular structure and physicochemical property data. Assessed the neurotoxicity potential of each compound by determining its active or inactive status together with probability scores (Cheng *et al.*, 2012; Yang *et al.*, 2019).

Toxicity Prediction using STOPTOX

Toxicological evaluation of the selected imidazole derivatives was carried out using STOPTOX and pkCSM. The STOPTOX web server (<https://stoptox.mml.unc.edu/>) was employed to assess acute oral toxicity, providing qualitative predictions based on machine learning models trained on experimentally validated

datasets in accordance with OECD guidelines. The pkCSM was used to predict quantitative LD₅₀ values. The combined use of these tools enabled a comprehensive evaluation of the safety profile of the compounds (Borba *et al.*, 2022).

Swiss Target predication

Potential biological targets of the selected compounds were predicted using SwissTargetPrediction (<http://www.swisstargetprediction.ch/>) based on chemical similarity principles. This analysis provided insights into possible mechanisms underlying their anticonvulsant activity (Gfeller *et al.*, 2014). It suggested GABA-A receptors, GRM4/GRM5 and ADORA1/ADORA2A as potential targets, which require molecular docking and experimental validation.

RESULTS AND DISCUSSION

A comprehensive *in silico* evaluation of the imidazole derivatives was carried out to assess their pharmacokinetic and toxicity profiles relevant to anticonvulsant drug development. Computational tools, including SwissADME, pkCSM, STOPTOX, and admetSAR, were employed to predict key ADMET parameters. To provide a benchmark for comparison, the physicochemical and ADMET properties of the clinically approved antiepileptic drug phenytoin were also evaluated using the same computational tools and included for comparative analysis.

Physicochemical Parameters

The physicochemical properties of imidazole derivatives were determined in order to evaluate their ability to affect brain function. The detailed physicochemical properties of the designed imidazole derivatives (A1-A29) are presented in (Table 1). SwissADME used to compute essential parameters included MW, HBD, HBA, Log P, Number of Rotatable Bonds (NRB), TPSA, Molar Refractivity (MR), aqueous solubility (Log S), and Lipinski's rule of five violations.

Lipinski's rule defines oral bioavailability through four parameters including MW below (<500 Da), Log P (<5), HBD (≤5), and HBA restricted to (≤10). The NRB (≤10) and TPSA (≤140 Å²). The analysed compounds exhibited MWs that are within the acceptable limits resulting in positive outcomes for their capacity to be absorbed through oral administration. The Log P value demonstrated hydrophilicity and lipophilicity balance, which is crucial for membrane permeability and BBB penetration. The TPSA values of most compounds were below 90 Å² supporting their potential to show CNS activity. HBD and HBA, along with the rotatable bonds, satisfied the Lipinski's rule of five.

Prediction of Physicochemical Properties

Phenytoin exhibited a molecular weight of 252.27 g/mol, a consensus LogP of 1.95, and a TPSA of 58.20 Å², while complying with Lipinski's rule of five without any violations.

It also showed high gastrointestinal absorption, blood-brain barrier permeability, a bioavailability score of 0.55, and a predicted neurotoxicity of 31.48%. All the compounds A1-A29 (Table 2) exhibited MW within the acceptable range (217-438 Da), complying with Lipinski's rule of five. The selected lead compounds (A21, A20, A13, A14, A16, A17, A8, and A9, except A28), showed optimal MW (244-288 Da), indicating favorable drug-likeness. Log P, ranged from 1.5 to 2.5, suggesting a balanced hydrophilic-lipophilic profile important for membrane permeability and BBB penetration (Singh *et al.*, 2020). The selected compounds exhibited moderate Log P values, with A21 (2.36) and A20 (2.06) showing optimal lipophilicity for CNS activity. A13 (1.70), A14 (1.71), A16 (1.50), A17 (1.54), A8 (1.39), and A9 (1.35) all belong to the acceptable hydrophilic-lipophilic range that assists BBB permeability. TPSA values ranged from 44.12 to 115.96 Å², where values below 90 Å² are considered ideal for CNS penetration (Pajouhesh and Lenz, 2005). A21 showed the lowest TPSA value of 44.12 Å² and demonstrated strong potential for crossing the BBB. A13/A14 (57.01 Å²), A8/A9 (61.19 Å²), and A20 (70.42 Å²) fall within the optimal CNS range, while A15 (101.65 Å²) and A27 (115.96 Å²) exceed this threshold, indicating their brain penetration capacity is diminished. The selected compounds displayed HBD values between 0-1 and HBA values between 3-5, are favorable for permeability and absorption. The NRB ranged from 4 to 8, satisfying Veber's criterion (≤10), with A20 showing slightly higher flexibility (NRB=8), which enhance molecular interactions without significantly affecting stability (Lipinski *et al.*, 2001a).

