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Research Article

3D-QSAR and Molecular Docking Studies of Antiarrhythmic Activity of Cardiac Sodium Channel (PDB: 8F6P) with Simulation Dynamic on a Series of Phenytoin Derivatives

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ABSTRACT

Background: Cardiac arrhythmias are life-threatening disorders associated with abnormal electrical conduction in the heart, primarily regulated by ion channels such as the cardiac sodium channel (Nav1.5). In the present study, a series of phenytoin derivatives (MB-1 to MB-8) were designed and evaluated for their antiarrhythmic potential targeting the cardiac sodium channel 8F6P using integrated computational approaches, including 3D-QSAR, molecular docking, ADMET prediction, toxicity assessment, and molecular interaction analysis. **Materials and Methods:** Physicochemical evaluation revealed that all compounds complied with Lipinski's rule of five and Veber criteria, indicating good oral drug-likeness and bioavailability. ADMET profiling demonstrated high gastrointestinal absorption, non-permeability across the blood-brain barrier, and minimal inhibition of key cytochrome P450 enzymes for most derivatives, suggesting a favorable pharmacokinetic profile. Toxicity studies indicated that the majority of compounds belong to toxicity class 5 with high LD_{50} values (5000 mg/kg), reflecting low acute toxicity. **Results:** Molecular docking analysis showed that most derivatives exhibited stronger binding affinity than the standard drug (-8.7 kcal/mol), with MB-2 (-9.8 kcal/mol), MB-5 (-9.7 kcal/mol), and MB-7 (-9.6 kcal/mol) demonstrating the highest affinity. Interaction analysis revealed that hydrogen bonding, π-π stacking, hydrophobic interactions, and π-sulfur interactions play key roles in stabilizing ligand-protein complexes, particularly involving residues such as PHE399, MET395, LEU400, and THR1711. **Conclusion:** Overall, the study identifies MB-2, MB-5, and MB-7 as promising candidates with enhanced binding affinity, favorable pharmacokinetic properties, and acceptable safety profiles. These findings provide valuable insights for the rational design of novel antiarrhythmic agents and warrant further validation through molecular dynamics simulations and experimental studies.

Keywords: 3D-QSAR, ADMET prediction, Antiarrhythmic agents, Cardiac sodium channel, Drug-likeness, Molecular docking, Molecular dynamics simulation, Phenytoin derivatives, Structure-activity relationship, Toxicity prediction.

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INTRODUCTION

The exploration and synthesis of novel molecules with a wide range of pharmacological activities achievable through the modulation of a diverse spectrum of biochemical pathways (Andriana *et al*., 2019), holds great therapeutic potential in the therapeutic intervention of a wide range of pathological conditions (Jaysing *et al*., 2025). A major factor in the occurrence of mortality is cardiovascular disease. There are 25% of the death is due to arrhythmia (Nattel *et al*.,2008). Arrhythmia is defined as an abnormality in the electrical impulse during the cardiac cycle dynamics. The electrical activity of the cardiac cycle is regulated by the ion channels, such as sodium, potassium, and calcium channels. The abnormalities in the function of these channels may lead to arrhythmias (Roselli *et al*., 2016). The antiarrhythmic agents are used to treat arrhythmias. According to Vaughan William, antiarrhythmic agents are classified into four classes: sodium channel blockers, beta blockers, potassium channel blockers, and others. phenytoin, Mexilitin, and lidocaine, etc, are examples of the class 1(sodium channel blocker) antiarrhythmic agents (Kiec-Kononowicz, 2003). phenytoin (5,5-diphenylhydantoin-2,4-dione) has a Hydantoin ring with the two phenyl ring substituted at position 5. Phenytoin is mostly used in the treatment of partial seizures and tonic-clonic seizures. It also has other biological activities like anticancer, anti-inflammatory, and anti-immune, as well as antiarrhythmic agents. Mostly, the hydantoin derivatives are used as

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anticonvulsant agents (Wadghane *et al.*, 2023). The exordium for developing novel drugs with pleiotropic pharmacological effect are most successfully discovered in the field of pharmaceutical research that mitigates the need for polypharmacy, including strategies for treatment that simultaneously reduce iatrogenic side effects, eliminate symptoms to achieve the positive results through adjuvant therapeutic mechanisms (Andriana *et al.*, 2019). Even if they have a great potential for therapeutic use its crucial to consider the adverse effects (Syed *et al.*, 2020). The technique used to study how the protein and the ligand interact is called molecular docking, and it also explains the binding energy, binding interactions, and molecular interactions (Meng *et al.*, 2011). The purpose of the investigation was to determine molecular interaction between the phenytoin derivatives and cardiac sodium channel (PDB ID:8F6P)to treat the ventricular arrhythmia (Lenaeus *et al.*, 2023). As well as to screen the synthetic compounds, physicochemical properties, and ADMET Parameters. phenytoin shows a narrow therapeutic window; it also shows hepatotoxicity and multiple drug interactions, hence phenytoin is rarely used as an antiarrhythmic agent (Yager *et al.*, 2015). Currently, there is an inadequate treatment was Available for arrhythmia due to the adverse effects and side effects of the drugs (Steinberg *et al.*, 1986). Phenytoin is frequently used as a medication for the treatment of arrhythmia due to its narrow therapeutic windows, drug interactions, side effects. phenytoin is mostly absorbed theough the duodenum and primary metabolism is by the liver and eliminated through the urine (Chua *et al.*, 2000). The causes of arrhythmia includes factors like alcohol abuse, drug abuse, smoking, mental stress, hypertension, hyperthyroidism etc. (Dr Sumanta Mondal, 2018). the phenytoin derivatives shows anticonvulsant as well as antiarrhytmic activity (Czopek *et al.*, 2016).

MATERIALS AND METHODS

Molecular docking and ligand preparations

Preceding the molecular docking, for the synthesized novel derivatives. We optimized by using the semi-empirical approach and the Dockamon -PyRx 1.0 software program for the computational analysis. Getting proteins ready, we used a variety of different cardiac sodium channel receptors (PDB ID 8F6P), an enzyme crystal structure via the RCSB, for docking studies. Software was installed on an HP Probook 440 notebook pc -14 inch computer and has Intel Core i5 113547 @ 2.40 GHz with 8.00GB RAM. Drug likeness, physicochemical characteristics, and ADMET of compounds were studied. Dockamon Pyrex 1.0 version was used for docking. Chain A was chosen. The water molecules are removed, and the addition of the polar hydrogen is done. The Compounds' 2D structure was drawn using ChemDraw 12.0 versions, and Chem 3D Pro12.0 was used for minimizing the energy. Dockamon Pyrex 1.0 is used for the docking process, while the Discovery Studio 2025 client is used to visualize the interactions. phenytoin used as a standard to compare the novel derivatives. The protein structure is in Figures 1, 2. The molecular docking was performed for derivatives 1-8.

