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1,2-Di(cyclopenta-2,4-dien-1-yl)ethane Derivatives as Potential Anti-Ischemic Agents

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Abstract

Ischemic heart disease (IHD) remains a leading global health challenge, necessitating the development of safer and more effective anti-ischemic agents. This study investigates the therapeutic potential of hypothetical di(cyclopenta-2,4-dien-1-yl)ethane derivatives using in-silico modeling, toxicity predictions, and molecular docking studies. Fourteen derivatives (W1–W10, W8b, W9b, W8c and W9c) were designed and screened for bioavailability, toxicity, and docking affinities against key ischemia-related targets: Prostaglandin H Synthase 2 (PTGS2), Tumor Necrosis Factor (TNF), and Matrix Metalloproteinase 9 (MMP9). Compounds W8c and W9c emerged as promising candidates, exhibiting minimal predicted toxicity and favorable binding energies of -6.6 kcal/mol, -5.4 kcal/mol, and -7.9 kcal/mol, respectively, for PTGS2, TNF, and MMP9. These findings indicate their potential to inhibit inflammation, oxidative stress, and extracellular matrix degradation associated with myocardial ischemia. Structural modifications, including the introduction of alkyl groups, enhanced their therapeutic profiles. This work lays the foundation for the rational design of next-generation anti-ischemic agents with improved efficacy, safety, and bioavailability. Future research will focus on synthesizing and validating these derivatives in preclinical and clinical settings to address the challenges of IHD treatment.

Keywords: Anti-Ischemic, Prostaglandin Synthase, Tumor Necrosis Factor, In-Silico, 1,2-DI(Cyclopenta-2,4-Dien-1-YL) Ethane Derivatives

Introduction

Cardiovascular diseases are some of the leading causes of death globally. This accounts for approximately 18 million deaths annually, with ischemic heart disease (IHD) contributing significantly to this menace [1]. The disease results from the narrowing or blockage of coronary arteries due to atherosclerosis or vasospasm and it is characterized by reduced blood supply to myocardial tissue. Its pathophysiology involves an imbalance between myocardial oxygen demand and supply which often leads to metabolic disturbances, hypoxia and eventual cell death if left untreated [2]. The global burden of IHD has necessitated the development of anti-ischemic agents specifically designed to restore myocardial oxygen balance.

These agents act by improving coronary blood flow, reducing oxygen demand, or enhancing myocardial tolerance to ischemia [3]. Some of the existing therapeutic options include nitrates, beta-blockers, calcium channel blockers, and metabolic modulators [4]. While these drugs have significantly reduced IHD mortality rates, their use is often associated

with adverse effects, drug tolerance, and limited efficacy in certain patient populations [5]. Hence the need for deliberate search of novel anti-ischemic therapies with improved safety and efficacy.

Limitations of Existing Anti-Ischemic Agents

The pharmacological management of myocardial ischemia depends on agents targeting the primary determinants of oxygen balance and Beta-blockers plays significant role in this regard. Despite their efficacy, beta-blockers are contraindicated in patients with conditions such as asthma and severe bradycardia, and they may cause fatigue and depression [6]. Similarly, nitrates, which act as vasodilators to improve coronary perfusion, are limited by the development of tolerance with long-term use, necessitating "nitrate-free" intervals that can compromise continuous symptom relief. There are also calcium channel blockers which have demonstrated efficacy by dilating coronary arteries and reducing afterload [7]. However, their use is associated with adverse effects such as peripheral edema, headache, and dizziness, particularly at higher doses. Although promising, metabolic modulators, such as ranolazine, inhibits late sodium currents by reducing intracellular calcium overload and improves diastolic relaxation [8]. Its use is limited by cost and contraindications in patients with severe hepatic impairment.

Advances in Anti-Ischemic Drug Development

Limitations of existing therapies have driven the exploration of novel pharmacological targets and mechanisms for ischemic heart disease. Advances in molecular biology and drug discovery technologies have enabled the identification of key pathways involved in myocardial ischemia, including oxidative stress, inflammation, and mitochondrial dysfunction [9]. For example, studies have shown that targeting reactive oxygen species (ROS) with antioxidants or mitochondrial-targeted therapies can reduce ischemia-reperfusion injury, a major complication of myocardial ischemia [10]. Additionally, anti-inflammatory agents targeting cytokines such as interleukin-1 β and tumor necrosis factor-alpha have shown promise in reducing myocardial damage and improving cardiac function in preclinical models [11].

The application of computational tools has revolutionized the drug discovery process, allowing for the rapid identification and optimization of lead compounds with anti-ischemic potential. Structure-based drug design and in-silico modeling have facilitated the design of molecules that interact specifically with ischemia-relevant targets, such as adenosine receptors and potassium channels [12]. Modified heterocyclic compounds are hypothesized to exert their effects by modulating mitochondrial function, reducing oxidative stress, and enhancing myocardial resistance to ischemia-induced injury [13].

In-silico evaluations have also demonstrated their ability to interact with key ischemia-related targets, including mitochondrial ATP-sensitive potassium channels and adenosine receptors [14]. The integration of computational and experimental approaches also exemplifies the evolving paradigm of drug discovery, wherein in-silico tools complement traditional laboratory methods to accelerate the development of novel therapeutics [15]. This study aims to contribute to the development of novel anti-ischemic agents by investigating the pharmacological properties of some designed di(cyclopenta-2,4-dien-1-yl)ethane derivatives through in-silico evaluations and SAR studies, the research seeks to elucidate the efficacy and safety underlying the anti-ischemic effects of these compounds, providing insights into their therapeutic potential.

Methodology

The methodology outlined in this study was designed to evaluate the potential of di(cyclopenta-2,4-dien-1-yl)ethane derivatives as anti-ischemic agents through a combination of computational analysis, toxicity predictions, and docking studies. This research aimed to identify derivatives with favorable pharmacological profiles while minimizing toxicity risks. The approach was structured to explore their binding affinities to relevant targets and predict their safety and effectiveness as therapeutic candidates.