MR values (56.75-77.83) fall within the acceptable range (40-130 m³·mol⁻¹), indicating suitable molecular size and polarizability for drug-receptor interactions (König and Vellido, 2024). The predicted log S values for the compounds were within the acceptable range (-6.0 to 0.5), with A21 (-3.55), A20 (-2.96), A13/A14 (-2.90), and A8/A9 (~-2.30) indicating good aqueous solubility, while A28 (-5.06) showed relatively low solubility. All compounds showed zero violations of Lipinski's rule, and their physicochemical profiles also satisfied Veber's and Muegge's criteria, confirming strong drug-likeness. Overall, compounds A21, A20, A13, A14, A16, A17, A8, and A9 demonstrated favorable

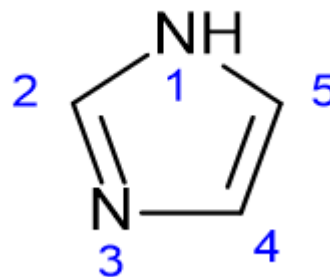


Figure 1: Imidazole structure.

Table 1: Physicochemical properties of the synthesized imidazole derivatives along with the reference drug phenytoin.

Sample Codes	Formula	MW	HBD	HBA	Log P	NRB	TPSA	MR	Log S	Violations
A1	C ₁₁ H ₁₀ N ₂ O ₃	218.212	1	4	0.90	4	64.35	56.75	-2.04	0
A2	C ₁₁ H ₁₀ N ₂ O ₃	218.212	1	4	0.97	4	64.35	56.75	-2.22	0
A3	C ₁₁ H ₁₀ N ₂ O ₃	218.212	1	4	0.98	4	64.35	56.75	-2.22	0
A4	C ₁₃ H ₁₂ N ₂ O ₄	260.249	0	5	1.11	6	70.42	66.1	-2.13	0
A5	C ₁₁ H ₁₀ N ₂ O ₃	218.212	1	4	0.90	4	64.35	56.75	-2.04	0
A6	C ₁₁ H ₁₀ N ₂ O ₃	218.212	1	4	0.97	4	64.35	56.75	-2.22	0
A7	C ₁₂ H ₁₀ N ₂ O ₄	246.222	1	5	0.96	5	81.42	61.69	-2.19	0
A8	C ₁₃ H ₁₂ N ₂ O ₃	244.25	0	4	1.39	5	61.19	64.92	-2.28	0
A9	C ₁₃ H ₁₂ N ₂ O ₃	244.25	0	4	1.35	5	61.19	64.92	-2.33	0
A10	C ₁₂ H ₁₀ N ₂ O ₄	246.222	1	5	0.97	5	81.42	61.69	-2.19	0
A11	C ₁₂ H ₁₀ N ₂ O ₄	246.222	1	5	1.01	5	81.42	61.69	-2.19	0
A12	C ₁₁ H ₁₁ N ₃ O ₂	217.288	1	3	0.85	4	70.14	59.13	-2.00	0
A13	C ₁₄ H ₁₁ N ₃ O ₂	253.261	0	4	1.70	4	57.01	70.03	-2.90	0
A14	C ₁₄ H ₁₁ N ₃ O ₂	253.261	0	4	1.71	4	57.01	70.03	-2.90	0
A15	C ₁₂ H ₁₀ N ₂ O ₅	262.221	2	6	0.50	5	101.65	64.16	-2.13	0
A16.	C ₁₄ H ₁₀ N ₂ O ₄	270.44	0	5	1.50	4	74.33	70.77	-2.63	0
A17	C ₁₄ H ₁₀ N ₂ O ₄	270.244	0	5	1.54	4	74.33	70.77	-2.71	0
A18	C ₁₃ H ₁₂ N ₂ O ₃	244.25	0	4	1.22	6	61.19	64.70	-2.30	0
A19.	C ₁₃ H ₁₂ N ₂ O ₄	260.249	1	5	1.19	5	81.42	66.95	-2.48	0