Protein Preparation

The integration of these computational methodologies allows for a comprehensive understanding of structure-activity relationships and molecular interactions at an atomic level. In this context, the present study focuses on a series of phenytoin derivatives to evaluate their antiarrhythmic potential through 3D-QSAR modeling, docking analysis against the cardiac sodium channel (PDB ID: 8F6P), and molecular dynamics simulations. This combined approach aims to identify key structural determinants responsible for activity, predict binding affinities, and assess the stability of ligand-protein complexes, ultimately contributing to the development of novel and effective antiarrhythmic agents.

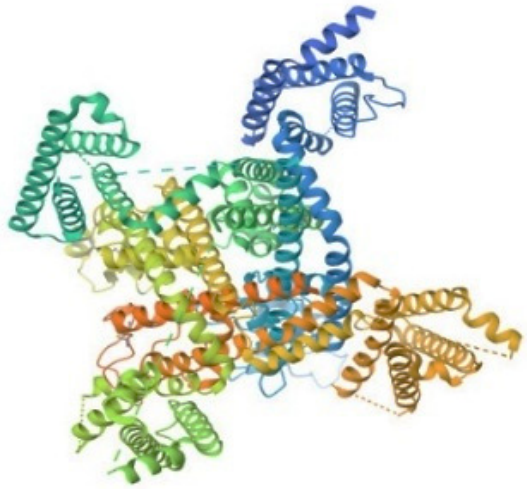


Figure 1: Protein structure (8F6P).

RESULTS

Toxicity Prediction and Safety Assessment

The toxicity profile of the designed phenytoin derivatives (MB-1 to MB-8) was evaluated using *in silico* predictive models, focusing on acute toxicity (LD_{50}), toxicity class, prediction accuracy, organ-specific toxicities, and interaction with the sodium channel receptor. These parameters are essential for assessing the safety and therapeutic viability of potential antiarrhythmic agents. The LD_{50} values indicate that most compounds (MB-1, MB-2, MB-3, MB-4, MB-7, and MB-8) fall within 5000 mg/kg, corresponding to toxicity class 5**,** which suggests relatively low acute toxicity. In contrast, MB-5 and MB-6 exhibited lower LD_{50} values (1690 mg/kg), placing them in toxicity class 3, indicating moderate toxicity. Despite this, their toxicity levels

remain within an acceptable range for drug candidates, provided careful dose optimization is considered. The prediction accuracy was consistent (54.26%) for most compounds, except for MB-6, which showed a higher accuracy (67.38%), indicating greater confidence in its predicted toxicity profile. This enhances the reliability of toxicity predictions for MB-6 compared to the rest of the series. In terms of organ-specific toxicity, most compounds demonstrated a predominantly Inactive (I) profile for hepatotoxicity, nephrotoxicity, and cardiotoxicity, which is a favorable characteristic. However, MB-5 and MB-6 showed active (A) predictions for hepatotoxicity and neurotoxicity, suggesting a potential risk of liver and nervous system-related adverse effects. These findings highlight the need for cautious optimization of these derivatives. Neurotoxicity predictions indicated that several compounds (MB-1, MB-2, MB-3, and MB-7) may exhibit activity, whereas MB-4 and MB-8 showed inactive behavior, suggesting comparatively safer neurological profiles. Nephrotoxicity was predicted to be inactive for most compounds, although MB-7 displayed slightly higher activity probability, warranting further investigation. Importantly, cardiotoxicity predictions were inactive for all compounds, which is particularly desirable given the target application in cardiac arrhythmias. This suggests that the designed derivatives are unlikely to induce adverse cardiac effects beyond their intended pharmacological action. The interaction with the sodium channel receptor revealed mixed activity profiles. MB-1 showed active interaction, supporting its potential efficacy as a sodium channel blocker, whereas most other compounds demonstrated inactive predictions, indicating the need for further validation through molecular docking and dynamic simulations. Overall, the toxicity assessment suggests that the majority of the compounds possess a favorable safety profile with low acute toxicity and minimal organ-specific risks. Among the series, MB-1, MB-2, MB-3, and MB-4 appear safer due to their higher LD_{50} values and largely inactive toxicity predictions. MB-6, despite moderate toxicity, stands out due to higher prediction reliability, while MB-5 requires careful consideration due to its relatively increased toxicity risks.

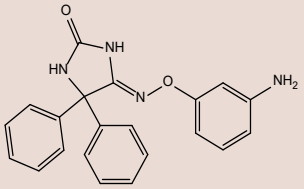
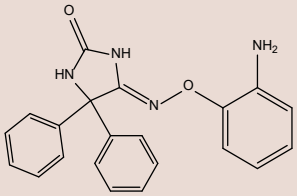
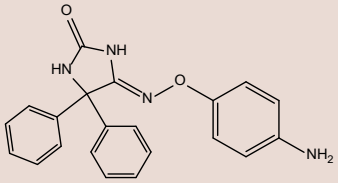
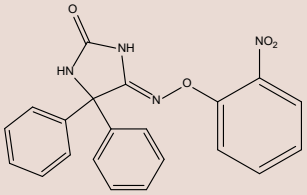
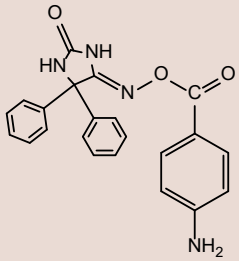
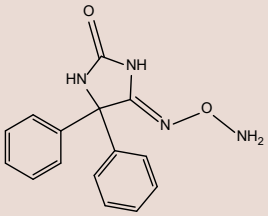
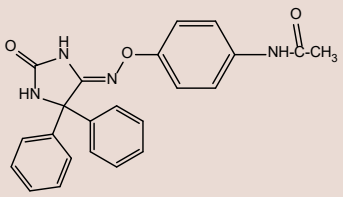
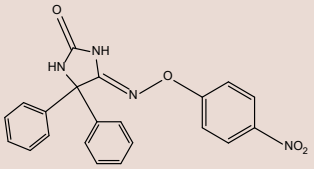
Physicochemical and Drug-Likeness Analysis