Design of Hypothetical Derivatives

Ten di(cyclopenta-2,4-dien-1-yl)ethane derivatives (W1-W10) were conceptualized and their structures drawn using Chem Draw 14.0. The structures were saved in .sdf for docking purpose while the SMILES data were copied to online web servers for toxicity and drug-likeness assessment. After toxicity and drug-likeness check, W8 and W9 were further structurally modified through the removal of the pie bond linking the di(cyclopenta-2,4-dien-1-yl)ethane molecules. It was also necessary to elongate the distance between the twin moieties by at least 2 carbon atoms and substitute one hydrogen atom at position 2 by methyl groups (as shown in Figure 1) to achieve non-toxicity and good drug-likeness.

Selection of Anti-Ischemic Drugs and Molecular Design

Medications to treat myocardial ischemia include blood thinner, nitrates, adrenergic blockers, metabolic modifiers, potassium-channel openers, beta blockers, calcium channel blockers and cholesterol-lowering medications [16]. To establish a reference framework, six of these FDA-approved anti-ischemic drugs: Aspirin (Pubchem ID: 2244), Ranolazine (56959), Amlodipine (2162), Atorvastatin (60823), Carvedilol (2585) and Nitroglycerin (4510) were selected and prepared in .sdf. These drugs represent different pharmacological mechanisms and served as standards for comparison. The derivatives of di(cyclopenta-2,4-dien-1-yl)ethane (designated as W1–W10, W8b, W9b, W8c, and W9c (Figure 2)) were also designed using Chem draw 14.0 software

Physicochemical and Pharmacokinetic Profiling

The physicochemical and pharmacokinetic properties of the hypothetical derivatives and standard drugs were assessed using the Swiss ADME webserver. Key parameters (which influence drug action and delivery) evaluated included oral bioavailability (using the bioavailability radar to identify compounds with favorable absorption and distribution profiles), drug-likeness (assessment using Lipinski's Rule of Five and related criteria) and physicochemical space (which examines properties such as polarity, lipophilicity and solubility) [17,18].

Toxicity Predictions

To ensure safety, toxicity profiles of the derivatives and standard drugs were predicted using the Protox II webserver. The following endpoints were assessed: hepatotoxicity (predicted likelihood of liver toxicity), carcinogenicity (potential risk of cancer development), immunotoxicity (effects on the immune system), mutagenicity (risk of genetic mutations) and cytotoxicity (potential to cause cellular toxicity). The results provided probabilities of activity for each toxicity endpoint, allowing for the exclusion of high-risk candidates [19].

Molecular Docking Studies

Molecular docking studies were performed using Pyrx 0.8 Autodock to evaluate the binding affinities of derivatives and standard drugs to three key ischemia-related targets. Prior to this, the protein structures in .pdb were downloaded from rcsb.org, prepared using Discovery studio, and had their energy minimized and converted to pdbqt using Autodock Vina. Protein molecules used in this study are: Prostaglandin H Synthase 2 (PTGS2): associated with inflammation and oxidative stress during ischemia (PDB ID: 5F19), Tumor Necrosis Factor (TNF): a cytokine involved in ischemia-induced inflammation (PDB ID: 2AZ5) and Matrix Metalloproteinase 9 (MMP9): linked to extracellular matrix remodeling during ischemic injury (PDB ID: 4JIJ). The binding affinities of designed compounds and reference drugs to these targets were predicted using docking tools, with results presented in terms of binding energies and root-mean-square deviations (RMSD) of binding poses.

Results

Design of Hypothetical Derivatives Of 1,2-DI(Cyclopenta-2,4-Dien-1-YL)Ethane

Figure 1 presents the chemical structures of hypothetical derivatives of 1,2-di(cyclopenta-2,4-dien-1-yl)ethane, a class of compounds being investigated as potential anti-ischemic agents. The compounds, denoted as W1 to W10 (and some additional variations W8b, W9b, W8c, W9c), aimed to retain bioactive characteristics while minimizing toxicity. These structures vary in substituent groups to explore the chemical diversity needed for efficacy. Each modification introduces variability in functional groups affecting hydrophilicity, lipophilicity, and reactivity. Subtle variations in electron-donating or withdrawing groups which might alter binding efficiency with target proteins and pathways relevant in myocardial ischemia management. This structural optimization aims at enhanced bioavailability, reduced adverse effects, and better therapeutic outcomes compared to the standard drugs analyzed in Figure 2.

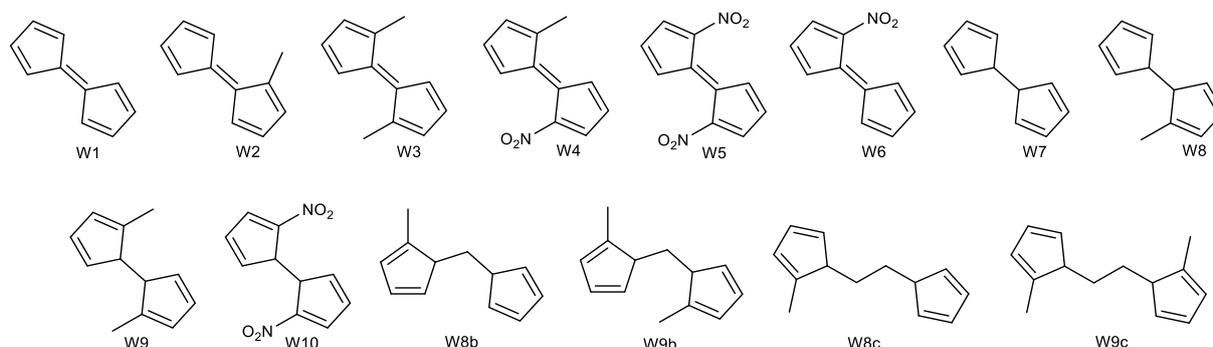


Figure 1: Structures of Hypothetical Derivatives of DI(Cyclopenta-2,4-Dien-1-YL)Ethane as Anti-Ischemic Agents

Toxicity Prediction of Anti-Ischemic Standard Drugs

Table 1 provides a comprehensive toxicity profile of six FDA-approved anti-ischemic drugs: Aspirin, Ranolazine, Amlodipine, Atorvastatin, Carvedilol, and Nitroglycerin. These drugs represent various pharmacological mechanisms and are well-established in clinical use. Hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity were assessed using the Protox II webserver, a reliable in silico tool for toxicity prediction. The results show that all drugs except Atorvastatin are inactive for hepatotoxicity, suggesting minimal risk to liver function.

