Molecular Docking, Binding Interaction Analysis and ADME Assessment of Apixaban Analogues as Potential Candida albicans N-Myristoyltransferase Inhibitors

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Abstract

Background: The growing incidence of fungal infections caused by *Candida albicans* and the emergence of antifungal resistance necessitate the development of new therapeutic agents. N-Myristoyltransferase (NMT), an essential enzyme involved in fungal growth and survival, represents a promising target for antifungal drug discovery.

Objective: This study aimed to evaluate Apixaban analogues as potential inhibitors of *Candida albicans* N-myristoyltransferase through molecular docking and ADME analysis.

Materials and Methods: Fifteen Apixaban analogues were designed and subjected to molecular docking against *Candida albicans* N-myristoyltransferase (PDB ID: 1IYL) using AutoDockVina. The docking protocol was validated by re-docking the co-crystallized ligand R64. Binding interactions were analyzed using Discovery Studio Visualizer, while pharmacokinetic and drug-likeness properties were assessed through in silico ADME prediction.

Results: The docking validation yielded an RMSD value of 1.38 Å, confirming the reliability of the docking protocol. Several analogues demonstrated stronger binding affinities than the reference ligand R64 (-9.7 kcal/mol). Compound 9 exhibited the highest docking score (-11.0 kcal/mol), followed by Compounds 2, 3, and 15 (-10.6 kcal/mol). Interaction analysis revealed favorable binding with key active-site residues. ADME evaluation indicated acceptable pharmacokinetic characteristics and drug-likeness profiles for the majority of the designed compounds.

Conclusion: The designed Apixaban analogues showed promising inhibitory potential against *Candida albicans* N-myristoyltransferase. Among them, Compound 9 emerged as the most promising lead candidate, warranting further experimental validation as a potential antifungal agent.

Keywords: Candida albicans, N-Myristoyltransferase, Apixaban analogues, Molecular docking, ADME, Antifungal agents

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1. Introduction

1.1 Global Burden of Fungal Infections

Fungal infections continue to represent a major public health concern worldwide, particularly among immunocompromised individuals, hospitalized patients, and those receiving long-term antimicrobial therapy[1]. Although bacterial and viral infections often receive greater attention, invasive fungal diseases contribute substantially to morbidity and mortality[2]. The increasing prevalence of chronic illnesses, organ transplantation procedures, cancer chemotherapy, and human immunodeficiency virus (HIV) infections has led to a growing population of individuals susceptible to opportunistic fungal pathogens[3]. In addition to their clinical impact, fungal infections impose a considerable economic burden on healthcare systems due to prolonged hospital stays, diagnostic challenges, and treatment-related costs. The emergence of drug-resistant fungal strains has further complicated disease management and highlights the urgent need for the discovery of new antifungal agents with improved efficacy and safety profiles[4], [5].

1.2 Candida albicans and Antifungal Resistance

Among the various fungal pathogens affecting humans, *Candida albicans* remains one of the most frequently encountered opportunistic species. It is a normal component of the human microbiota but can cause superficial or invasive infections when

host immune defenses become compromised[6], [7]. Clinical manifestations range from oral and vaginal candidiasis to life-threatening bloodstream and systemic infections[8]. Despite the availability of antifungal drugs such as azoles, echinocandins, and polyenes, treatment outcomes are increasingly threatened by the development of resistance mechanisms[9]. Alterations in drug targets, overexpression of efflux pumps, biofilm formation, and genetic adaptations enable fungal cells to survive therapeutic exposure[10], [11]. These resistance-associated factors reduce treatment effectiveness and emphasize the importance of identifying novel molecular targets for antifungal drug development[9].

1.3 Candida albicans N-Myristoyltransferase as a Therapeutic Target

N-Myristoyltransferase (NMT) is an essential enzyme that catalyzes the transfer of myristic acid to the N-terminal glycine residue of specific proteins[12]. This post-translational modification plays a critical role in protein localization, signal transduction, membrane association, and cellular regulation[13], [14]. In *Candida albicans*, NMT is indispensable for growth, viability, and pathogenicity, making it an attractive target for antifungal intervention[15]. Inhibition of this enzyme disrupts key biological processes required for fungal survival, ultimately leading to impaired cellular function[16]. Furthermore, structural and biochemical differences between fungal and human NMT enzymes provide opportunities for the development of selective inhibitors with reduced host toxicity. Consequently, NMT has emerged as a promising molecular target in contemporary antifungal drug discovery programs[17].

1.4 Importance of Apixaban Scaffold in Drug Design

Apixaban is a well-established small-molecule drug recognized for its favorable pharmacokinetic characteristics, structural stability, and diverse functional groups capable of molecular interactions[18]. The presence of aromatic rings, heterocyclic moieties, and hydrogen bond-forming functionalities makes the Apixaban scaffold a valuable template for medicinal chemistry optimization[19]. Structural modification of existing drug scaffolds is a widely accepted strategy for generating new bioactive compounds with enhanced biological properties[20]. By introducing suitable substitutions and molecular alterations, it is possible to improve target affinity, selectivity, and physicochemical behavior. These attributes make the Apixaban framework a suitable starting point for the design of novel antifungal candidates targeting essential fungal enzymes[21].

1.5 Rationale for Designing Novel Apixaban Analogues

The search for new antifungal agents requires compounds capable of interacting effectively with critical fungal targets while maintaining favorable pharmacokinetic properties. Considering the therapeutic relevance of NMT and the structural versatility of the Apixaban scaffold, the design of novel Apixaban analogues offers a promising approach for lead discovery. Rational structural modifications can enhance binding interactions within the active site of the target enzyme and potentially improve inhibitory activity[22]. In addition, computational approaches such as molecular docking and ADME prediction enable rapid screening of designed compounds before experimental evaluation[23], [24]. This strategy reduces development costs and facilitates the identification of promising lead molecules for further investigation.

1.6 Aim and Objectives of the Study

The present study was undertaken to explore the potential of newly designed Apixaban analogues as inhibitors of *Candida albicans* N-myristoyltransferase using computational techniques. The specific objectives were to design a series of novel analogues, evaluate their binding affinity through molecular docking studies, investigate their interactions with key active-site residues, and assess their pharmacokinetic and drug-likeness properties using in silico ADME analysis. The ultimate goal was to identify promising lead compounds that could serve as potential candidates for future synthesis and experimental antifungal evaluation.

2. Materials and Methods

2.1 Protein Preparation

The three-dimensional crystal structure of *Candida albicans* N-myristoyltransferase was obtained from the Protein Data Bank (PDB) using the accession code **1IYL**[25]. This structure was selected because it contains a co-crystallized inhibitor and provides detailed information regarding the active-site architecture required for molecular docking studies. The downloaded protein structure was subjected to a series of preparation steps to ensure its suitability for computational analysis.

Initially, all crystallographic water molecules, non-essential ions, and other heteroatoms that were not directly involved in ligand binding were removed from the protein structure. The elimination of these molecules helps minimize unnecessary interactions that may interfere with docking calculations and allows accurate identification of the active binding pocket.