A20.	C ₁₅ H ₁₆ N ₂ O ₄	288.303	0	5	2.06	8	70.42	75.62	-2.96	0
A21.	C ₁₅ H ₁₂ N ₂ O ₂	252.273	0	3	2.36	4	44.12	72.24	-3.55	0
A22	C ₁₃ H ₁₂ N ₂ O ₃	244.25	0	4	1.27	6	61.19	64.70	-2.03	0
A23	C ₁₃ H ₁₂ N ₂ O ₃	244.25	0	4	1.24	6	61.19	64.70	-2.03	0
A24	C ₁₄ H ₁₆ N ₂ O ₅	292.291	2	6	0.49	7	93.81	73.32	-1.60	0
A25	C ₁₄ H ₁₄ N ₂ O ₄	274.276	1	5	1.38	7	81.42	71.08	-2.34	0
A26	C ₁₄ H ₁₄ N ₂ O ₅	290.275	2	6	0.54	7	101.65	72.24	-1.72	0
A27	C ₁₁ H ₁₀ N ₄ O ₄	262.225	1	5	0.30	5	115.96	67.96	-2.03	0
A28	C ₁₁ H ₇ Br ₃ N ₂ O ₂	438.901	0	3	3.27	4	44.12	77.83	-5.06	0
A29	C ₁₃ H ₁₂ N ₂ O ₃	244.25	0	4	1.38	5	61.19	64.92	-2.28	0
Phenytoin	C ₁₅ H ₁₂ N ₂ O ₂	252.27	2	2	1.95	2	58.20	77.50	-3.30	0

physicochemical profiles based on balanced MW, lipophilicity, polarity, and flexibility making them suitable for development as CNS-active anticonvulsant candidates (Ntie-Kang *et al.*, 2013).

Radar plots were employed to compare the multidimensional physicochemical profiles of the studied compounds. Each axis corresponds (Figure 2) to a specific descriptor, including Lipophilicity (LIPO), Molecular Size (SIZE), Polarity (POLAR), Solubility (INSOLU), Saturation (INSATU), and molecular Flexibility (FLEX). The extent of each axis indicates the relative magnitude of each property, and the resulting shape reflects the overall physiochemical profile of each compound. Compounds A8 and A9 demonstrate favorable alignment with their target

property range, with only minor deviations in INSATU. The compounds A21, A14, A16, and A17 showed significant differences from each other because their INSATU parameter showed variations in saturation levels. These differences indicate variations in structural rigidity and degree of saturation. These features may influence solubility and conformational flexibility. A13 was the least favorable, as many parameters were above optimal levels, especially low saturation, which resulted in low drug-likeness and poor oral absorption. The most promising candidate was A20 because all its parameters were within optimal limits, suggesting that it had balanced properties for oral absorption.