Toxicity prediction and probability of common Anti-ischemic FDA approved drugs						
Target	Aspirin	Ranolazine	Amlodipine	Atorvastatin	Carvedilol	Nitroglycerin
Hepatotoxicity	Inactive (0.51)	Inactive (0.95)	Inactive (0.83)	Active (0.76)	Inactive (0.89)	Inactive (0.80)
Carcinogenicity	Inactive (0.86)	Inactive (0.64)	Inactive (0.61)	Inactive (0.64)	Inactive (0.66)	Inactive (0.55)
Immunotoxicity	Inactive (0.99)	Inactive (0.97)	Inactive (0.99)	Inactive (0.92)	Active (0.94)	Inactive (0.87)
Mutagenicity	Inactive (0.97)	Inactive (0.77)	Inactive (0.76)	Inactive (0.91)	Inactive (0.68)	Inactive (0.74)
Cytotoxicity	Inactive (0.94)	Inactive (0.54)	Inactive (0.61)	Inactive (0.64)	Inactive (0.56)	Inactive (0.71)

Table 1: Toxicity Prediction of Anti-Ischemic Standard Drugs (Aspirin, Ranolazine, Amlodipine, Atorvastatin, Carvedilol and Nitroglycerin) Using Protox II Webserver

Toxicity Prediction of Hypothetical Derivatives

Table 2a-c evaluate the toxicity profiles of hypothetical derivatives (W1–W10, W8b, W9b, W8c, and W9c) of di(cyclopenta-2,4-dien-1-yl)ethane using Protox II webserver to predict hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity. These parameters are critical for identifying derivatives with high therapeutic potential and minimal safety risks. Most derivatives demonstrated favorable toxicity profiles. For example, compounds W8c and W9c were inactive for all the parameters (i.e. non-hepatotoxic, -immunotoxic, -mutagenic, -carcinogenic and -cytotoxic), making them promising candidates for further study. However, some derivatives, such as W6 and W10, exhibited activity for carcinogenicity and mutagenicity. This highlights the structural variations among the derivatives and their potential impact on safety profiles.

Toxicity prediction of di(cyclopenta-2,4-dien-1-yl)ethane derivatives					
Target	W1	W2	W3	W4	W5
Hepatotoxicity	Inactive (0.80)	Inactive (0.80)	Inactive (0.80)	Inactive (0.62)	Inactive (0.63)
Carcinogenicity	Active (0.66)	Active (0.59)	Active (0.61)	Active (0.60)	Inactive (0.51)
Immunotoxicity	Inactive (0.95)	Inactive (0.80)	Inactive (0.93)	Inactive (0.96)	Inactive (0.99)
Mutagenicity	Inactive (0.78)	Inactive (0.80)	Inactive (0.85)	Active (0.63)	Active (0.79)
Cytotoxicity	Inactive (0.73)	Inactive (0.72)	Inactive (0.74)	Inactive (0.76)	Inactive (0.73)

Table 2a: Toxicity Prediction of Hypothetical Derivatives (W1-W5) Of DI(Cyclopenta-2,4-Dien-1-YL) Ethane Designed as Potential Anti-Ischemic Agents

Toxicity prediction of di(cyclopenta-2,4-dien-1-yl)ethane derivatives					
Target	W6	W7	W8	W9	W10
Hepatotoxicity	Inactive (0.63)	Inactive (0.87)	Inactive (0.80)	Inactive (0.80)	Inactive (0.65)
Carcinogenicity	Active (0.57)	Active (0.65)	Active (0.59)	Active (0.61)	Inactive (0.50)
Immunotoxicity	Inactive (0.94)	Inactive (0.99)	Inactive (0.98)	Inactive (0.99)	Inactive (0.98)
Mutagenicity	Active (0.70)	Inactive (0.80)	Inactive (0.80)	Inactive (0.85)	Active (0.82)
Cytotoxicity	Inactive (0.76)	Inactive (0.79)	Inactive (0.72)	Inactive (0.74)	Inactive (0.73)

Table 2b: Toxicity Prediction of Hypothetical Derivatives (W6-W10) Of DI(Cyclopenta-2,4-Dien-1-YL) Ethane Designed as Potential Anti-Ischemic Agents

Overall, Table 2a, 2b and 2c provide crucial insights into the toxicity profiles of the hypothetical derivatives, paving the way for selecting lead compounds such as W8c and W9c. These compounds exhibit non-toxicity compared to other derivatives and some if the standard drugs, thus making them good candidates for synthesis, preclinical evaluation and eventual clinical trials.

Toxicity prediction of di(cyclopenta-2,4-dien-1-yl)ethane derivatives				
Target	W8b	W9b	W8c	W9c
Hepatotoxicity	Inactive (0.83)	Inactive (0.83)	Inactive (0.80)	Inactive (0.80)
Carcinogenicity	Active (0.56)	Active (0.56)	Inactive (0.51)	Inactive (0.54)
Immunotoxicity	Inactive (0.97)	Inactive (0.98)	Inactive (0.98)	Inactive (0.98)
Mutagenicity	Inactive (0.79)	Inactive (0.84)	Inactive (0.84)	Inactive (0.87)
Cytotoxicity	Inactive (0.75)	Inactive (0.77)	Inactive (0.84)	Inactive (0.80)

Table 2c: Toxicity Prediction of Modified Hypothetical Derivatives of DI(Cyclopenta-2,4-Dien-1-YL)Ethane Designed as Potential Anti-Ischemic Agents

Physicochemistry of Anti-Ischemic Standard Drugs

Figure 2 depicts the oral bioavailability physicochemical space for six FDA-approved anti-ischemic standard drugs: Aspirin, Ranolazine, Amlodipine, Atorvastatin, Carvedilol, and Nitroglycerin, using the Swiss ADME webserver. This tool maps the pharmacokinetic profiles of these drugs based on specific descriptors like lipophilicity (expressed as Log P) and water solubility. These features directly impact their oral bioavailability, making the analysis crucial for evaluating drug efficiency in treating myocardial ischemia. The figure visually compares how well each drug conforms to optimal ranges within the bioavailability radar (e.g., parameters like size, flexibility, solubility, saturation, and polarity).