Subsequently, missing hydrogen atoms were added to the protein structure to reproduce physiological protonation conditions and improve the reliability of molecular interaction studies. The addition of hydrogen atoms is essential for accurate prediction of hydrogen-bonding interactions between the receptor and ligand molecules. Non-polar hydrogen atoms were merged with their corresponding

carbon atoms to simplify the docking calculations and reduce computational complexity.

To further enhance structural accuracy, appropriate atomic charges were assigned to the protein using the Gasteiger charge method. Charge assignment plays a crucial role in determining electrostatic interactions within the binding site and contributes significantly to docking performance. The prepared protein structure was then examined for structural consistency, and any missing parameters required for docking simulations were corrected.

Protein optimization was performed using the UCSF Chimera molecular visualization platform. The optimization process involved structural refinement, hydrogen addition, charge calculation, and preparation of the final receptor model. The optimized protein structure was subsequently converted into the appropriate format required for molecular docking studies. The prepared receptor was used throughout the study for evaluating the binding affinity and interaction profiles of the designed Apixaban analogues against *Candida albicans* N-myristoyltransferase. The overall computational workflow adopted for the design, docking evaluation, and ADME assessment of the novel Apixaban analogues is illustrated in **Figure 1**.

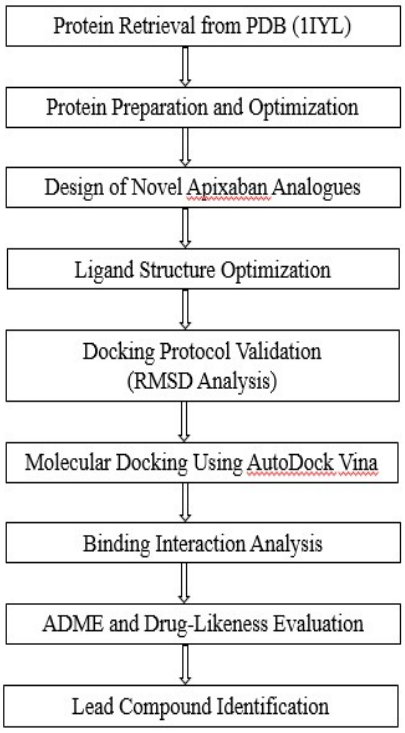


Figure 1: Workflow of the complete computational study.

Figure 1. Schematic workflow of the computational methodology employed for the identification of potential Candida albicans N-myristoyltransferase inhibitors, including protein preparation, ligand design, molecular docking, interaction analysis, and ADME evaluation.

2.2 Ligand Design and Optimization

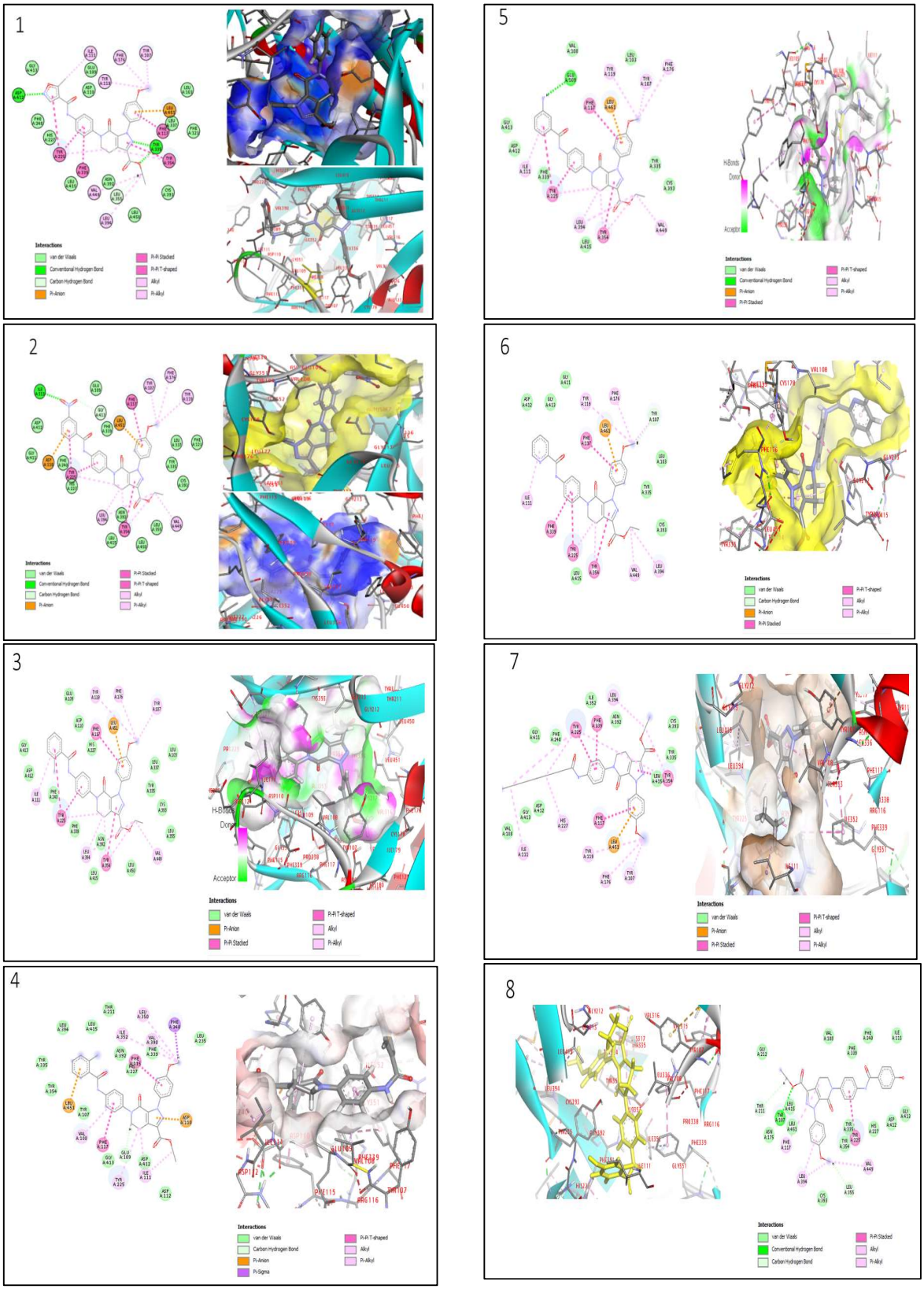
A series of fifteen novel Apixaban analogues were designed to investigate their potential inhibitory activity against *Candida albicans* N-myristoyltransferase. The design strategy was based on structural modification of the parent Apixaban scaffold through the introduction of different substituents at selected positions to enhance binding affinity, molecular interactions, and pharmacokinetic characteristics. The structural modifications were performed with the objective of improving the interaction of the designed compounds with key amino acid residues present within the active site of the target enzyme.