Pharmacokinetic Analysis using pkCSM

(Table 2) Water solubility values ranged from -1.462 to -0.675 log mol/L (Ntie-Kang *et al.*, 2013), indicating moderate solubility that enabled for oral absorption. A8 and A9 (-0.675) showed higher solubility among all the derivatives. Caco-2 permeability values ranged from 0.248 to 1.29 log P, and A21 (1.29), A13/A14 (~1.224), and A8/A9 (~1.22) showing high permeability. A16 and A17 (0.248) exhibited lower permeability results than other compounds. All compounds exhibited excellent human intestinal absorption (~99.8-100%), indicating strong oral bioavailability. Skin permeability values ranged from ~ -2.7 to

-2.9 log K_p were within acceptable limits, while all compounds maintained a bioavailability score of 0.55 demonstrating their strong drug-likeness. The VD_{ss} values ranged from -2.898 to 1.941 log L/kg, indicating variability in tissue distribution. A21 (1.941), A8 and A9 (1.814), A13 and A14 (1.733), and A16 and A17 (1.607) exhibited higher VD_{ss} values, suggesting extensive tissue distribution. In contrast, A20 (-2.898) revealed limited tissue distribution and high retention in the systemic circulation.

A21 (0.182) and A13/A14 (~0.017) exhibited positive or near zero log BB values, indicating favorable BBB penetration. A8/A9 (-0.057) was also found to be an acceptable level of permeability,

Table 2: Predicted ADMET profiles of the selected lead compounds together with phenytoin for comparative evaluation.

Parameter	Phenytoin	A21	A20	A13	A14	A16	A17	A8	A9
Absorption									
Water solubility (log mol/L)	-3.138	-1.462	-1.328	-1.012	-1.012	-1.163	-1.163	-0.675	-0.675
Caco2 permeability (log Papp, cm/s)	1.262	1.29	0.984	1.224	1.224	0.248	0.248	1.22	1.22
Intestinal absorption (human) %	94.481	99.845	100	100	100	100	100	100	100
Skin permeability (log K _p)	-2.753	-2.71	-2.898	-2.843	-2.843	-2.916	-2.916	-2.847	-2.847
BioS (from Swiss ADME)	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Distribution									
VD _{ss} (human) (log L/Kg)	-0.219	1.941	-2.898	1.733	1.733	1.607	1.607	1.814	1.814
BBB permeability (log BB)	0.075	0.182	-0.898	0.017	0.017	-0.761	-0.761	-0.057	-0.057
BBB permeability (Swiss ADME)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
CNS permeability (Log PS)	-2.3	-1.3	-2.664	-2.286	-2.286	-2.416	-2.416	-2.496	-2.496
Metabolism									
CYP2D6 inhibitor	No	No	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No	No	No
Excretion									
Total Clearance	0.361	0.731	0.887	0.705	0.774	0.647	0.661	0.84	0.784
Renal OCT2 substrate	No	No	No	No	No	No	No	No	No
Toxicity									
Neurotoxicity from (admet SAR %)	31.48	44.45	18.15	32.25	47.52	31.12	25.87	30.13	31.35
Hepatotoxicity	Yes	No	No	No	No	No	No	No	No
hERG	No	No	No	No	No	No	No	No	No
Oral Rat Acute Toxicity (LD ₅₀ in mol/Kg)	2.068	2.646	2.461	2.693	2.693	2.655	2.655	2.482	2.482