The evaluation of physicochemical and drug-likeness properties plays a crucial role in determining the suitability of compounds for further development as therapeutic agents. In the present study, a series of phenytoin derivatives (MB-1 to MB-8) was assessed based on key parameters, including rotatable bonds, Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD), consensus Log P, Lipinski's rule of five, Veber criteria, and synthetic accessibility. All the studied molecules demonstrated zero violations of Lipinski's rule of five, indicating favorable drug-likeness characteristics such as appropriate molecular weight, lipophilicity, and hydrogen bonding capacity. Similarly, none of the compounds showed any Veber rule violations, suggesting good oral bioavailability attributed to acceptable flexibility and polar surface properties. These findings collectively indicate that the entire dataset possesses desirable pharmacokinetic attributes for oral drug candidates. The number of rotatable bonds, which reflects molecular flexibility, ranged from 2 to 6. Compounds such as MB-5 and MB-6 exhibited lower flexibility (2 and 3 rotatable bonds, respectively), which may contribute to better binding specificity and reduced entropic penalties upon interaction with the target protein. In contrast, MB-7 showed the highest flexibility with 6 rotatable bonds, which could enhance conformational adaptability but may slightly affect binding stability. Hydrogen bonding characteristics are essential for ligand-protein interactions. The HBA values ranged from 2 to 5, while the HBD values varied between 2 and 3. Compounds MB-4 and MB-8 exhibited higher HBA values (5), which may facilitate stronger hydrogen bonding interactions with the active site residues of the cardiac sodium channel. Meanwhile, a balanced HBA and HBD profile in compounds such as MB-1, MB-2, and MB-3 suggests optimal interaction potential without excessive polarity. The consensus Log P values, ranging from 1.72 to 3.22, indicate moderate lipophilicity across all derivatives. This range is considered optimal for membrane permeability and absorption. Notably, MB-6 showed the lowest Log P (1.72), suggesting higher hydrophilicity, which may improve solubility but could limit membrane permeability. On the other hand, MB-5 exhibited the highest Log P (3.22), reflecting enhanced lipophilicity that may favor membrane penetration. Synthetic Accessibility (SA) scores varied between 2.20 and 3.43, indicating that all compounds are relatively easy to synthesize. MB-5 demonstrated the lowest SA score (2.20), suggesting it is the most synthetically feasible candidate, whereas MB-4 showed a slightly higher value (3.43), indicating moderate synthetic complexity. Overall, the analyzed dataset exhibits a favorable balance between physicochemical properties, drug-likeness, and synthetic feasibility. Among the compounds, MB-5 stands out due to its optimal lipophilicity, minimal flexibility, and highest synthetic accessibility, making it a promising candidate for further molecular docking and dynamic simulation studies. Conversely, compounds such as MB-4 and MB-8, with higher hydrogen bonding capacity, may offer enhanced interaction potential with the target protein. These results provide a strong foundation for subsequent structure-based studies, including molecular docking and molecular dynamics simulations, to further elucidate the binding behavior and stability of these phenytoin derivatives against the cardiac sodium channel target.

ADMET and Pharmacokinetic Profile

The pharmacokinetic and toxicity profile of drug candidates is a critical determinant in their success during drug development. In the present study, ADMET-related parameters of phenytoin derivatives (MB-1 to MB-8) were systematically evaluated, including bioavailability score, skin permeability (Log Kp), Cytochrome P450 (CYP) enzyme inhibition, Blood-Brain Barrier

Table 1: Structural data of the derivatives.

Code	Structure	Smiles
MB-1		NC1=CC(O/N=C(N2)/C(C3=CC=CC=C3)(C4=CC=CC=C4)NC2=O)=CC=C1
MB-2		O=C(NC/1(C2=CC=CC=C2)C3=CC=CC=C3)NC1=N/OC4=CC=CC=C4N
MB-3		O=C(NC/1(C2=CC=CC=C2)C3=CC=CC=C3)NC1=N/OC4=CC=C(N)C=C4
MB-4		O=C(NC/1(C2=CC=CC=C2)C3=CC=CC=C3)NC1=N/OC4=CC=CC=C4[N+]([O-])=O
MB-5		O=C(NC/1(C2=CC=CC=C2)C3=CC=CC=C3)NC1=N/OC(C4=CC=C(N)C=C4)=O
MB-6		O=C(NC/1(C2=CC=CC=C2)C3=CC=CC=C3)NC1=N/ON
MB-7		O=C(NC/1(C2=CC=CC=C2)C3=CC=CC=C3)NC1=N/OC4=CC=C(NC(C)=O)C=C4
MB-8		O=C(NC/1(C2=CC=CC=C2)C3=CC=CC=C3)NC1=N/OC4=CC=C([N+]([O-])=O)C=C4

(BBB) permeability, and Gastrointestinal (GI) absorption. All the compounds exhibited a bioavailability score of 0.55, indicating a favorable probability of achieving adequate systemic exposure upon oral administration. This uniformity across the dataset suggests that structural modifications within the series did not adversely impact overall bioavailability. The skin permeability coefficient (Log Kp) values ranged from -6.38 to -5.41 cm/s. These negative values indicate low transdermal permeability, which is typical for orally administered drugs. Among the compounds, MB-5 showed relatively higher permeability (-5.41 cm/s), whereas MB-6 and MB-7 exhibited lower permeability (-6.38 and -6.29 cm/s, respectively), suggesting limited dermal absorption potential. Cytochrome P450 enzyme inhibition is an essential parameter for predicting drug-drug interaction risks. Most compounds were found to be non-inhibitors of CYP3A4 and CYP2D6, which is advantageous as these enzymes are primarily responsible for drug metabolism. However, certain derivatives such as MB-3, MB-4, MB-7, and MB-8 demonstrated inhibitory activity against CYP2C9 and CYP2C19, which may increase the likelihood of metabolic interactions. Additionally, MB-1, MB-2, MB-3, MB-4, and MB-8 showed inhibition of CYP1A2, whereas MB-5 and MB-6 did not inhibit this isoform, indicating a comparatively safer metabolic profile. None of the compounds were predicted to be BBB permeant**,** suggesting limited Central Nervous System (CNS) penetration. This characteristic may be beneficial for antiarrhythmic agents, as reduced CNS exposure can minimize neurological side effects. All derivatives demonstrated high Gastrointestinal (GI) absorption, which supports their suitability for oral administration. This finding is consistent with their compliance with Lipinski and Veber rules, as discussed previously. Overall, the ADMET analysis indicates that the majority of the compounds possess a favorable pharmacokinetic profile with good oral absorption and minimal CYP-related liabilities. Among the series, MB-6 emerges as a particularly promising candidate due to its non-inhibitory behavior across all evaluated CYP isoforms, acceptable permeability, and high GI absorption. In contrast, compounds such as MB-3, MB-4, MB-7, and MB-8 may require further optimization to reduce potential drug-drug interaction risks associated with CYP2C9 and CYP2C19 inhibition. These findings provide valuable insights into the pharmacokinetic behavior of the studied compounds and support their Further evaluation through molecular docking and molecular dynamics simulations to confirm their therapeutic potential.