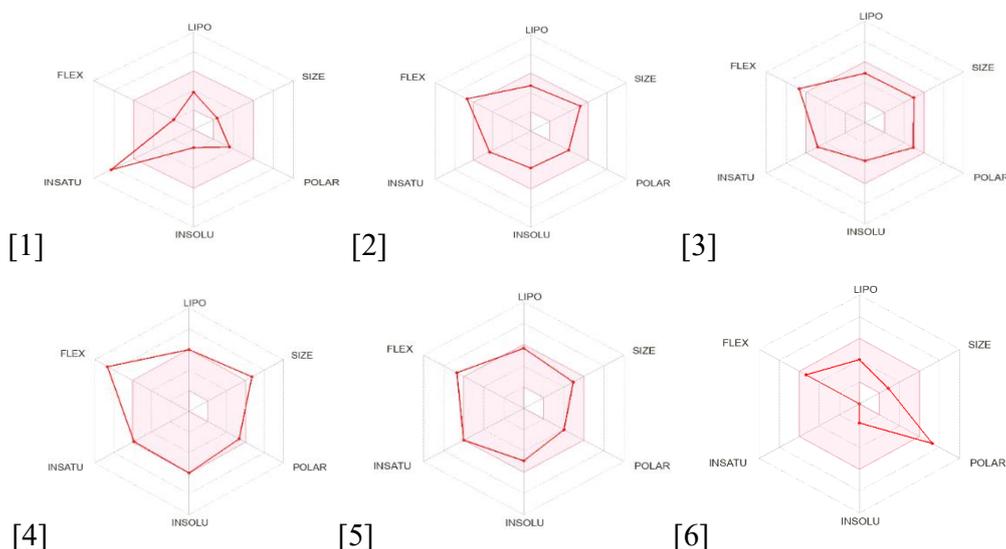


Figure 2: Oral Bioavailability Physicochemical Space for Anti-Ischemic Standard Drugs (Aspirin, Ranolazine, Amlodipine, Atorvastatin, Carvedilol and Nitroglycerin [1 – 6] Respectively) Using Swissadme Webserver

Optimal bioavailability is generally indicated by data points within a defined zone, signifying potential efficacy in crossing biological barriers like the intestinal membrane. For anti-ischemic therapy, the chosen drugs represent a spectrum of therapeutic effects such as blood thinning, cholesterol reduction, and vasodilation. The results imply that despite structural and functional variability, all mapped compounds mostly align within the acceptable bioavailability region where deviation indicates specific pharmacological trade-offs.

Physicochemistry of Designed DI(Cyclopenta-2,4-Dien-1-YL)Ethane Derivatives

Figure 3a and 3b display the oral bioavailability physicochemical space of these hypothetical derivatives, mirroring the Swiss ADME approach used in Figure 2.