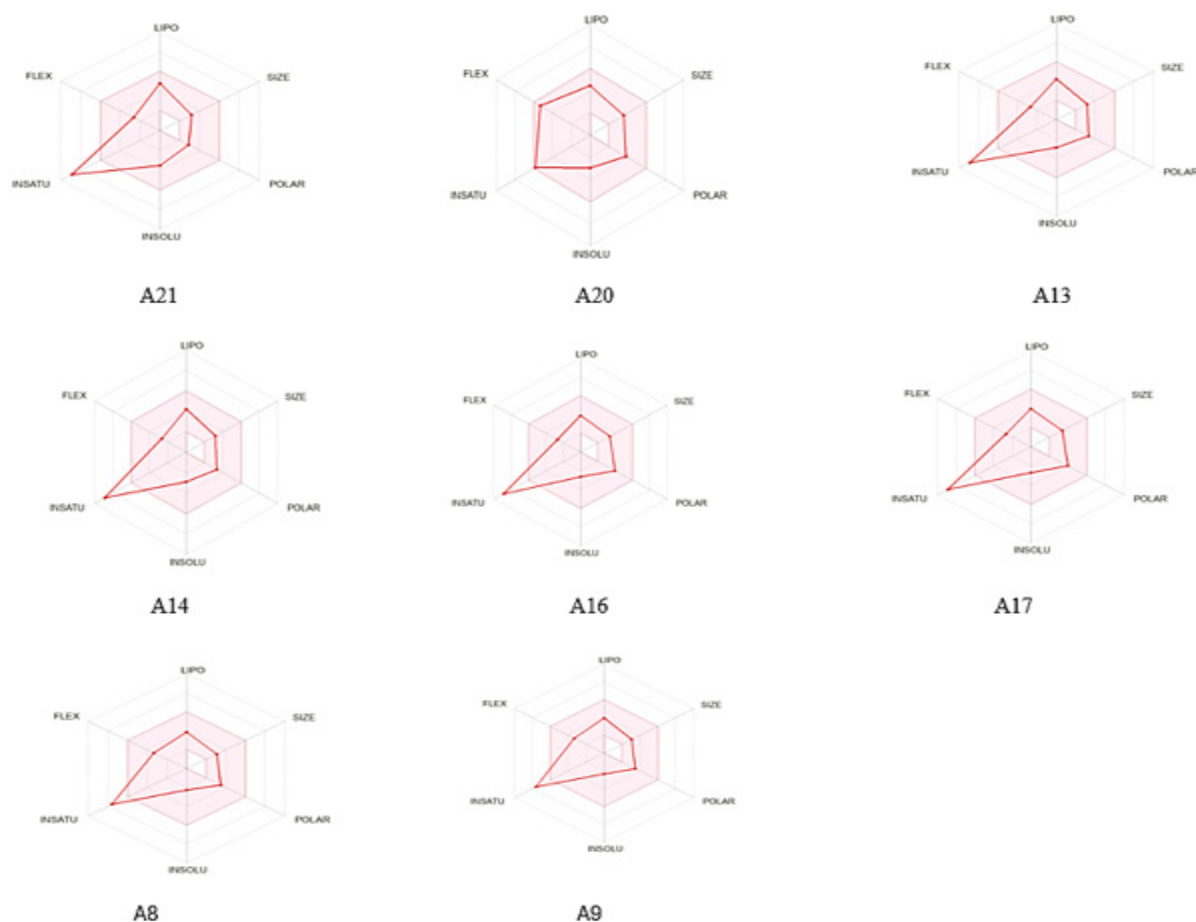


Figure 2: Bioavailability radar plots of the selected compounds (A21, A20, A13, A14, A16, A17, A8, and A9), showing six key physicochemical properties: Lipophilicity (LIPO), Molecular Size (SIZE), Polarity (POLAR), Solubility (INSOLU), Flexibility (FLEX), and saturation (INSATU). The pink shaded area represents the optimal range for oral drug-likeness, while the red polygons depict each compound's profile. Compounds A20, A8, and A9 exhibit the closest alignment with the optimal space, whereas A21, A14, A16, A17, and A13 show deviations, particularly in saturation and flexibility, indicating areas for potential structural optimization.

while A20 (-0.898) and A16/A17 (~ -0.761) had lower levels of BBB penetration. CNS Penetration (log PS) ranged from -1.3 and -2.664, established A21 as the most effective penetration -1.3. The selected compounds were found to have no inhibitory effects on CYP2D6 and CYP3A4 enzymes, indicating low risk of drug-drug interactions.

Total clearance values measured between 0.647 and 0.887. A20 (0.887) and A8 (0.84) had higher clearance rates resulting faster elimination. A16 (0.647) displayed lower clearance rates extending its time in the body. None of the compounds showed no interaction with renal OCT2.