Molecular Docking Score Analysis

The molecular docking scores of the designed phenytoin derivatives (MB-1 to MB-8) were compared with the standard reference compound against the cardiac sodium channel 8F6P to evaluate their binding affinity. Docking score is a crucial parameter that reflects the strength of ligand-protein interaction, where more negative values indicate stronger binding and higher affinity toward the target receptor. The standard compound exhibited a docking score of -8.7 kcal/mol**,** which served as a baseline for comparison. Notably, the majority of the designed derivatives demonstrated better binding affinity than the standard, indicating successful structural optimization of the phenytoin scaffold. Among all compounds, MB-2 (-9.8 kcal/mol) showed the highest binding affinity**,** followed closely by MB-5 (-9.7 kcal/mol) and MB-7 (-9.6 kcal/mol)**.** These compounds exhibited significantly improved docking scores compared to the standard, suggesting strong and stable interactions within the active site of the sodium channel. The superior performance of MB-2 can be attributed to its multiple hydrogen bonds and extensive hydrophobic interactions observed in the docking interaction analysis. Compounds MB-4 (-9.4 kcal/mol) and MB-1 (-9.3 kcal/mol) also demonstrated favorable binding affinities, supported by a combination of hydrogen bonding and π-π stacking interactions with key amino acid residues. Similarly, MB-3 (-9.2 kcal/mol) showed good binding potential, although slightly lower than the top-performing derivatives due to fewer stabilizing interactions. On the other hand, MB-8 (-8.9 kcal/mol) exhibited a docking score close to the standard, indicating moderate binding affinity. In contrast, MB-6 (-8.1 kcal/mol) showed the lowest binding affinity among the series, even lower than the standard compound, suggesting weaker interaction with the receptor. This

Table 2: Toxicity Prediction and Safety Assessment.

Comp. Code	LD_{50} (mg/kg)	Toxicity class	Prediction accuracy %	Hepatotoxicity	Neurotoxicity	nephrotoxicity	cardiotoxicity	Sodium channel Receptor
MB-1	5000	5	54.26	I(0.72)	A(0.63)	I(0.58)	I(0.73)	A(O.58)
MB-2	5000	5	54.26	I(0.71)	A(0.62)	I(0.58)	I(0.73)	I(0.55)
MB-3	5000	5	54.26	I(0.72)	A(0.63)	I(0.58)	I(0.73)	I(0.58)
MB-4	5000	5	54.26	I(0.64)	I(0.65)	I(0.61)	I(0.74)	I(0.67)
MB-5	1690	3	54.26	A(0.70)	A(0.52)	I(0.56)	I(0.72)	I(0.57)
MB-6	1690	3	67.38	A(0.72)	A(0.61)	I(0.50)	I(0.74)	I(0.57)
MB-7	5000	5	54.26	I(0.70)	A(0.54)	I(0.65)	I(0.76)	I(0.54)
MB-8	5000	5	54.26	I(0.65)	I(0.64)	I(0.61)	I(0.71)	I(0.71)

may be due to differences in its binding orientation or reduced hydrophobic interactions within the active site (Tables 1-7).

Overall, the docking score trend can be summarized as: MB-2 > MB-5 > MB-7 > MB-4 > MB-1 > MB-3 > MB-8 > Standard > MB-6 These findings

clearly indicate that most of the designed compounds possess enhanced binding affinity compared to the reference drug. In particular, MB-2, MB-5, and MB-7 emerge as the most promising candidates based on their superior docking scores and favorable interaction profiles.

Molecular Docking Interaction Analysis

The molecular docking study of the phenytoin derivatives (MB-1 to MB-8) with the cardiac sodium channel 8F6P provided detailed insights into ligand-protein binding interactions, including hydrogen bonding, hydrophobic contacts, and π-related interactions. These interactions play a crucial role in stabilizing the ligand within the active site and influencing biological activity. Hydrogen bonds are key contributors to binding specificity and stability. Among the studied compounds, MB-2, MB-4, MB-6, and MB-8 exhibited strong and multiple hydrogen bonding interactions. MB-2 formed three conventional hydrogen bonds with LEU1659 and PHE399, indicating strong anchoring within the binding pocket. MB-4 showed multiple hydrogen bonds involving GLY1663, PHE1660, and PHE399, suggesting enhanced binding stability. In contrast, MB-3 and MB-5 showed limited or no conventional hydrogen bonding, suggesting comparatively weaker electrostatic interactions. Hydrophobic interactions were predominant across all compounds and contributed significantly to binding affinity. Aromatic residues such as PHE399, PHE1667, and PHE1762 were frequently involved in π-π stacking interactions, which stabilize the ligand within the hydrophobic pocket. Additionally, π-alkyl interactions with residues like LEU400, VAL1766, and LEU1464 were observed in most compounds, further enhancing hydrophobic stabilization. Interactions involving sulfur-containing residues such as MET395 and MET1670 were consistently observed in several compounds (MB-1, MB-2, MB-3, MB-4, MB-5, and MB-7). These π-sulfur interactions contribute to binding affinity and are particularly relevant in stabilizing ligands within ion channel proteins. Compounds MB-1 and MB-7 exhibited amide-π stacked interactions involving residues such as ILE1662 and GLY1663. These interactions further enhance ligand orientation and contribute to the overall stability of the complex. The docking results indicate that hydrogen bonding combined with aromatic and hydrophobic interactions plays a crucial role in stabilizing the ligand-protein complex. Residues such as PHE399, MET395, LEU400, and THR1711 appear to be key contributors within the active site of the cardiac sodium

Table 3: Physicochemical and Drug-Likeness Analysis.

Molecule	Rotatable bonds	HBA	HBD	Consensus Log P	Lipinski violation	Veber violations	Synthetic accessibility
MB-1	4	3	3	2.96	0	0	3.28
MB-2	4	3	3	2.98	0	0	3.32
MB-3	4	3	3	3.02	0	0	3.23
MB-4	5	5	2	2.75	0	0	3.43
MB-5	2	2	2	3.22	0	0	2.20
MB-6	3	4	3	1.72	0	0	2.89
MB-7	6	4	3	3.06	0	0	3.36
MB-8	5	5	2	2.75	0	0	3.27

Table 4: ADMET and Pharmacokinetic Profile.