The chemical structures of all designed analogues were drawn using ACD/ChemSketch software. This platform was utilized for the construction and visualization of two-dimensional molecular structures as well as the generation of corresponding three-dimensional conformations required for computational studies. Each analogue was carefully examined to ensure proper valency, bond connectivity, and structural integrity prior to further analysis.

Following structure generation, the designed ligands were subjected to geometry optimization and energy minimization to obtain stable molecular conformations. Energy minimization is an essential step that reduces steric clashes, bond strain, and unfavorable atomic interactions within the molecule. The optimized structures represent energetically favorable conformations that are more suitable for molecular docking simulations and interaction analysis.

The minimized ligand structures were subsequently converted into the appropriate file formats required for docking studies. These prepared ligands were then employed for molecular docking against *Candida albicans* N-myristoyltransferase to evaluate their binding affinity and interaction patterns within the enzyme active site. The workflow ensured that all compounds were analyzed under standardized conditions, thereby enabling reliable comparison of their docking performance and pharmacokinetic properties.

The chemical structures of the fifteen designed Apixaban analogues used in the present investigation are shown in **Figure 2**.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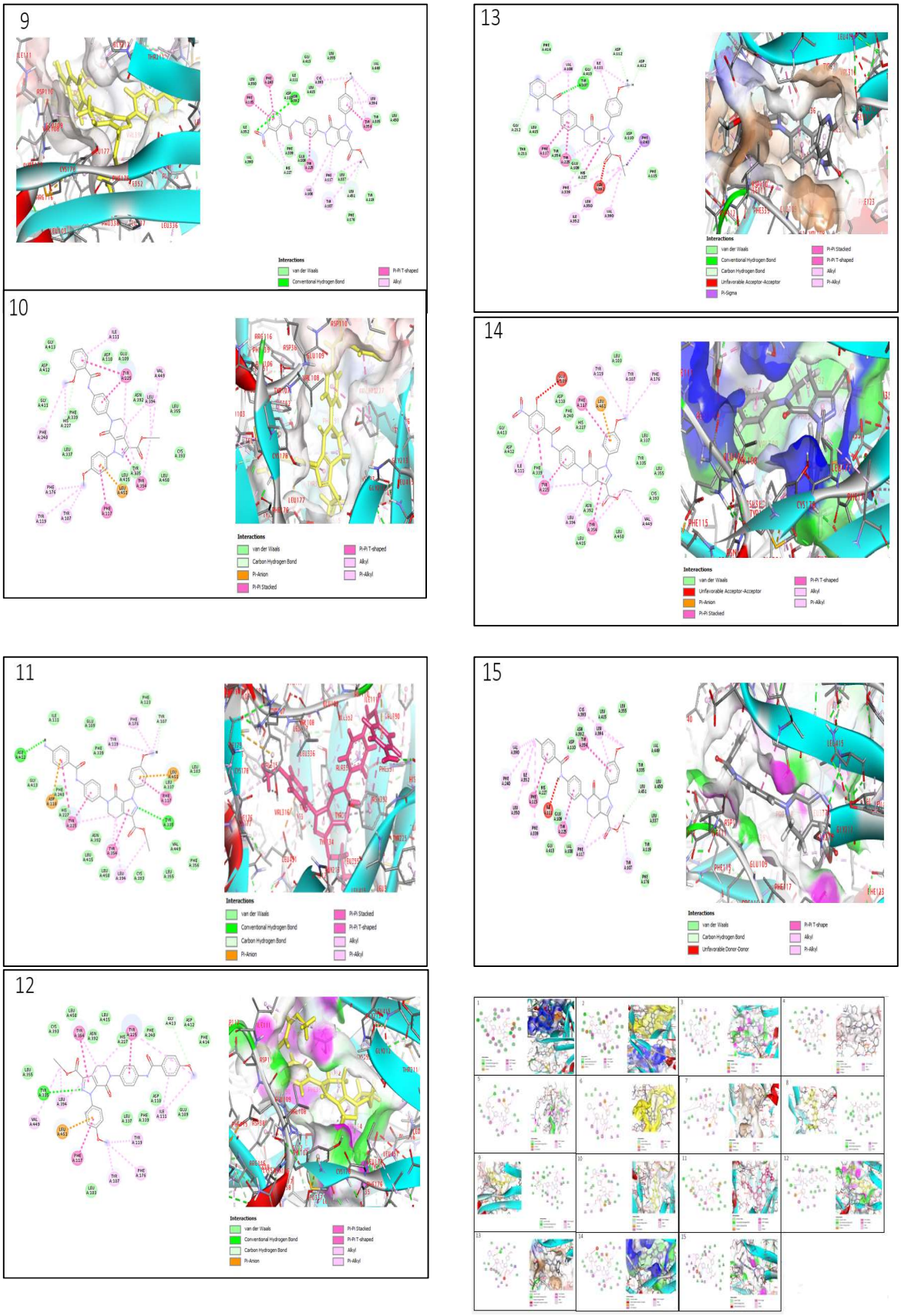

Figure 2. Chemical structures of the fifteen

designed Apixaban analogues developed for molecular docking and ADME evaluation against *Candida albicans* N-myristoyltransferase

Figure 2 illustrate the two-dimensional chemical structures of the designed Apixaban analogues evaluated in this study. Structural modifications were introduced into the parent scaffold to investigate their effects on molecular docking performance and predicted ADME characteristics against Candida albicans N-myristoyltransferase.

2.3 Molecular Docking Protocol

Molecular docking studies were carried out to investigate the binding affinity and interaction patterns of the designed Apixaban analogues against Candida albicans N-myristoyltransferase. Docking simulations were performed using AutoDockVina, an extensively utilized molecular docking program known for its accuracy, computational efficiency, and reliable prediction of ligand–protein binding conformations[26]. The prepared protein structure and optimized ligand molecules were converted into the required file formats prior to docking calculations.

The active binding pocket of Candida albicans N-myristoyltransferase was identified based on the location of the co-crystallized inhibitor present in the crystal structure[25]. A grid box was generated to encompass the entire binding region and to allow sufficient space for ligand flexibility during docking simulations. The grid center coordinates were set at X = 13.82, Y = 48.84, and Z = 1.68, while the grid dimensions were maintained at 21 × 21 × 21 Å with a grid spacing of 1.0 Å. These parameters ensured complete coverage of the active-site residues involved in ligand recognition and binding.

During the docking procedure, each designed Apixaban analogue was individually docked into the active site of the target protein. Multiple binding conformations were generated by the docking algorithm, and the pose exhibiting the lowest binding free energy was selected as the most favorable binding orientation. The docking score, expressed in kcal/mol, was used to estimate the strength of ligand–protein interactions, where more negative values indicated stronger predicted binding affinity.

The resulting docked complexes were further analyzed to identify key molecular interactions between the ligands and active-site amino acid residues. Hydrogen bonding, hydrophobic contacts, π–π interactions, π–alkyl interactions, and other non-covalent interactions were examined using Discovery Studio Visualizer. The generated docking poses and interaction profiles were subsequently employed for comparative analysis and identification of potential lead compounds among the designed Apixaban analogues.