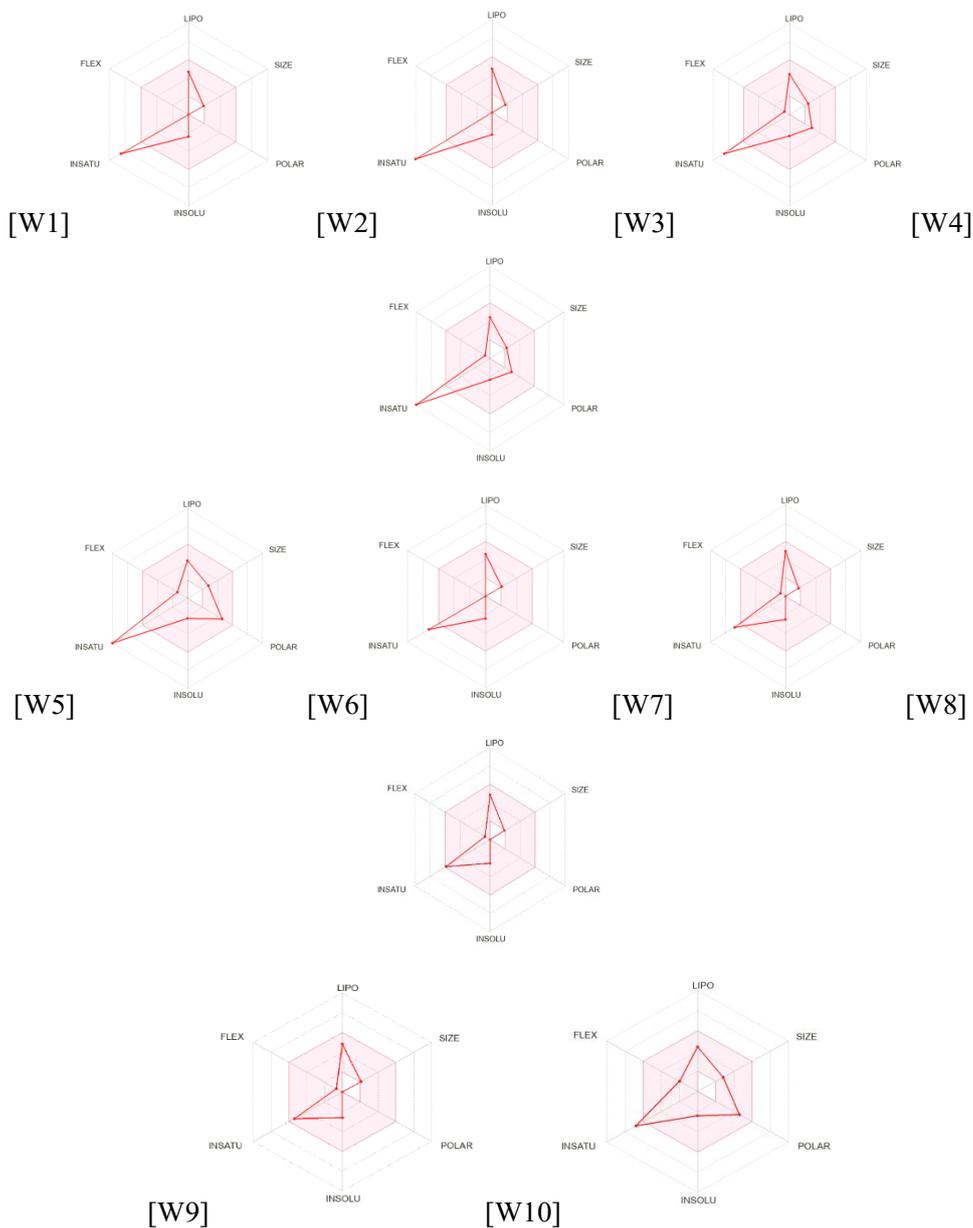


Figure 3a: Oral Bioavailability Physicochemical Space for Hypothetical Derivatives [W1 – W10] Respectively) of DI(Cyclopenta-2,4-Dien-1-YL)Ethane Using Swiss ADME Webserver

By analyzing W1-W10, W8b, W9b, W8c, and W9c in a standardized manner, the figure compares their bioavailability profiles to those of existing anti-ischemic drugs. The visual representation helps assess the structural modifications' impact on parameters such as lipophilicity, solubility, and size.

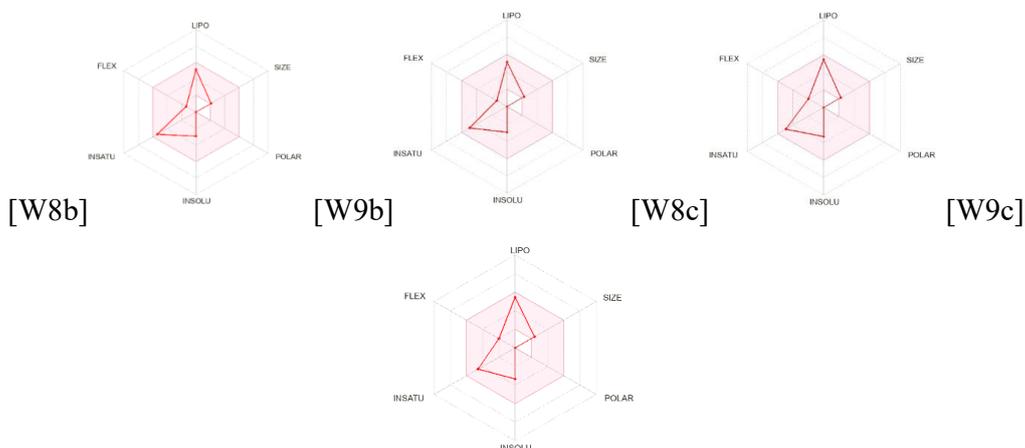


Figure 3b: Oral Bioavailability Physicochemical Space for Structurally Modified Derivatives (W8b, W9b, W8c And W9c) of DI(Cyclopenta-2,4-Dien-1-YL)Ethane Using Swissadme Webserver

Analysis of Compound W8c-Tumor Necrosis Factor Complex

Table 4 evaluates the binding affinities of the derivatives and standard drugs to Tumor Necrosis Factor (TNF), a cytokine involved in ischemia-induced inflammation. TNF plays a crucial role in promoting myocardial injury through its pro-inflammatory effects, making it a key target for anti-ischemic therapies [21]. The docking studies revealed that W8c binds to TNF with a moderate affinity of -5.4 kcal/mol, comparable to Carvedilol (-5.3 kcal/mol) and slightly lower than Atorvastatin (-6.8 kcal/mol). This binding affinity suggests that W8c can effectively inhibit TNF's activity, potentially reducing inflammation and mitigating ischemic damage.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
2az5 Atorvastatin uff E=1459.86	-6.8	0	0
2az5 Ranolazine uff E=644.89	-6.4	0	0
2az5 W8c E=419.64	-5.4	0	0
2az5 Carvedilol uff E=630.09	-5.3	0	0
2az5 W9c uff E=428.36	-5.3	0	0
2az5 Amlodipine uff E=594.18	-5.1	0	0
2az5 Aspirin uff E=419.53	-4.9	0	0
2az5 Nitroglycerin uff E=69.17	-4.2	0	0

Table 4: Summary of Docking Study on the Non-Toxic Derivatives of DI(Cyclopenta-2,4-Dien-1-YL)Ethane and Anti-Ischemic Standard Drugs with Tumor Necrosis Factor (TNF) (PDB ID: 2AZ5)

Analysis of W8c-Tumor Necrosis Factor (TNF) Binding

In Figure 6, the 2D and 3D interaction highlights how W8c interacts with key residues in the active site of TNF. Critical amino acids such as Tyrosine, Leucine and Proline form n-sigma, n-n stacked and n-alkyl bonds with W8c. Bond lengths typically range between 3.73 and 4.75 Å. These residue interactions are significant as they prevent TNF from binding to its receptor, thereby inhibiting the inflammatory cascade triggered by myocardial ischemia.

Hydrophobicity and Solvent Accessibility Surface in W8c-TNF Complex

Figure 7 expands on the hydrophobicity and solvent accessibility relationships in the W8c-TNF complex. Hydrophobic facilitated anchoring through van der Waals interactions with W8c's hydrophilic regions.