Molecule	Bioavaibilty score	Log kp (cm/s)	CYP3A4 inhibitor	CYP2D6 inhibitor	CYP2C9 inhibitor	CYP2C19 inhibitor	CYP1A2 inhibitor	BBB Permeant	GI Absorption
MB-1	0.55	-5.94	NO	NO	NO	NO	YES	NO	HIGH
MB-2	0.55	-5.94	NO	NO	NO	NO	YES	NO	HIGH
MB-3	0.55	-5.70	NO	NO	YES	YES	YES	NO	HIGH
MB-4	0.55	-5.76	NO	NO	YES	YES	YES	NO	HIGH
MB-5	0.55	-5.41	NO	YES	NO	NO	NO	NO	HIGH
MB-6	0.55	-6.38	NO	NO	NO	NO	NO	NO	HIGH
MB-7	0.55	-6.29	NO	NO	YES	YES	NO	NO	HIGH
MB-8	0.55	-5.76	NO	NO	YES	YES	YES	NO	HIGH

Figure 2: Docking graph with derivatives.

Table 5: Molecular Docking Score Analysis.

Analouge	Docking score
Standard	-8.7
MB-1	-9.3
MB-2	-9.8
MB-3	-9.2
MB-4	-9.4
MB-5	-9.7
MB-6	-8.1
MB-7	-9.6
MB-8	-8.9

channel. Among the studied derivatives, MB-4, MB-6, and MB-8 emerge as promising candidates due to their strong and diverse interaction profiles, suggesting enhanced binding affinity and potential antiarrhythmic activity. These findings align well with physicochemical and ADMET results, supporting their selection for further validation through molecular dynamics simulations. Overall, the docking analysis provides a comprehensive understanding of the molecular basis of ligand binding and highlights critical structural features required for the design of potent sodium channel blockers.

DISCUSSION

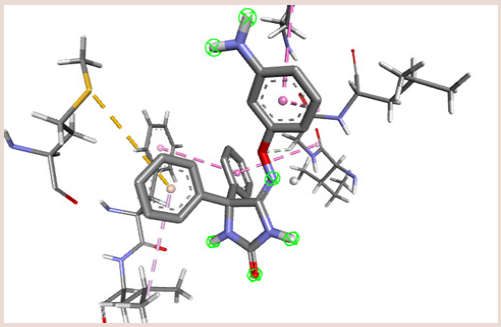
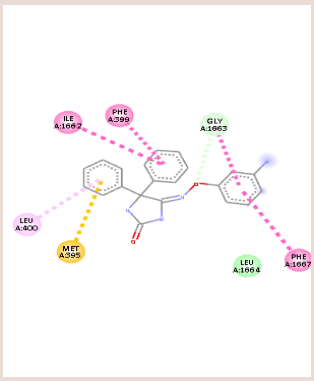
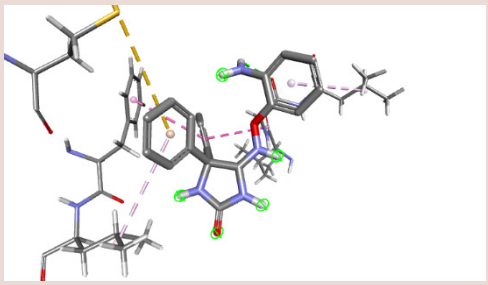
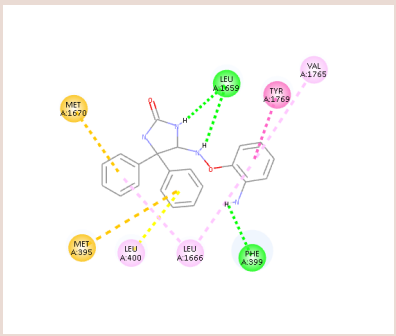
The present study integrates multiple computational techniques to evaluate the antiarrhythmic potential of phenytoin derivatives against the cardiac sodium channel. The combined analysis of physicochemical properties, ADMET profile, toxicity prediction, and molecular docking provides a comprehensive understanding of structure-activity relationships. All compounds demonstrated excellent compliance with drug-likeness rules, confirming their suitability as orally active agents. The moderate Log P values and optimal hydrogen bonding parameters suggest a balanced hydrophilic-lipophilic profile, which is essential for membrane permeability and receptor interaction. Notably, compounds such as MB-5 and MB-6, with lower rotatable bonds, exhibited reduced molecular flexibility, which may enhance binding specificity. The ADMET analysis further supports the drug-like nature of the compounds. High gastrointestinal absorption across all derivatives indicates good oral bioavailability, while the absence of BBB permeability suggests reduced central nervous system side effects, which is advantageous for cardiovascular drugs. Additionally, minimal inhibition of major CYP enzymes (especially CYP3A4 and CYP2D6) reduces the likelihood of drug-drug interactions. However, certain compounds (MB-3, MB-4, MB-7, and MB-8) showed inhibition of CYP2C9 and CYP2C19, indicating the need for further optimization. Toxicity prediction results revealed that most compounds possess low acute toxicity (class 5), making them relatively safe candidates. Although MB-5 and MB-6 showed moderate toxicity (class 3), their profiles remain acceptable with proper dose regulation. Importantly, all compounds were predicted to be non-cardiotoxic, which is critical for antiarrhythmic drug development. Molecular docking results demonstrated that structural modifications significantly enhanced binding affinity compared to the standard drug. MB-2 emerged as the most potent compound, supported by strong hydrogen bonding and hydrophobic interactions. The presence of key interactions such as π-π stacking with aromatic