2.4 Validation of Docking Protocol

To ensure the reliability and accuracy of the molecular docking procedure, a validation study was performed by re-docking the co-crystallized ligand (R64) into the active site of Candida albicans N-myristoyltransferase. Docking validation is an essential step in computational drug discovery, as it assesses the ability of the docking protocol to reproduce the experimentally observed binding orientation of the native ligand within the target protein[26].

The co-crystallized ligand was extracted from the crystal structure and subsequently re-docked into the predefined binding pocket using the same docking parameters employed for the designed Apixaban analogues. The predicted binding pose obtained from the docking simulation was then compared with the experimentally determined crystallographic conformation. The similarity between the two conformations was evaluated using root mean square deviation (RMSD) analysis[27].

The re-docking experiment produced an RMSD value of 1.38 Å with a docking score of −9.7 kcal/mol, indicating excellent agreement between the native and predicted ligand orientations. Generally, RMSD values below 2.0 Å are considered indicative of a reliable docking protocol capable of accurately reproducing experimentally observed binding modes. The obtained RMSD value therefore confirmed the suitability of the selected docking parameters and validated the use of the docking protocol for subsequent evaluation of the designed Apixaban analogues.

To evaluate the reliability of the docking protocol, the co-crystallized ligand R64 was re-docked into the active site of *Candida albicans* N-myristoyltransferase. The superimposition of the experimental ligand pose and the predicted docking conformation is presented in **Figure 3.** The close overlap between the two structures confirms the ability of the docking procedure to accurately reproduce the experimentally observed binding mode.

The close alignment of the two conformations with an RMSD value of 1.38 Å demonstrates the accuracy and reliability of the molecular docking protocol. Key active-site residues involved in ligand recognition and binding are indicated.

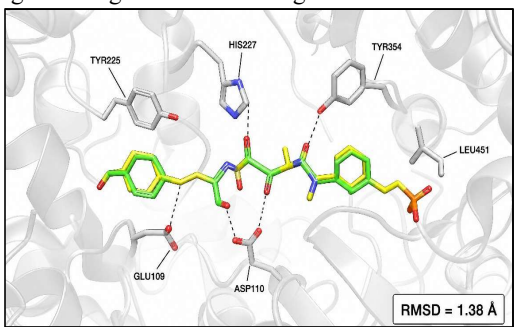

Figure 3.Superimposition of the native co-crystallized ligand (green) and the redocked ligand (yellow) within the active site of *Candida albicans* N-myristoyltransferase (PDB ID: 1IYL)

2.5 Binding Interaction Analysis

The molecular interactions between the designed Apixaban analogues and Candida albicans N-myristoyltransferase were analyzed using Discovery Studio Visualizer[28], [29]. This software was employed to investigate the binding orientation of the docked ligands within the active site and to identify the key amino acid residues contributing to ligand stabilization. Detailed interaction analysis provides valuable information regarding the molecular basis of ligand recognition and helps explain variations in binding affinity among the designed compounds.

Following molecular docking, the most favorable binding pose of each ligand was selected based on the lowest docking energy. The selected complexes were subsequently subjected to interaction profiling to characterize the nature and extent of ligand–protein interactions. Particular attention was given to hydrogen bonding, hydrophobic contacts, and π-based interactions, as these non-covalent forces play a crucial role in determining the stability of protein–ligand complexes.

Hydrogen-bond interactions were examined to identify residues involved in strong directional contacts with the docked ligands. These interactions contribute significantly to binding specificity and are often associated with enhanced ligand affinity. The hydrogen-bonding patterns observed within the active site were evaluated in terms of interacting residues and binding orientation.

Hydrophobic interactions were also analyzed because they facilitate favorable accommodation of the ligands within the binding pocket. Residues participating in alkyl, π-alkyl, and other hydrophobic contacts were identified to assess their contribution to complex stabilization. These interactions are important for maintaining the structural integrity of the ligand–protein complex and enhancing overall binding strength.

In addition, π-based interactions, including π–π stacking and π–π T-shaped interactions, were investigated. Such interactions commonly occur between aromatic rings of the ligands and aromatic amino acid residues present within the active site. These contacts contribute to ligand stabilization and frequently play a significant role in improving docking performance.

The interaction profiles generated using Discovery Studio Visualizer were subsequently used to identify key active-site residues involved in ligand recognition and to compare the binding behavior of the designed Apixaban analogues. The resulting interaction maps provided important insights into the molecular features responsible for enhanced binding affinity and assisted in the selection of promising lead compounds for further evaluation.

2.6 ADME Prediction

The pharmacokinetic and drug-likeness properties of the designed Apixaban analogues were evaluated using the SwissADME web server[30]. SwissADME is a widely utilized computational platform that provides comprehensive information regarding the absorption, distribution, metabolism, excretion, and physicochemical characteristics of small molecules[23]. The generated data were employed to assess the suitability of the designed compounds as potential drug candidates prior to experimental investigation.

Drug-likeness evaluation was performed using established empirical rules commonly applied in early-stage drug discovery. Lipinski's Rule of Five was used to assess oral drug-likeness based on molecular weight, lipophilicity, hydrogen bond donors, and hydrogen bond acceptors[31]. Compounds satisfying these criteria are generally considered to possess favorable oral bioavailability and acceptable physicochemical properties.

In addition, Veber's rule was applied to evaluate oral bioavailability based on the number of rotatable bonds and topological polar surface area (TPSA)[32]. Molecules meeting Veber's criteria are typically associated with improved membrane permeability and gastrointestinal absorption. Egan's rule was further employed to examine the balance between lipophilicity and polarity, which are important determinants of oral drug absorption[33].

The designed analogues were also assessed according to Muegge's drug-likeness filter, which integrates multiple molecular descriptors to identify compounds with favorable characteristics for drug development[34]. Compliance with these filters provides an indication of the overall suitability of the compounds for further pharmaceutical investigation.

Pharmacokinetic predictions generated by SwissADME included gastrointestinal absorption, blood–brain barrier permeability, skin permeability, bioavailability score, and cytochrome P450 enzyme inhibition profiles. These parameters were analyzed to estimate the absorption behavior, metabolic stability, and potential drug–drug interaction risks of the designed compounds. The obtained ADME profiles were subsequently used to compare the pharmacokinetic suitability of the analogues and to support the identification of promising lead candidates for further antifungal development.

3. Results and Discussion

The designed apixaban analogues were evaluated using a comprehensive computational approach involving molecular docking and ADME prediction studies. The objective was to identify compounds

with strong binding affinity toward Candida albicans N-myristoyltransferase while maintaining favorable pharmacokinetic characteristics. The obtained results provided valuable insights into the binding behavior, drug-likeness, and lead optimization potential of the designed derivatives.

3.1 Docking Validation Results

Validation of the molecular docking protocol is a critical step to ensure the reliability of the predicted ligand–protein interactions. In the present study, the docking procedure was validated through re-docking of the co-crystallized ligand R64 into the active site of *Candida albicans* N-myristoyltransferase (PDB ID: 1IYL). The predicted binding pose obtained after docking was compared with the experimentally determined crystallographic conformation using root mean square deviation (RMSD) analysis.