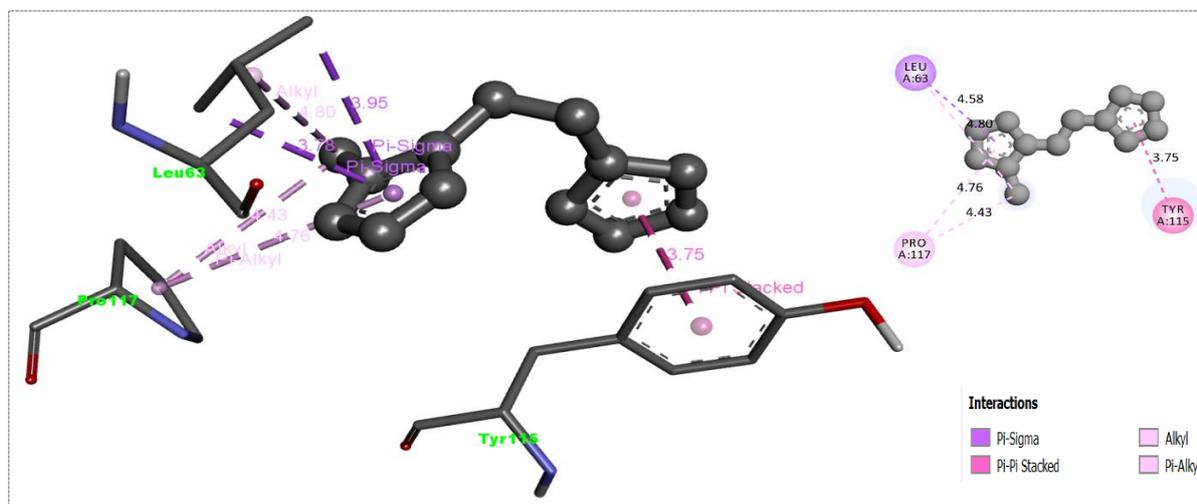


Figure 6: 2D and 3D Structures of W8c-Tumor Necrosis Factor Complex Showing Configuration, Binding Residues Interaction, Types and Bond Lengths

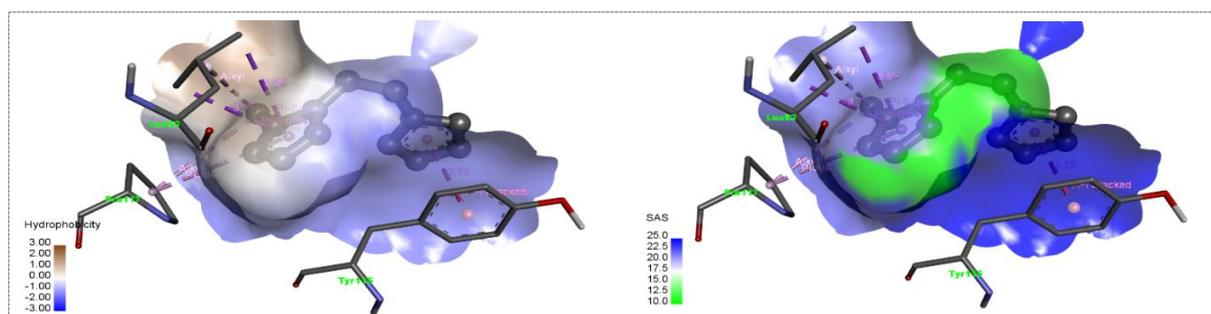


Figure 7: 3D Structures of W8c-Tumor Necrosis Factor Complex Showing Hydrophobicity/ Hydrophilicity Interactions and Solvent Accessibility Relationship (SAS)

Analysis of Compound W8c-Matrix Metalloproteinase 9 Complex

Matrix metalloproteinase 9 (MMP9) plays a critical role in extracellular matrix remodeling during ischemic injury, contributing to tissue damage and adverse cardiac remodeling [22]. Table 5 provides the binding affinities of selected derivatives and standard drugs to MMP9, shedding light on their potential to inhibit this pathological process. W8c displayed a binding affinity of -7.9 kcal/mol, comparable to Ranolazine (-8.8 kcal/mol) and Carvedilol (-7.9 kcal/mol). This strong binding suggests that W8c can potentially inhibit MMP9 activity, preventing excessive extracellular matrix degradation and promoting tissue preservation. W9c also showed a high binding affinity of -7.5 kcal/mol, further supporting the therapeutic potentials of the nontoxic derivatives.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
4jjj_Ranolazine E=644.89	-8.8	0	0
4jjj_W8c E=419.64	-7.9	0	0
4jjj_Carvedilol E=630.09	-7.9	0	0
4jjj_Aspirin E=419.53	-7.8	0	0
4jjj_W9c uff E=428.36	-7.5	0	0
4jjj_Atorvastatin E=1459.86	-6.9	0	0
4jjj_Amlodipine E=594.18	-5.9	0	0
4jjj_Nitroglycerin E=69.17	-5.4	0	0

Table 5: Summary of Docking Study on the Non-Toxic Derivatives of DI(Cyclopenta-2,4-dien-1-yl)Ethane and Anti-Ischemic Standard Drugs with Matrix Metalloproteinase 9 (MMP9) (PDB ID: 4JIJ)

Analysis of Compound W8c-Matrix Metalloproteinase 9 Complex

In the W8c-MMP9 binding study shown in Figure 8, the amino acids involved include catalytic site residues Histidine, Tyrosine and Arginine form π -sigma, π - π T-shaped, π -alkyl and π - π stacked bonds with W8c. These interactions block the active site, inhibiting MMP9's enzymatic activity involved in extracellular matrix degradation.