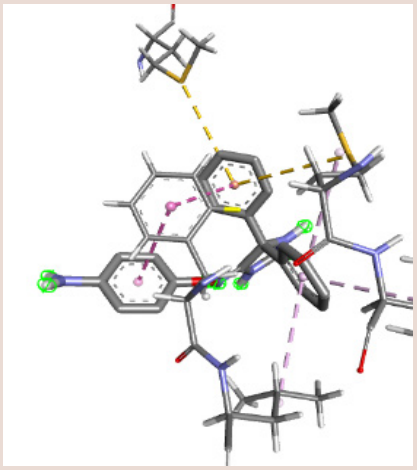
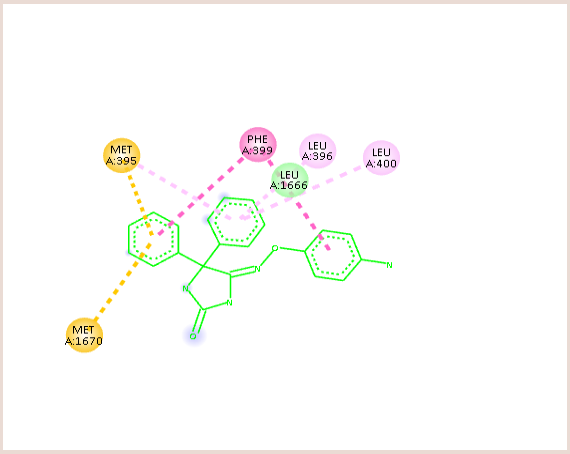
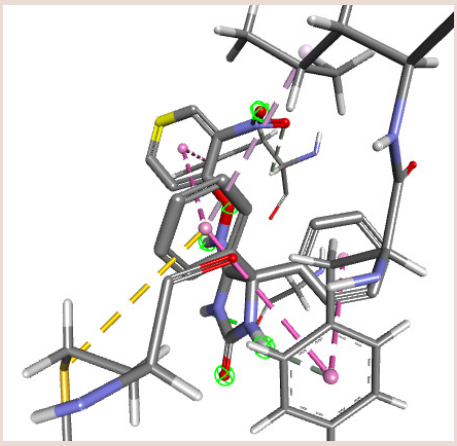
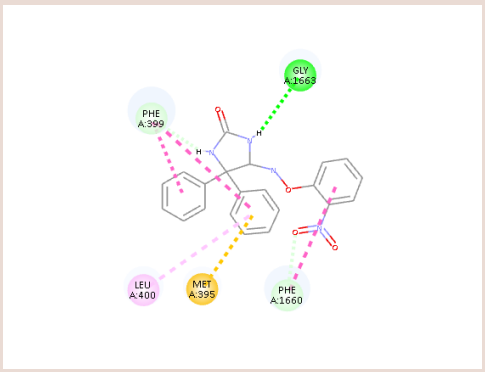
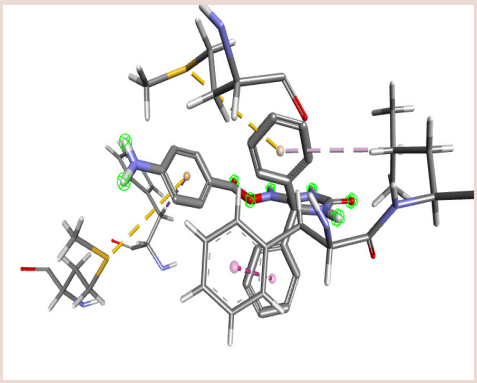
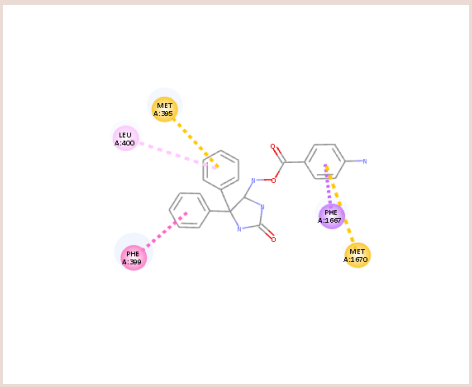
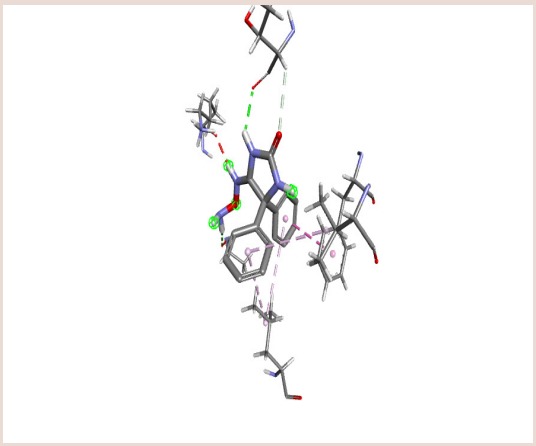
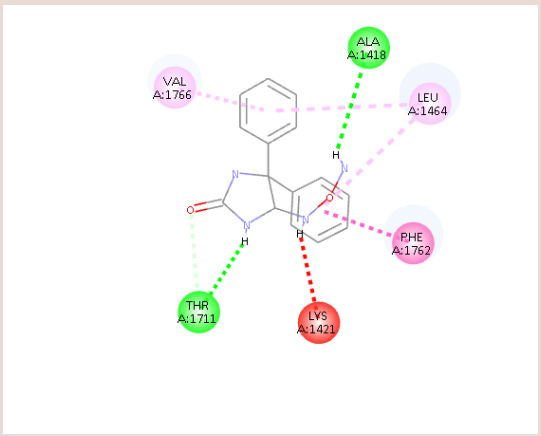
Table 6: Chemical interactions between the amino acids and chemicals.