The re-docking experiment yielded an RMSD value of 1.38 Å, indicating a high degree of similarity between the native and predicted ligand conformations. In molecular docking studies, RMSD values below 2.0 Å are generally considered acceptable and demonstrate that the docking protocol can reliably reproduce the experimentally observed binding orientation. The low RMSD value obtained in this study confirms the accuracy of the selected docking parameters and validates the suitability of the docking methodology for evaluating the designed Apixaban analogues.

Furthermore, the native ligand R64 exhibited a docking score of −9.7 kcal/mol, reflecting favorable binding within the active site of the target enzyme. The close agreement between the crystallographic and redocked conformations, together with the observed docking score, provides confidence in the reliability of the docking protocol and supports its application for subsequent screening of the designed compounds.**Table 1** summarizes the docking validation statistics obtained from the re-docking experiment.

Table 1. Docking validation statistics for the molecular docking protocol.

Protein	Native Ligand	RMSD (Å)	Docking Score (kcal/mol)
Candida albicans N-Myristoyltransferase (PDB ID: 1IYL)	R64	1.38	-9.7

Table 1 illustrate theresults of docking protocol validation using the co-crystallized ligand R64. The low RMSD value indicates successful reproduction of the experimental binding pose and confirms the suitability of the docking parameters for subsequent molecular docking studies.

3.2 Docking Scores of Designed Analogues

To investigate the binding potential of the designed apixaban analogues against *Candida albicans* N-myristoyltransferase (PDB ID: 1IYL), molecular docking studies were performed using AutoDockVina. The docking score, expressed in kcal/mol, was used to estimate the binding affinity of each ligand toward the active site of the target protein, where more negative values indicate stronger predicted interactions. The docking results and ranking of the designed compounds are presented in **Table 2.**

Table 2. Molecular docking scores and ranking of the designed Apixaban analogues against Candida albicans N-myristoyltransferase

Compound Number	Docking Score (kcal/mol)	Rank
Compound 9	-11	1
Compound 2	-10.6	2
Compound 3	-10.6	3
Compound 15	-10.6	4
Compound 5	-10.5	5
Compound 6	-10.4	6
Compound 10	-10.4	7
Compound 11	-10.3	8
Compound 14	-10.1	9
Compound 12	-9.9	10
Compound 4	-9.8	11
Compound 8	-9.7	12
R64 (Reference Ligand)	-9.7	Reference
Compound 1	-9.3	13
Compound 7	-9.2	14
Compound 13	-9.1	15

Table 2 illustrate the molecular docking scores and ranking of the designed Apixaban analogues against *Candida albicans* N-myristoyltransferase. The compounds were ranked according to their predicted binding energies, with more negative docking scores indicating stronger ligand–protein interactions and greater binding affinity toward the target enzyme.

The molecular docking study revealed notable differences in the binding affinities of the designed Apixaban analogues toward Candida albicans N-myristoyltransferase. The docking scores obtained for the compounds ranged from −9.1 to −11.0 kcal/mol, indicating generally strong interactions with the target enzyme. The reference ligand R64 exhibited a docking score of −9.7 kcal/mol and was used as a benchmark for comparative evaluation.

Among all evaluated analogues, Compound 9 demonstrated the highest binding affinity with a docking score of −11.0 kcal/mol, suggesting a highly favorable interaction within the active site. Compounds 2, 3, and 15 also displayed excellent docking performance, each producing a docking score of −10.6 kcal/mol. Similarly, Compounds 5, 6, 10, and 11 showed strong binding affinities, with docking energies ranging from −10.3 to −10.5

kcal/mol. These values were considerably more favorable than that of the reference ligand, indicating the potential of these analogues as promising inhibitors of *Candida albicans* N-myristoyltransferase.

The superior binding affinities observed for the top-ranked compounds may be attributed to their ability to establish multiple stabilizing interactions within the active site. Interaction analysis revealed the presence of hydrogen bonds, hydrophobic contacts, π–π interactions, π–anion interactions, and alkyl interactions involving key amino acid residues such as TYR225, TYR354, HIS227, ASP110, GLU109, LEU451, and PHE117. These interactions contributed to enhanced ligand stabilization and improved docking scores.

A comparative representation of the docking energies of all designed compounds and the reference ligand is presented in Figure 4.

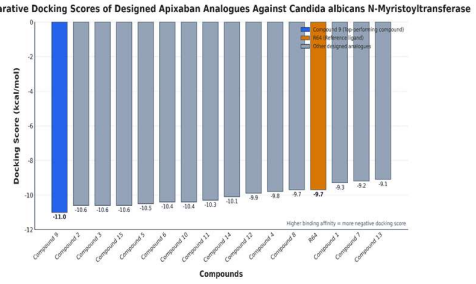

Figure 4.Comparative docking scores of the designed Apixaban analogues and the reference ligand R64 against *Candida albicans* N-myristoyltransferase.

More negative docking energies indicate stronger predicted binding affinity toward the target protein, with Compound 9 exhibiting the highest docking affinity among all evaluated compounds.

3.3 Binding Interaction Analysis of Lead Compounds

To gain a deeper understanding of the molecular basis underlying the observed binding affinities, detailed interaction analyses were performed for the top-ranked Apixaban analogues using Discovery Studio Visualizer. The study focused on identifying key non-covalent interactions, including hydrogen bonds, hydrophobic contacts, π–π interactions, π–anion interactions, and other stabilizing forces that contribute to ligand binding within the active site of Candida albicans N-myristoyltransferase. Such interactions play a crucial role in determining the strength and stability of ligand–protein complexes and are often associated with enhanced inhibitory potential.

Among the evaluated compounds, Compounds 9, 2, 3, and 15 demonstrated the most favorable docking scores and were therefore selected for detailed interaction analysis. These lead compounds exhibited extensive interactions with important active-site residues, suggesting strong binding compatibility within the enzyme binding pocket. The interaction profiles revealed the involvement of several conserved amino acid residues, including TYR225, TYR354, HIS227, ASP110, GLU109, LEU451, and PHE117, which are known to contribute significantly to ligand recognition and stabilization.

A comparative summary of the molecular interactions observed for the top-performing Apixaban analogues is presented in **Table 3.** The table provides an overview of docking scores, hydrogen-bonding interactions, π-based interactions, hydrophobic contacts, and key amino acid residues involved in ligand binding within the active site of Candida albicans N-myristoyltransferase.

Table 3. Binding interaction summary of the top-performing Apixaban analogues.