The oral rat acute toxicity (LD_{50}) values ranged from 2.461 to 2.693 mol/kg, where higher values indicate lower toxicity. A13/A14 (2.693) showed the highest LD_{50} values, suggesting superior safety, followed by A16/A17 (~2.655) and A21 (2.646), while A20 (2.461) demonstrated lower LD_{50} values that still remained with acceptable limits. Among these, A21 showed superior pharmacokinetics, supporting its anticonvulsant potential.

Neurotoxicity Analysis using admetSAR

admetSAR is used to assess the neurotoxicity potential for selected imidazole derivatives. Among the selected compounds, A20 (18.15%) and A17 (25.87%) exhibiting lower neurotoxic potential compared to A14 (47.52%) and A21 (44.45%). Indicating improved safety profiles for CNS applications.

Toxicity Analysis (STOPTOX)

The STOPTOX evaluation of compound A20 (Figure 3) revealed that it had the least neurotoxicity (18.15%) of all the compounds chosen for consideration, implying safety in terms of acute oral toxicity. The prediction reliability of the results was predicted at 51%, within the applicability domain of the model. Its LD_{50} of 2.461 mol/kg indicating acceptable acute toxicity.

The applicability domain confirms that the result is reliable, and a dice similarity value above the threshold further confirms prediction validity. The fragment contribution analysis shows that A20's structural components interact with non-toxic behaviour dominating the green sections of the analysis while

only a few minor areas display potential toxic effects through the red segments. A20 demonstrates an effective acute oral safety profile for assessment. The structure consists of ester (-COO-), ether/alkoxy (-O-), and alkyl chain moieties due to hydrolytic metabolism and rapid elimination.

In contrast, the red-colored regions indicate functional groups that may increase toxicity risk. The nitrogen-containing heterocyclic ring structure of the compound primarily determines its main associations. Biological targets such as enzymes and receptors can be affected by these heterocycles.

Computational Target Profiling of Compound A20

Target prediction for compound A20 was carried out using the SwissTargetPrediction platform based on chemical similarity principles for identifying potential protein targets (Table 3). The analysis revealed multiple targets belonging to ligand-gated ion channels, G protein-coupled receptors, and kinases, all exhibiting comparable probability scores (~ 0.0979). Among these, CNS related targets were prioritized due to their relevance in seizure modulation. The GABA-A receptor was identified as a key CNS target involved in inhibitory neurotransmission and anticonvulsant activity. It was also predicted that metabotropic glutamate receptors GRM4 and GRM5, together with adenosine receptors ADORA1 and ADORA2A, would have the ability to modulate both excitatory pathways and neuromodulator

pathways. These targets suggest a multi-target mechanism involving enhanced GABA signaling and reduced neuronal hyperexcitability, contributing to anticonvulsant activity.

SAR Analysis of Selected Imidazole Derivatives A20

The imidazole nucleus blue Region (1-5) with nitrogen atoms enables hydrogen bonding and receptor interaction. The ester linkage in the green region (6-9, -COO-) enhances molecular flexibility and polarity balance, observed in A20 (Figure 4), contributing to improved pharmacokinetics with log BB (-0.898). The substituent in the red region (10-15) of the aromatic benzene ring significantly influences activity by modulating lipophilicity and polarity. The second ester linkage at green region (16-18, 21) provides additional flexibility and spatial orientation between the aromatic ring and side chain.

The propyl ester side chain pink region: 18-20, (-COO-CH₂-CH₂-CH₃) plays a crucial role in modulating the physicochemical and pharmacokinetic properties of the compound. It enhances lipophilicity (Log P ~ 2 -3) and provides structural flexibility, facilitating membrane permeability and receptor adaptability. The presence of this moiety is associated with lower neurotoxicity (18.15%). Substitution of a fused naphthalene ring at the position of the alkyl side chain position increases molecular rigidity and steric bulkiness. This leads to higher neurotoxicity (44.45%), indicating reduced safety despite comparable lipophilicity. For