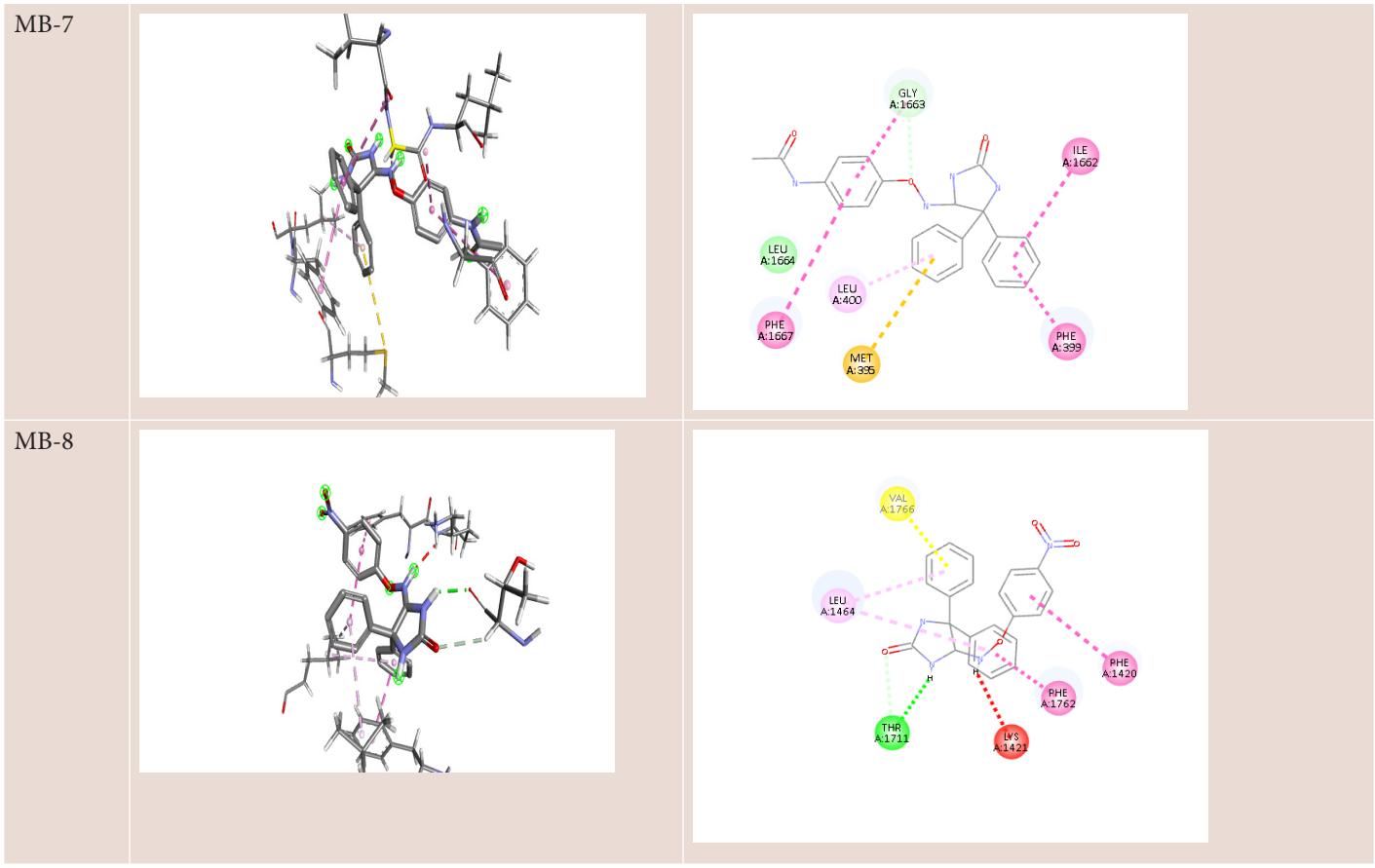
MB-1			
GLY1663	2.52833	Hydrogen Bond	Carbon Hydrogen Bond
MET395	5.07121	Other	Pi-Sulfur
PHE399	4.33634	Hydrophobic	Pi-Pi Stacked
PHE1667	5.68692	Hydrophobic	Pi-Pi Stacked
ILE1662:GLY1663	4.74659	Hydrophobic	Amide-Pi Stacked
GLY1663:LEU1664	4.01296	Hydrophobic	Amide-Pi Stacked
LEU400	5.07421	Hydrophobic	Pi-Alkyl
MB-2			
LEU1659	2.36827	Hydrogen Bond	Conventional Hydrogen Bond
LEU1659	2.5846	Hydrogen Bond	Conventional Hydrogen Bond
PHE399	2.09307	Hydrogen Bond	Conventional Hydrogen Bond
MET395	5.31883	Other	Pi-Sulfur
MET1670	5.09345	Other	Pi-Sulfur
TYR1769	5.07768	Hydrophobic	Pi-Pi Stacked
LEU1666	5.23828	Hydrophobic	Pi-Alkyl
LEU400	5.01235	Hydrophobic	Pi-Alkyl
LEU1666	5.48371	Hydrophobic	Pi-Alkyl
VAL1765	5.33056	Hydrophobic	Pi-Alkyl
MB-3			
MET395	5.08002	Other	Pi-Sulfur
MET1670	4.9839	Other	Pi-Sulfur
PHE399	4.44085	Hydrophobic	Pi-Pi Stacked
MET395	5.21227	Hydrophobic	Pi-Alkyl
LEU396	5.09972	Hydrophobic	Pi-Alkyl
LEU400	5.10869	Hydrophobic	Pi-Alkyl
MB-4			
GLY1663	2.73538	Hydrogen Bond	Conventional Hydrogen Bond
PHE1660	3.00854	Hydrogen Bond	Carbon Hydrogen Bond
PHE399	2.74398	Hydrogen Bond	Pi-Donor Hydrogen Bond
MET395	4.96578	Other	Pi-Sulfur
PHE399	4.97634	Hydrophobic	Pi-Pi Stacked
PHE399	5.02917	Hydrophobic	Pi-Pi Stacked
PHE1660	5.38613	Hydrophobic	Pi-Pi T-shaped
LEU400	5.22736	Hydrophobic	Pi-Alkyl
MB-5			
PHE1667	2.65312	Hydrophobic	Pi-Sigma
MET395	5.10189	Other	Pi-Sulfur
MET1670	5.16027	Other	Pi-Sulfur
PHE399	4.43818	Hydrophobic	Pi-Pi Stacked
LEU400	5.12703	Hydrophobic	Pi-Alkyl
MB-6			
THR1711	2.22704	Hydrogen Bond	Conventional Hydrogen Bond

ALA1418	2.82861	Hydrogen Bond	Conventional Hydrogen Bond
THR1711	2.92847	Hydrogen Bond	Carbon Hydrogen Bond
PHE1762	3.9783	Hydrophobic	Pi-Pi Stacked
LEU1464	5.11533	Hydrophobic	Pi-Alkyl
VAL1766	5.036	Hydrophobic	Pi-Alkyl
LEU1464	5.49529	Hydrophobic	Pi-Alkyl
MB-7			
GLY1663.	2.34454	Hydrogen Bond	Carbon Hydrogen Bond
MET395	5.18476	Other	Pi-Sulfur
PHE399	4.5149	Hydrophobic	Pi-Pi Stacked
PHE1667	5.88957	Hydrophobic	Pi-Pi Stacked
ILE1662:GLY1663	4.68286	Hydrophobic	Amide-Pi Stacked
GLY1663:LEU1664	3.8798	Hydrophobic	Amide-Pi Stacked
LEU400	5.07306	Hydrophobic	Pi-Alkyl
MB-8			
THR1711	2.02078	Hydrogen Bond	Conventional Hydrogen Bond
THR1711	2.70141	Hydrogen Bond	Carbon Hydrogen Bond
PHE1762	3.99845	Hydrophobic	Pi-Pi Stacked
PHE1420	4.19334	Hydrophobic	Pi-Pi T-shaped
LEU1464	5.47286	Hydrophobic	Pi-Alkyl
VAL1766	4.69414	Hydrophobic	Pi-Alkyl
LEU1464	5.48036	Hydrophobic	Pi-Alkyl

Table 7: 2D and 3D interaction with Chemical interactions between the amino acids and chemicals.

Code	3D Image	2D Image
MB-1		
MB-2		

MB-3		
MB-4		
MB-5		
MB-6		



residues (PHE399, PHE1667) and π-sulfur interactions with MET395 contributed to the stabilization of ligand-protein complexes. Furthermore, residues such as GLY1663, LEU400, THR1711, and MET1670 were consistently involved in ligand binding, indicating their importance in the active site of the sodium channel. Compounds MB-4, MB-6, and MB-8 demonstrated strong hydrogen bonding interactions, which enhance binding specificity, whereas MB-1 and MB-7 showed stable hydrophobic and amide-π interactions. Overall, the results highlight that a combination of hydrogen bonding and hydrophobic interactions is essential for effective sodium channel inhibition. The improved docking scores and interaction profiles of MB-2, MB-5, and MB-7 strongly support their potential as lead candidates for further development.