Compound	Docking Score (kcal/mol)	Hydrogen Bonds	Pi Interactions	Hydrophobic Contacts	Key Residues
Compound 9	-11	ASN392, HIS227, LEU451	TYR225, TYR354, PHE240, PHE115	VAL108, TYR107, PHE117, LEU394, CYS393, VAL449	ASN392, HIS227, LEU451, TYR225, TYR354, ASP110, GLU109
Compound 2	-10.6	ILE111, GLY413	TYR225, TYR354, PHE117, LEU451, ASP110	TYR107, TYR119, PHE176, VAL449, LEU394	ILE111, TYR225, TYR354, ASP110, GLU109, LEU451
Compound 3	-10.6	—	TYR225, TYR354, PHE117, LEU451	ILE111, LEU394, VAL449, TYR107, PHE176, TYR11	TYR225, TYR354, LEU451, ASP110, GLU109

				9	
Compound 15	-10.6	LEU 451	TYR225, TYR354	VAL390, PHE240, PHE339, PHE117, ILE352, LEU350, LEU394, TYR107, CYS393	TYR 225, TYR 354, LEU 451, ASP 110, GLU 109

Table 3illustrate thesummary of the key molecular interactions exhibited by the top-ranked Apixaban analogues within the active site of *Candida albicans* N-myristoyltransferase. The table includes docking scores, hydrogen-bonding interactions, π-based interactions, hydrophobic contacts, and the principal amino acid residues contributing to ligand stabilization and binding affinity.

Compound 9exhibited the highest binding affinity among all designed analogues, with a docking score of −11.0 kcal/mol. detailed interaction analysis revealed the formation of a conventional hydrogen bond with ASN392 and carbon hydrogen-bond interactions involving HIS227 and LEU451. In addition, the compound established multiple π–π T-shaped interactions with TYR225, TYR354, PHE240, and PHE117. Several hydrophobic contacts involving VAL108, TYR107, PHE117, LEU394, CYS393, and VAL449 further contributed to the stability of the complex. The presence of both hydrogen-bonding and extensive aromatic interactions within the active site is likely responsible for the superior binding affinity of Compound 9. The two-dimensional interaction profile and three-dimensional binding orientation of Compound 9 within the active site of Candida albicans N-myristoyltransferase are presented in Figure 5A and Figure 5B, respectively.

Compound 2demonstrated excellent binding affinity with a docking score of −10.6 kcal/mol. The ligand formed a conventional hydrogen bond with ILE111 and a carbon hydrogen-bond interaction with GLY413. Strong π–π stacking interactions were observed with TYR354 and PHE117, while TYR225 contributed through π–π T-shaped interactions. Additional stabilization was provided by π–anion interactions involving LEU451 and ASP110 together with hydrophobic contacts formed with TYR107, TYR119, PHE176, VAL449, and LEU394. These interactions collectively supported the favorable docking score obtained for Compound 2. The corresponding two-dimensional interaction map is shown in Figure 5C.

Compound 3also produced a docking score of −10.6 kcal/mol and displayed a binding pattern similar to that of Compound 2. The ligand established significant π–π stacking interactions with TYR354 and PHE117 along with a π–π T-shaped interaction involving TYR225. A π–anion interaction with LEU451 and extensive hydrophobic contacts with ILE111, LEU394, VAL449, TYR107, PHE176, and TYR119 further enhanced complex stability. The predominance of aromatic and hydrophobic interactions contributed substantially to the favorable binding affinity observed for this analogue. The two-dimensional interaction map of Compound 3 is presented in Figure 5D.

Compound 15was among the top-performing analogues, exhibiting a docking score of −10.6 kcal/mol. Interaction analysis revealed a carbon hydrogen-bond interaction with LEU451 and multiple π–π T-shaped interactions involving TYR225 and TYR354. The ligand further established extensive hydrophobic interactions with VAL390, PHE240, PHE339, PHE117, ILE352, LEU350, LEU394, TYR107, and CYS393. These interactions collectively contributed to strong ligand accommodation within the active-site region and supported the favorable docking performance of Compound 15.

Overall, the interaction analysis indicated that aromatic residues such as TYR225, TYR354, and PHE117, together with catalytic-site residues including ASP110, GLU109, HIS227, and LEU451, play important roles in ligand recognition and stabilization. The interaction profile of Compound 9 was particularly favorable, supporting its selection as the most promising lead candidate for further pharmacokinetic evaluation and antifungal investigation.To gain deeper insight into the molecular basis of ligand binding, the interaction pattern of the top-ranked compound was analyzed using Discovery Studio Visualizer. The analysis revealed the involvement of several key active-site residues through hydrogen bonding, hydrophobic contacts, and π-interactions, which contributed to the stability of the protein–ligand complex. The detailed binding interactions of Compound 9 with Candida albicans N-myristoyltransferase are illustrated in Figure 5.

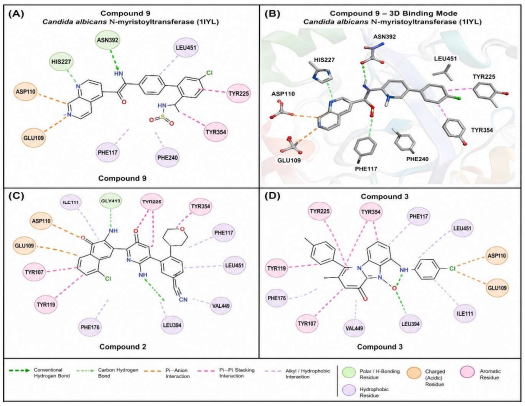

Figure 5.Binding interaction analysis of the lead Apixaban analogues with *Candida albicans* N-myristoyltransferase (PDB ID: 1IYL)

(A) Two-dimensional interaction map of Compound 9 showing hydrogen-bonding, π-based interactions, and hydrophobic contacts with key active-site residues. **(B)** Three-dimensional binding orientation of Compound 9 within the active-site cavity highlighting ligand–protein interactions. **(C)** Two-dimensional interaction map of Compound 2 illustrating the major interactions responsible for ligand stabilization within the enzyme binding pocket. **(D)** Two-dimensional interaction map of Compound 3 showing the principal interactions involved in ligand recognition and binding within the active site.

3.4 Structure–Activity Relationship (SAR)

The structure–activity relationship analysis was performed to identify the molecular features responsible for the enhanced binding affinity of the designed Apixaban analogues toward *Candida albicans* N-myristoyltransferase. Comparative evaluation of the docking results revealed that modifications introduced on the aromatic ring system significantly influenced the interaction profile and binding strength of the compounds within the enzyme active site.

The highest-ranked compounds, particularly Compounds 9, 2, 3, and 15, contained structural modifications that promoted favorable interactions with key active-site residues. These analogues demonstrated improved docking scores compared with the reference ligand R64, suggesting that strategic substitution of the parent Apixaban scaffold enhanced ligand–protein recognition and stabilization. The presence of aromatic moieties facilitated π–π stacking and π–π T-shaped interactions with residues such as TYR225, TYR354, and PHE117, which contributed substantially to binding affinity.

Aromatic ring modifications played an important role in determining ligand orientation within the binding pocket. Compounds possessing appropriately substituted aromatic rings exhibited stronger hydrophobic and aromatic interactions, allowing improved accommodation within the active-site cavity. These interactions enhanced the stability of the ligand–protein complexes and were associated with more favorable docking energies.