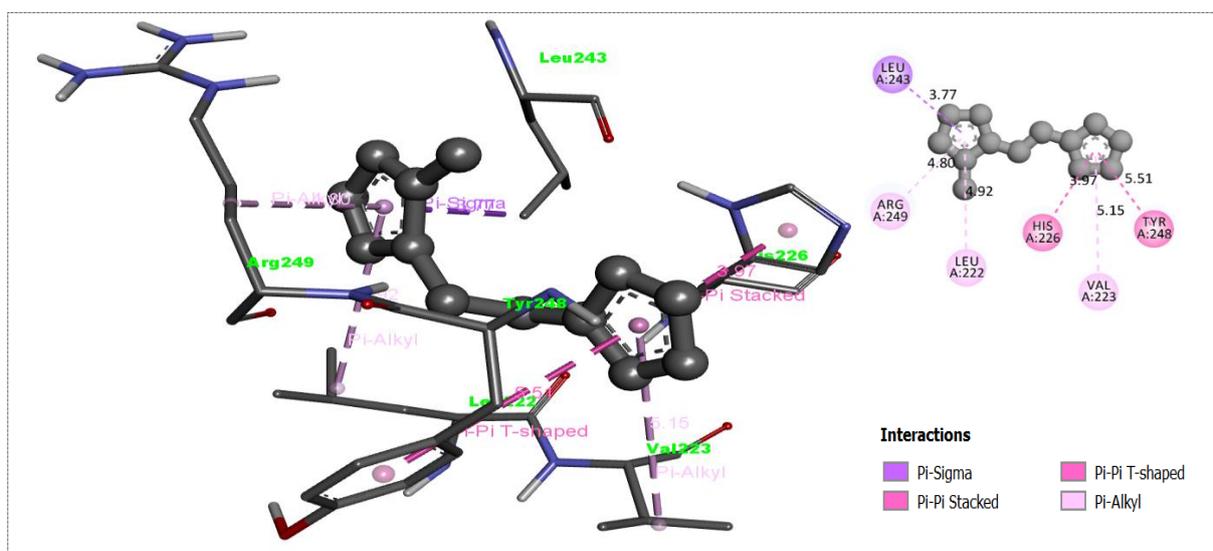


Figure 8: 2D and 3D Structures of W8c-Matrix Metalloproteinase 9 Complex Showing Configuration, Binding Residues Interaction, Types and Bond Lengths

Hydrophobicity and Solvent Accessibility Surface in W8c-MMP9 Complex

Figure 9 focuses on solvent exposure and hydrophobicity profiles in the W8c-MMP9 complex. Residues exhibit significant hydrophobic contact with W8c's core, while maintaining hydrophilic and polar interactions.

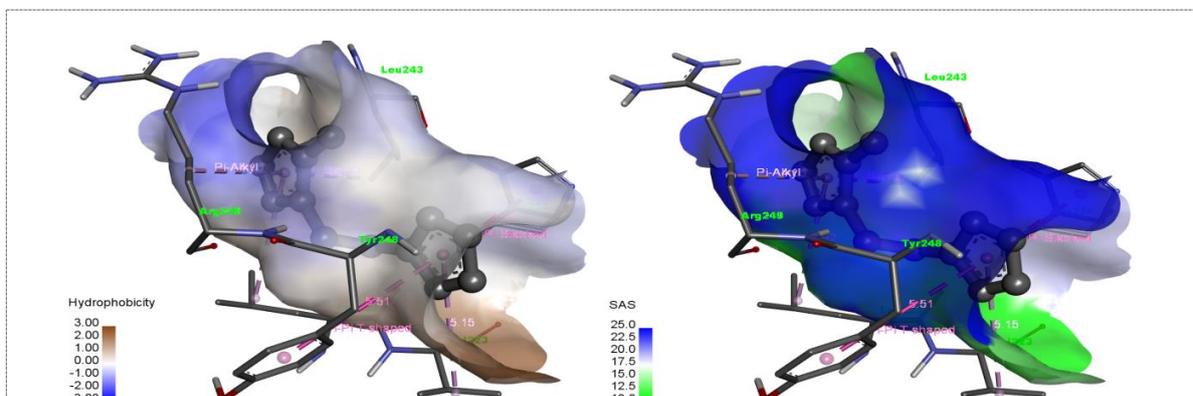


Figure 9: 3D Structures of W8c-Matrix Metalloproteinase 9 Complex Showing Hydrophobicity/Hydrophilicity Interactions and Solvent Accessibility Relationship (SAS)

Proposed Base-Catalyzed Pathway for Lead Compound W8c

A general synthetic pathway designed for the synthesis of W8c is shown in Figure 10. The reaction involves a base-catalyzed reaction between commercially accessible 5-methylcyclopenta-1,3-diene and 5-(chloromethyl)cyclopenta-1,3-diene. This method allowed for the efficient generation of the desired di(cyclopenta-2,4-dien-1-yl)ethane scaffold with minimal side reactions, short reaction time, and good yield.

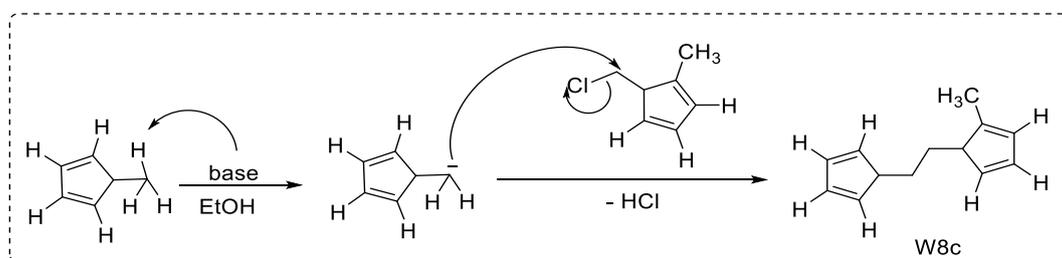


Figure 10: Proposed Base-Catalysed Reaction Of 5-Methylcyclopenta-1,3-Diene with 5-(Chloromethyl) Cyclopenta-1,3-Diene Leading to the Formation of Lead Non-Toxic Derivative W8c

Discussion

These results highlight the general safety of these standard drugs but also reveal areas for improvement, particularly concerning Atorvastatin's hepatotoxicity and Carvedilol's immunotoxicity. Such insights reinforce the need for novel anti-ischemic agents with improved safety profiles. The data serve as a reference point for comparing the toxicity profiles of the hypothetical derivatives explored in this study. By minimizing these risks in the newly designed compounds, safer and more effective anti-ischemic therapies can be developed. Atorvastatin's active profile in this category indicates a higher probability of liver-related adverse effects, consistent with its known potential to elevate liver enzyme levels. Carvedilol also displayed activity in immunotoxicity, implying a potential adverse impact on the immune system modulation while all six drugs were inactive for carcinogenicity, mutagenicity and cytotoxicity, which aligns with their safety profiles as approved medications.