CONCLUSION

In this study, a series of phenytoin derivatives were successfully designed and evaluated using an integrated computational approach targeting the cardiac sodium channel 8F6P. The results demonstrate that all compounds possess favorable drug-likeness properties, good pharmacokinetic profiles, and acceptable toxicity levels. Molecular docking analysis revealed that most derivatives exhibit stronger binding affinity than the standard drug, with MB-2, MB-5, and MB-7 identified as the most promising candidates. These compounds showed stable interactions within the active site through hydrogen bonding, hydrophobic interactions, and π-related interactions. The overall findings suggest that structural modification of the phenytoin scaffold can significantly enhance antiarrhythmic activity while maintaining safety and pharmacokinetic suitability. This study provides a strong foundation for further validation through molecular dynamics simulations and *in vitro*/*in vivo* experimental studies. In conclusion, the identified lead compounds have the potential to serve as effective and safer alternatives for the treatment of cardiac arrhythmias.

ACKNOWLEDGEMENT

None.

ABBREVIATIONS

3D-QSAR: 3-Dimensional Quantitative Structure-Activity Relationship; **ADMET:** Absorption, Distribution, Metabolism, Excretion, and Toxicity; **PDB:** Protein Data Bank; **RCSB:** Research Collaboratory for Structural Bioinformatics; **LD_{50}:** Median Lethal Dose.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Andriana, Y., Xuan, T. D., Quy, T. N., Minh, T. N., Van, T. M., and Viet, T. D. (2019). Antihyperuricemia, Antioxidant, and Antibacterial Activities of Tridax procumbens L. Foods, 8(1), 21. https://doi.org/10.3390/foods8010021

Chua, H. C., Venketasubramanian, N., Tjia, H., and Chan, S. P. (2000). Elimination of phenytoin in toxic overdose. Clinical Neurology and Neurosurgery, 102(1), 6-8. https://doi.org/10.1016/S0303-8467(99)00074-8

Czopek, A., Byrtus, H., Zagórska, A., Siwek, A., Kazek, G., Bednarski, M., Sapa, J., and Pawłowski, M. (2016). Design, synthesis, anticonvulsant, and antiarrhythmic properties of novel N-Mannich base and amide derivatives of β-tetralinohydantoin. Pharmacological Reports, 68(5), 886-893. https://doi.org/10.1016/j.pharep.2016.04.018

Dr Sumanta Mondal. (2018). PPH 308: MEDICINAL CHEMISTRY-II_Unit: I: Anti-arrhythmic drugs. https://doi.org/10.13140/RG.2.2.35530.00965

Kiec-Kononowicz, K. (2003). Synthesis, structure and antiarrhythmic properties evaluation of new basic derivatives of 5,5-diphenylhydantoin. European Journal of Medicinal Chemistry, 38(6), 555-566. https://doi.org/10.1016/S0223-5234(03)00075-8

Lenaeus, M., Gamal El-Din, T. M., Tonggu, L., Zheng, N., and Catterall, W. A. (2023). Structural basis for inhibition of the cardiac sodium channel by the atypical antiarrhythmic drug ranolazine. Nature Cardiovascular Research, 2(6), 587-594. https://doi.org/10.1038/s44161-023-00271-5

Meng, X.-Y., Zhang, H.-X., Mezei, M., and Cui, M. (2011). Molecular docking: A powerful approach for structure-based drug discovery. Current Computer-Aided Drug Design, 7(2), 146-157. https://doi.org/10.2174/157340911795677602

Nattel, S., Duker, G., and Carlsson, L. (2008). Model systems for the discovery and development of antiarrhythmic drugs. Progress in Biophysics and Molecular Biology, 98(2-3), 328-339. https://doi.org/10.1016/j.pbiomolbio.2008.10.009

Rohit Jaysing, B., Jyoti Ramkisan, B., Kamran Mehboob, S., Pratibha Shankar, J., Swapnali Baban, A., Madhuri Rajendra, L., Harshada Subhash, B., Sakshi Murlidhar, S., Saisha Rajendra, K., Pranav Dada, B., and Pradnya Dnyaneshwar, B. (2025). 3D-QSAR and Molecular Docking studies of COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) Enzyme Inhibitors with Simulation Dynamic on Series of Benzimidazole Derivatives. International Journal of Zoological Investigations, 11(2), 1218-1232. https://doi.org/10.33745/ijzi.2025.v11i02.121

Roselli, M., Carocci, A., Budriesi, R., Micucci, M., Toma, M., Di Cesare Mannelli, L., Lovece, A., Catalano, A., Cavalluzzi, M. M., Bruno, C., De Palma, A., Contino, M., Perrone, M. G., Colabufo, N. A., Chiarini, A., Franchini, C., Ghelardini, C., Habtemariam, S., and Lentini, G. (2016). Synthesis, antiarrhythmic activity, and toxicological evaluation of mexiletine analogues. European Journal of Medicinal Chemistry, 121, 300-307. https://doi.org/10.1016/j.ejmech.2016.05.046

Steinberg, M. I., Lacefield, W. B., and Robertson, D. W. (1986). Chapter 10. Class I and III Antiarrhythmic Drugs. In Annual Reports in Medicinal Chemistry (Vol. 21, pp. 95-108). Elsevier. https://doi.org/10.1016/S0065-7743(08)61120-3

Syed, A., Benit, N., Alyousef, A. A., Alqasim, A., and Arshad, M. (2020). *In vitro* antibacterial, antioxidant potentials and cytotoxic activity of the leaves of Tridax procumbens. Saudi Journal of Biological Sciences, 27(2), 757-761. https://doi.org/10.1016/j.sjbs.2019.12.031

Wadghane, S., Bhor, R., Shinde, G., Kolhe, M., and Rathod, P. (2023). A Review on the Some Biological Activities of the Hydantoin Derivatives. Journal of Drug Delivery and Therapeutics, 13(1), 171-178. https://doi.org/10.22270/jddt.v13i1.5904

Yager, N., Wang, K., Keshwani, N., and Torosoff, M. (2015). Phenytoin as an effective treatment for polymorphic ventricular tachycardia due to QT prolongation in a patient with multiple drug intolerances. BMJ Case Reports, 2015, bcr2015209521. https://doi.org/10.1136/bcr-2015-209521

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