Electron-donating substituents were observed to positively influence binding affinity by increasing electron density within aromatic systems and strengthening aromatic interactions with active-site residues. Such substitutions promoted enhanced π-based interactions and improved molecular complementarity within the binding pocket. The superior performance of several lead compounds may be partially attributed to the presence of these electron-rich functional groups.

Conversely, electron-withdrawing substituents contributed to binding through modulation of molecular polarity and interaction potential. In selected analogues, these groups facilitated favorable contacts with catalytic residues and improved overall binding orientation. The balance between electron-donating and electron-withdrawing effects appeared to be important for achieving optimal interaction patterns and maximizing docking performance.

Overall, the SAR analysis demonstrated that the combination of aromatic ring optimization and strategic electronic modifications significantly influenced binding affinity toward *Candida albicans* N-myristoyltransferase. The results suggest that enhanced aromatic interactions, favorable hydrophobic contacts, and appropriate electronic characteristics are key determinants for the development of potent N-myristoyltransferase inhibitors based on the Apixaban scaffold.The major structure–activity relationship trends identified in the present study are summarized in **Figure 6**.

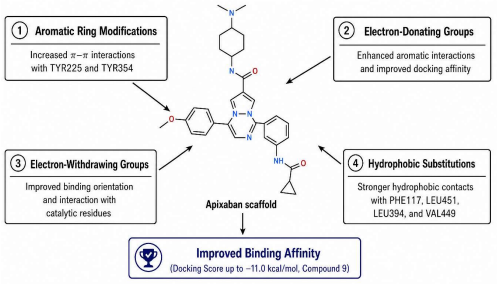

Figure 6.Structure–activity relationship (SAR)

Figure 6 SAR summary of the designed Apixaban analogues illustrating the influence of aromatic ring modifications and electron-donating/electron-withdrawing substituents on binding affinity toward *Candida albicans* N-myristoyltransferase.

3.5 ADME Analysis

To evaluate the pharmaceutical suitability of the synthesized apixaban derivatives, an in silico ADME assessment was performed using the SwissADME platform. The analysis included physicochemical characterization, drug-likeness

prediction, and pharmacokinetic profiling. These parameters are widely employed during early-stage drug discovery to identify compounds with favorable oral bioavailability and acceptable pharmacokinetic behavior.

To assess the physicochemical suitability of the synthesized apixaban derivatives for oral administration, key molecular descriptors including molecular weight, topological polar surface area (TPSA), lipophilicity (LogP), and rotatable bonds were evaluated using the SwissADME platform. The calculated physicochemical properties of all designed derivatives are presented in Table 4.

Table 4. Physicochemical properties of the synthesized compounds

Compound	Molecular Weight (g/mol)	TPSA (Å²)	Consensus LogP	Rotatable Bonds
1	515.52	128.79	3.19	9
2	556.55	143.07	0.22	10
3	544.99	102.76	4.34	9
4	623.88	102.76	4.93	9
5	525.56	128.78	3.35	9
6	511.53	115.65	3.36	9
7	546.66	102.76	5.21	15
8	526.54	122.99	3.49	9
9	569.56	148.58	3.63	10
10	540.57	111.99	3.83	10
11	525.56	128.78	3.34	9
12	540.57	111.99	3.88	10
13	545.97	115.65	3.71	9
14	571.54	168.81	2.96	10
15	544.99	102.76	4.4	9

Physicochemical descriptors predicted using SwissADME. TPSA = Topological Polar Surface Area; LogP = Consensus lipophilicity value; Rotatable Bonds indicate molecular flexibility.

The data presented in Table 4 demonstrated that most compounds possessed molecular weights between 500 and 600 g/mol with moderate to high lipophilicity. Compounds 3 and 15 exhibited favorable TPSA and LogP values that may support membrane permeability, whereas Compounds 9 and 14 showed relatively higher polarity due to elevated TPSA values. Overall, the physicochemical profiles suggested that several derivatives possessed characteristics compatible with oral drug candidates.

Drug-likeness assessment was subsequently performed to evaluate the compliance of the synthesized derivatives with established medicinal chemistry guidelines. Lipinski, Veber, Egan, and Muegge filters, along with the predicted bioavailability score, were employed to estimate the oral drug potential of the compounds. The results of the drug-likeness evaluation are summarized in Table 5.

Table 5. Drug-likeness evaluation of the synthesized compounds

Compound	Lipinski Violations	Veber Violations	Egan Violations	Muegge Violations	Bioavailability Score
1	2	0	0	0	0.17
2	2	1	1	0	0.17
3	1	0	0	1	0.55
4	1	0	0	2	0.55
5	1	0	0	0	0.55
6	1	0	0	0	0.55
7	1	1	0	1	0.55
8	1	0	0	0	0.55
9	2	1	1	0	0.17
10	1	0	0	0	0.55
11	1	0	0	0	0.55
12	1	0	0	0	0.55
13	1	0	0	0	0.55
14	2	1	1	1	0.17
15	1	0	0	1	0.55

Drug-likeness assessment generated using SwissADME. Lipinski, Veber, Egan, and Muegge rules were used to estimate oral drug potential. Bioavailability scores closer to 0.55 indicate improved probability of oral bioavailability.

The results summarized in Table 5 indicated that Compounds 3, 5, 6, 8, 10, 11, 12, 13, and 15 satisfied most of the evaluated drug-likeness criteria and achieved a bioavailability score of 0.55. In contrast, Compounds 2, 9, and 14 exhibited multiple violations that may adversely affect their oral bioavailability. These findings suggest that several derivatives possess favorable structural characteristics for further pharmaceutical development.

To further investigate the pharmacokinetic behavior of the designed derivatives, parameters related to absorption, distribution, metabolism, and skin permeation were predicted using SwissADME. These descriptors provide preliminary insight into the potential in vivo performance of the compounds. The predicted pharmacokinetic properties are presented in Table 6.

Table 6. Predicted pharmacokinetic properties of the synthesized compounds

Compound	GI Absorption	BBB Permeability	CYP Inhibition*	Skin Permeability (log Kp)
1	High	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	-6.97
2	Low	No	None	-6.85
3	High	No	CYP2C19, CYP2C9, CYP3A4	-5.89
4	High	No	CYP2C19, CYP2C9, CYP3A4	-5.87
5	High	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	-6.69
6	High	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	-6.65
7	High	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	-5.01
8	High	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	-6.47
9	Low	No	CYP2C19, CYP2C9, CYP3A4	-6.35
10	High	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	-6.32
11	High	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	-6.69
12	High	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	-6.32
13	High	No	CYP2C19, CYP2C9, CYP2D6, CYP3A4	-6.41
14	Low	No	CYP2C19, CYP2C9, CYP3A4	-6.48
15	High	No	CYP2C19, CYP2C9, CYP3A4	-5.89

*CYP inhibition represents the predicted cytochrome P450 isoforms inhibited by the compounds.