For toxicity prediction of hypothetical derivatives, W8b and W9b showed better safety margins compared to their unmodified counterparts, W8 and W9, respectively. This suggests that minor structural modifications, such as the addition of alkyl groups or the alteration of substituents, as seen in structure W8c and W9c, can significantly enhance the safety and therapeutic potential of these compounds. The analysis underscores the importance of iterative structural optimization in drug development. Phys for anti-ischemic therapy, the chosen drugs represent a spectrum of therapeutic effects such as blood thinning, cholesterol reduction, and vasodilation. The results imply that despite structural and functional variability, all mapped compounds mostly align within the acceptable bioavailability region where deviation indicates specific pharmacological trade-offs. Figure 2 sets the stage for assessing whether emerging derivatives match or surpass the oral absorption standards of these established drugs, vital for designing targeted and effective ischemic treatments.

Optimal bioavailability lies in ensuring these compounds fall within the predefined "ideal" pink zone. Many derivatives seem to lie within these acceptable ranges, indicating promising oral absorption potential. However, minor outliers suggest that certain structural modifications might reduce bioavailability or require further optimization. This analysis is crucial as compounds W1-W10, W8b, W9b, W8c, and W9c with superior bioavailability have higher systemic efficacy after administration. Figure 3 thus aids in refining drug candidates before transitioning to experimental and clinical evaluations, ensuring resource efficiency in drug development. Among the derivatives, W8c exhibited a binding affinity of -6.6 kcal/mol, comparable to Ranolazine (-6.5 kcal/mol) and superior to Nitroglycerin (-5.7 kcal/mol). This indicates

that W8c can potentially inhibit PTGS2 activity as effectively as Ranolazine, a clinically approved anti-ischemic drug. Other derivatives, such as W9c (-6.5 kcal/mol), also demonstrated strong binding affinities, further supporting their therapeutic potential.

Although atorvastatin and carvedilol had better binding energy than derivative W8c, their respective hepatotoxicity and immunotoxicity pose safety risks. W8c's binding with PTGS2 where bond lengths range from 2.1 to 3.3 Å, ensuring the compound's specificity in targeting PTGS2. This precise residue interaction inhibits PTGS2 enzymatic activity, reduces prostaglandin synthesis critical for inflammatory responses. Hydrophobicity and solvent accessibility surface in W8c-PTGS2 binding shows that residues like Ala443 and Ile408 provide hydrophobic anchoring forming π -sigma and π -alkyl bonds with polar groups on W8c. Reduced solvent exposure on these critical residues enhances binding stability, ensuring effective PTGS2 inhibition. These amino acid interactions optimize W8c's balance between potency and bioavailability, confirming its potential as a selective anti-inflammatory and anti-ischemic agent.

By targeting residues involved in Tumour Necrosis Factor(TNF) activity, W8c showcases both potency and specificity, ensuring minimal off-target effects. Solvent accessibility in residues highlights W8c's efficiency in leveraging water-mediated interactions, stabilizing the protein-ligand complex in dynamic environments. This balance between hydrophobicity and hydrophilicity ensured the strong, selective binding necessary to inhibit TNF. Reduced solvent accessibility enhances the longevity of the interaction, reinforcing W8c's effectiveness as a therapeutic agent. The binding profile of W8c was found to be comparable to Ranolazine, a well-established anti-ischemic drug, indicating its potential for clinical application. The binding selectivity, guided by precise residue engagement, makes W8c a promising agent in mitigating ischemia-induced tissue damage while limiting systemic toxicity side effects.

These interactions are critical for stabilizing the ligand-enzyme complex and blocking enzymatic activity. Solvent accessibility is notably reduced in these residues, enhancing the molecule's inhibitory profile. This balance ensures sustained binding and activity within the physiological environment. The coordination between these residues of the W8c-MMP9 complex solidifies W8c's role as a stable and efficient MMP9 inhibitor. The reaction involves a base-catalyzed reaction between commercially accessible 5-methylcyclopenta-1,3-diene and 5-(chloromethyl)cyclopenta-1,3-diene. The reaction underlines the practical feasibility of synthesizing the derivatives while maintaining structural novelty. The stepwise reaction mechanism highlights the importance of controlled base catalysis in achieving the desired product specificity. The reaction's practicality supports scaling potential for further pharmacological testing, an essential step in validating predictions from earlier figures

Conclusion

Despite the significant advancements in pharmacological treatments, challenges such as drug resistance, adverse effects, and limited efficacy in complex cases remain. This study underscores the importance of understanding the structure-activity relationships (SARs) of anti-ischemic agents to optimize their therapeutic potential. Through in-silico modeling and pharmacological evaluations, novel molecular scaffolds such as W8c and W9c, have emerged as promising candidates, demonstrating improved efficacy and reduced toxicity. The approach does not only address existing therapeutic gaps but also lay the groundwork for combating emerging challenges in ischemic heart disease management.

By focusing on innovation, safety, and accessibility, the future of anti-ischemic therapy holds great promise for reducing the global impact of ischemic heart disease as evident in the comparable efficacy of compounds W8c and W9c which in this study have emerged as promising candidates due to their favorable bioavailability, minimal predicted toxicity, and strong docking interactions with PTGS2, TNF, and MMP9. W8c (lead compound being prepared for synthesis, further in vitro and in vivo validations) demonstrated binding affinities of -6.6 kcal/mol (PTGS2), -5.4 kcal/mol (TNF), and -7.9 kcal/mol (MMP9), comparable to or exceeding those of standard drugs such as Ranolazine and Carvedilol. This in-silico study highlights the potential of di(cyclopenta-2,4-dien-1-yl)ethane and its derivatives as novel anti-ischemic agents and establishes a framework for their further exploration and development.

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