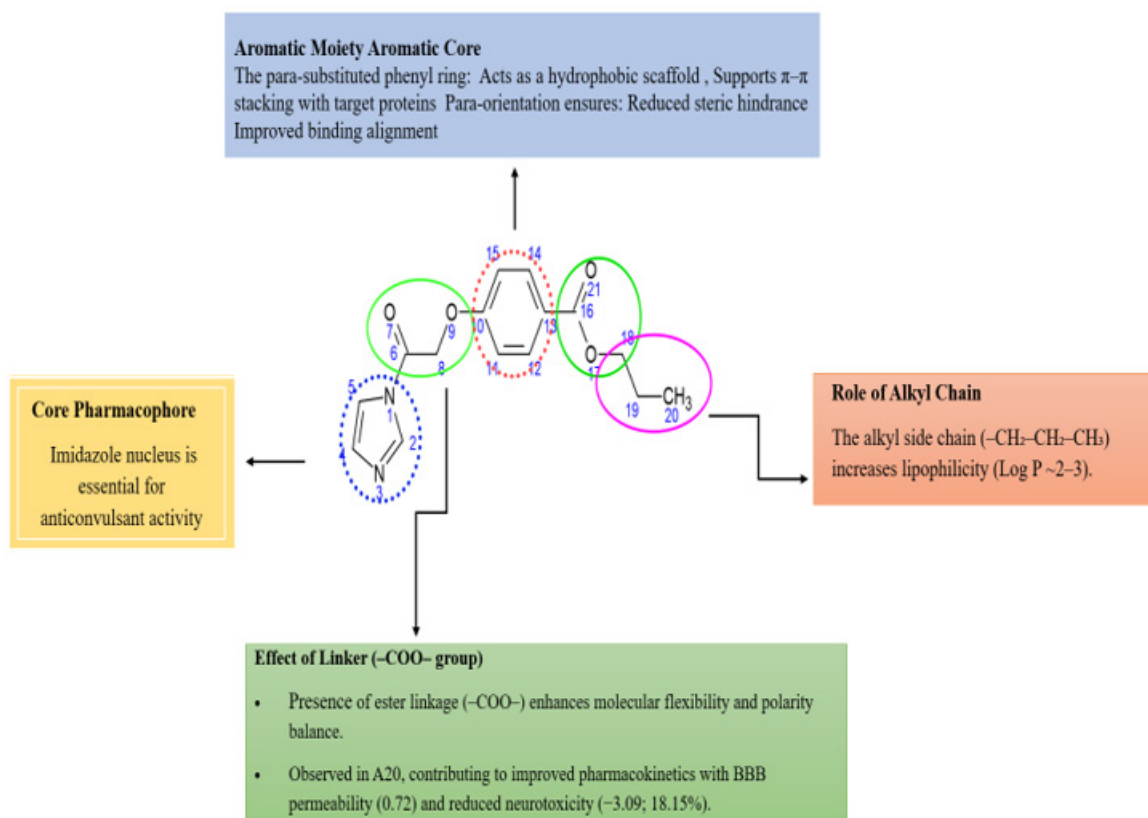
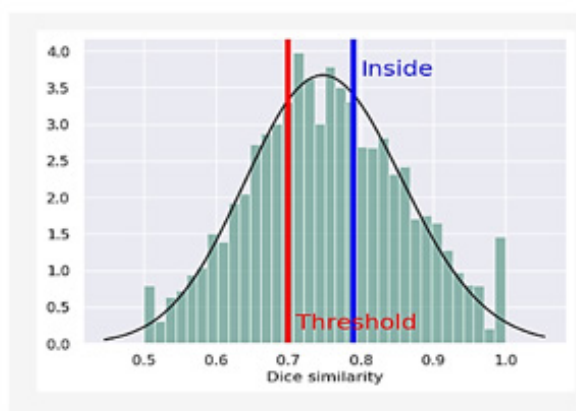


Figure 3: Acute Oral Toxicity Interpretation of the A21 by Stop tox.