Predicted pharmacokinetic properties obtained using SwissADME. GI absorption indicates gastrointestinal uptake; BBB permeability represents the ability to cross the blood-brain barrier; CYP inhibition identifies possible metabolic enzyme interactions; log Kp values describe skin permeation characteristics.

The pharmacokinetic evaluation revealed that most derivatives exhibited high gastrointestinal absorption, suggesting favorable oral uptake. None

of the compounds were predicted to permeate the blood-brain barrier, indicating a lower probability of central nervous system exposure. Compounds 2, 9, and 14 displayed comparatively lower gastrointestinal absorption, whereas Compound 3 demonstrated a favorable balance of absorption and drug-likeness characteristics. Additionally, the predicted CYP inhibition profiles suggested potential interactions with specific metabolic enzymes that should be further investigated experimentally.

Overall, the ADME assessment demonstrated that several of the designed apixaban derivatives possess favorable physicochemical and pharmacokinetic characteristics. Most compounds exhibited acceptable gastrointestinal absorption, satisfactory drug-likeness profiles, and limited blood-brain barrier permeability. Among the evaluated derivatives, Compound 3 showed a balanced combination of molecular properties and pharmacokinetic behavior, indicating its potential as a promising lead candidate for further antifungal investigation. These findings complement the molecular docking results and support the continued evaluation of the selected derivatives in future experimental studies.

3.6 Lead Optimization and Candidate Selection

The identification of a lead compound requires the integration of molecular docking performance with pharmacokinetic and drug-likeness characteristics. Although several synthesized apixaban derivatives demonstrated strong binding affinity toward Candida albicans N-myristoyltransferase, the final lead selection was based on a balanced assessment of docking score, ADME profile, and overall drug-likeness properties.

Compounds exhibiting favorable binding energies were further evaluated for their physicochemical characteristics, oral bioavailability, gastrointestinal absorption, and compliance with established drug-likeness criteria. This integrated approach enabled the prioritization of compounds with both strong target affinity and acceptable pharmacokinetic behavior.

Among the evaluated derivatives, Compounds 9, 2, 3, 5, and 15 emerged as the most promising candidates. Compound 9 demonstrated the strongest binding affinity toward the target protein with a docking score of −11.0 kcal/mol, indicating a highly stable protein–ligand complex. Furthermore, interaction analysis revealed multiple hydrophobic contacts, hydrogen bonding interactions, and π-interactions with key amino acid residues located within the active site of N-myristoyltransferase. These interactions contributed significantly to its superior docking performance.

Although Compound 3 exhibited a comparatively favorable ADME profile and higher predicted oral bioavailability, its docking score was slightly lower than that of Compound 9. Since the primary objective of the present investigation was the identification of potent inhibitors of fungal N-myristoyltransferase, binding affinity was considered the principal selection criterion, while ADME properties were used as supporting parameters.

The overall ranking of the lead candidates is presented in Table 7. Based on the combined evaluation of molecular docking and pharmacokinetic characteristics, Compound 9 was identified as the most promising lead molecule for further optimization and experimental validation. The exceptional binding affinity observed for Compound 9 suggests a strong potential for effective target inhibition, making it a suitable candidate for future synthesis, biological evaluation, and structure–activity relationship studies.

Table 7. Final ranking of lead compounds

Compound	Docking Score (kcal/mol)	ADME Assessment	Overall Rank
9	-11	Moderate	1
2	-10.6	Moderate	2
3	-10.6	Excellent	3
5	-10.5	Good	4
15	-10.6	Good	5

Table 7illustrate the final prioritization of lead compounds based on combined molecular docking performance and ADME evaluation.

The lead optimization study indicated that Compound 9 possesses the most favorable balance between target affinity and drug-like properties. Its superior docking score, extensive interactions within the active site, and acceptable pharmacokinetic profile collectively support its selection as the primary lead candidate. Consequently, Compound 9 may serve as a valuable scaffold for future optimization efforts aimed at developing novel antifungal agents targeting N-myristoyltransferase.

4. Conclusion

The present study employed a structure-based drug design approach to identify potential antifungal agents targeting *Candida albicans* N-myristoyltransferase. A series of fifteen apixaban analogues were rationally designed and evaluated through molecular docking and in silico ADME investigations to assess their therapeutic potential.

Molecular docking analysis revealed that several designed derivatives exhibited stronger binding affinities toward the target protein than the reference ligand R64, suggesting their potential to act as effective N-myristoyltransferase inhibitors. Detailed interaction studies demonstrated favorable binding patterns involving key amino acid residues within the active site, highlighting the suitability of the designed compounds for further investigation.

Among all evaluated derivatives, Compound 9 displayed the highest binding affinity with a docking score of −11.0 kcal/mol, indicating the formation of a highly stable protein–ligand complex. The extensive network of hydrophobic interactions and non-covalent contacts observed for Compound 9 further supported its identification as the most promising lead candidate within the series.

The ADME assessment demonstrated that the majority of the designed compounds possessed acceptable physicochemical characteristics, favorable drug-likeness properties, and suitable pharmacokinetic profiles. These findings suggest that the selected derivatives have the potential to exhibit adequate oral bioavailability and desirable drug-like behavior.

Overall, the combined docking and ADME results identified several promising lead molecules, particularly Compound 9, for further development. The findings of this study provide a strong foundation for future synthetic efforts and experimental biological evaluation. Further in vitro and in vivo studies are required to validate the predicted antifungal activity and establish the therapeutic potential of these novel apixaban-derived candidates.

5. Abbreviations

ADME – Absorption, Distribution, Metabolism, and Excretion; Å – Angstrom; BBB – Blood–Brain Barrier; CYP – Cytochrome P450; GI – Gastrointestinal; HBA – Hydrogen Bond Acceptor; HBD – Hydrogen Bond Donor; kcal/mol – Kilocalories per Mole; LogP – Octanol/Water Partition Coefficient; NMT – N-Myristoyltransferase; PDB – Protein Data Bank; RMSD – Root Mean Square Deviation; SAR – Structure–Activity Relationship; TPSA – Topological Polar Surface Area; 2D – Two-Dimensional; 3D – Three-Dimensional; AutoDockVina (ADV); Discovery Studio Visualizer (DSV); Molecular Docking (MD); SwissADME (Swiss Absorption, Distribution, Metabolism, and Excretion Prediction Platform)

6. Declarations

- **Funding:** The author declares that no specific funding was received for this research work from any funding agency in the public, commercial, or not-for-profit sectors.
- **Competing Interests:** The author declares that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
- **Ethical Approval:** Not applicable. This study was conducted entirely using computational and in silico methods, including molecular docking and ADME prediction, and did not involve human participants, animals, or biological samples.
- **Consent to Participate:** Not applicable.
- **Consent to Publish:** Not applicable.
- **Data Availability Statement:** The data generated or analyzed during this study are included in this published article and its supplementary information files. Additional data may be made available from the corresponding author upon reasonable request.
- **Acknowledgements:** The author would like to acknowledge the use of freely available computational resources and databases employed in this study, including the Protein Data Bank (PDB), AutoDockVina, Discovery Studio Visualizer, and SwissADME.

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