Table 3: Predicted molecular targets of compound A20 with UniProt IDs and probability scores.

Sl. No.	Target Name	Common Name	UniProt ID	Target Class	Probability	Role in Anticonvulsant Activity
1.	GABA-A receptor ($\alpha 5/\beta 3/\gamma 2$)	GABRA5 / GABRB3 / GABRG2	P31644 / P28472 / P18507	Ligand-gated ion channel	0.0979	Enhances inhibitory neurotransmission, reduces neuronal excitability
2.	Metabotropic glutamate receptor 5	GRM5	P41594	GPCR (Family C)	0.0979	Reduces excitatory glutamate signaling
3.	Metabotropic glutamate receptor 4	GRM4	Q14833	GPCR (Family C)	0.0979	Modulates synaptic transmission
4.	Adenosine A1 receptor	ADORA1	P30542	GPCR (Family A)	0.0979	Suppresses neuronal firing, neuroprotective
5.	Adenosine A2A receptor	ADORA2A	P29274	GPCR (Family A)	0.0979	Regulates CNS excitability

**Figure 4:** Structure-Activity Relationship (SAR) of imidazole derivative A20, highlighting the impact of structural features on BBB penetration and neurotoxicity.

A21, $TPSA < 90 \text{ \AA}^2$ favours BBB penetration. The combined results of integrated SAR and STOPTOX testing identify A20 as a safe and effective candidate for CNS activity.

CONCLUSION

In the current work, pharmacokinetic and toxicology profiles of selected imidazoles have been studied using *in silico* techniques through SwissADME, pkCSM, admetSAR, and STOPTOX. The findings indicated that all compounds exhibited promising pharmaceutical behavior and ADMET characteristics. Among these compounds, A20 exhibited an optimal balance with good pharmacokinetics and brain penetration and minimum toxicity, whereas A21 possessed higher CNS penetration but more toxicity towards neurons. In summary, these results show that structural modifications of the imidazole scaffold will have positive effects on the ADMET properties of these drugs. Comparison with the reference drug phenytoin further demonstrated that the selected lead compounds possess physicochemical and ADMET profiles comparable to those of a clinically established antiepileptic drug. Therefore, compound A20 may serve as a promising lead candidate for further molecular docking, molecular dynamics

simulations, synthesis, and experimental *in vitro* and *in vivo* validation.

ACKNOWLEDGEMENT

The authors sincerely thank the Faculty of Pharmacy, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University (ACU), B.G. Nagara, for their support in the preparation of this research article.

ABBREVIATIONS

ADMET: Absorption, Distribution, Metabolism, Elimination, and Toxicity; **MW:** Molecular Weight; **TPSA:** Topological Polar Surface Area; **CNS:** Central Nervous System; **BBB:** Blood-Brain Barrier; **TPSA:** Topological polar surface area; **CNS:** Central nervous system; **BBB:** Blood-brain-barrier; **GABA:** Gamma-Aminobutyric Acid; **QSAR:** Quantitative Structure-Activity Relationship; **HBD:** Hydrogen Bond Donors; **HBA:** Hydrogen Bond Acceptors; **SMILES:** Simplified Molecular Input Line Entry System; **Log P:** Logarithm of the Partition Coefficient; **VD_{ss}:** Volume of Distribution at Steady State; **LD₅₀:** Median Lethal Dose; **MR:** Molar Refractivity; **NRB:** Number of

Rotatable Bonds; **SAR**: Structure-Activity Relationship; **BioS**: Bioavailability Score; **LIPO**: Lipophilicity; **SIZE**: Molecular Size; **POLAR**: Polarity; **INSOLU**: Solubility; **INSATU**: Saturation; **FLEX**: Flexibility.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Nagaraj AP, Nagaraju PK. *In silico* SAR-Guided Discovery of Imidazole-Based Anticonvulsants with Optimized ADMET Profiles. *Int. J. Pharm. Investigation*. 2027;17(1):283-91.