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REVIEW ARTICLE

Design, Molecular Docking, Synthesis, and Evaluation of Apixaban Analogues with Antifungal Activity

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ABSTRACT
Invasive fungal infections are an increasing global health concern, compounded by rising resistance and dose-limiting toxicity of current antifungal agents. Apixaban, a clinically used anticoagulant, offers a privileged pyrazole–pyrazinone scaffold with modular P1/P2/P4 regions that can be repurposed for antifungal lead discovery. This review summarizes recent advances in the design, molecular docking, synthesis, and biological evaluation of apixaban analogues developed as antifungal candidates targeting fungal N-myristoyltransferase (NMT), a key enzyme in protein N-myristoylation that is essential for fungal viability and virulence. Particular emphasis is placed on structure-based design strategies that exploit crystallographic and modelled NMT structures to optimize interactions within the myristoyl-CoA and peptide binding pockets. In silico workflows combining library generation, docking, binding-mode analysis, and basic ADMET filtering are discussed in the context of prioritizing apixaban-derived scaffolds. Synthetic approaches enabling efficient construction of the apixaban core and late-stage diversification of P1, P2, and P4 regions, including click-chemistry-based triazole installation and heterocycle replacement, are critically outlined. Antifungal evaluation data from standardized in vitro assays against clinically relevant Candida, Aspergillus, and Cryptococcus species are reviewed alongside preliminary NMT inhibition and cytotoxicity results, enabling correlation of structure–activity relationships with predicted binding modes and drug-likeness. Remaining challenges—including limited in vivo validation, achieving selectivity over human NMT, and mitigating resistance risk—are highlighted. Overall, apixaban-based NMT inhibitors emerge as a promising chemical platform for next-generation antifungal agents and a productive direction for future AI-assisted optimization and translational research.
Keywords: Apixaban analogues; Antifungal agents; N-myristoyltransferase (NMT); Molecular docking; Structure–activity relationship (SAR);Drug repurposing

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INTRODUCTION

Global burden of fungal infections, resistance, and limitations of current antifungal therapy Fungal infections represent a major and growing global health concern, particularly among immunocompromised individuals, critically ill patients, and those undergoing intensive or long-term medical interventions such as organ transplantation, chemotherapy, or broad-spectrum antibiotic therapy.(1,2) Invasive mycoses caused by species of Candida, Aspergillus, and Cryptococcus are associated with unacceptably high morbidity and mortality, in many settings exceeding those observed for severe bacterial infections despite aggressive clinical management.(3) At the same time, the therapeutic armamentarium remains constrained to a limited number of drug classes—azoles, echinocandins, polyenes, and flucytosine—which collectively define a narrow antifungal pipeline.(4). The extensive and often prolonged use of these agents has driven the emergence and global dissemination of resistance, exemplified by azole-resistant *Candida* and *Aspergillus* species and the rapid spread of multidrug-resistant **Candida auris*.(5) In addition to resistance, currently available antifungal drugs suffer from significant shortcomings, including dose-limiting host toxicity, complex drug–drug interactions, and restricted spectra of activity, suboptimal oral bioavailability, and poor performance against biofilm-associated infections.(6) These converging challenges underscore an urgent need for

antifungal agents with novel mechanisms of action, broader and more predictable activity profiles, and improved safety and pharmacokinetic characteristics.(7)

Drug repurposing and privileged scaffolds: apixaban as a versatile heterocyclic core

Drug repurposing has emerged as an efficient strategy to accelerate antifungal discovery by exploiting existing clinical, pharmacological, toxicological, and pharmacokinetic knowledge. (8) In parallel, the concept of privileged scaffolds—defined as molecular frameworks capable of productive binding to multiple biological targets—has gained prominence in medicinal chemistry as a means to generate new leads from well-behaved core structures.(9) Such scaffolds provide a robust foundation for rapid optimization through rational substitution and systematic exploration of structure–activity relationships.(10). Apixaban, a clinically approved oral anticoagulant, exemplifies a privileged heterocyclic scaffold. Its compact, highly functionalized architecture incorporates pyrazole and pyrazinone motifs, multiple hydrogen-bond donors and acceptors, and clearly delineated regions that can be chemically modified.(11,12) These features confer attractive drug-like properties and make the apixaban core particularly amenable to scaffold diversification.(13) Of note, the modular P1, P2, and P4 regions that govern its original pharmacology can be strategically redesigned to modulate physicochemical characteristics and redirect biological activity toward non-coagulation targets, including fungal enzymes.(14)

Fungal N-myristoyltransferase (NMT) as an essential antifungal target

N-Myristoyltransferase (NMT) is a conserved acyltransferase that catalyzes the covalent attachment of myristic acid to the N-terminal glycine of substrate proteins, a lipid modification that is crucial for membrane association, intracellular trafficking, signal transduction, and specific protein–protein interactions.(15,16) In fungal pathogens, NMT is indispensable for cell viability, morphogenesis, and virulence, rendering it an attractive and mechanistically distinct target for antifungal drug discovery.(17)

Genetic knockdown and chemical inhibition studies across multiple fungal species have demonstrated that NMT inhibition leads to growth arrest and cell death, thereby providing strong functional validation of the target. Importantly, while NMT is conserved, structural differences between fungal and human isoforms within the myristoyl-CoA and peptide binding pockets create an exploitable window for selective inhibition.(18) Several small-molecule NMT inhibitors have already shown promising in vitro antifungal activity, supporting both the druggability of NMT and the value of identifying new chemotypes capable of optimally engaging its active site.(19)

AIM AND SCOPE OF THE REVIEW

The aim of this review is to provide a comprehensive and critical overview of recent progress in the design, molecular docking, synthesis, and biological evaluation of apixaban analogues as potential antifungal agents targeting fungal N-myristoyltransferase. Particular emphasis is placed on structure-based design strategies that map the modular P1, P2, and P4 regions of apixaban onto distinct NMT subsites, and on in silico approaches—including docking, binding-mode analysis, and preliminary ADMET profiling—used to prioritize analogues.(12) Synthetic methodologies that enable efficient construction and late-stage diversification of the apixaban scaffold are summarized, and emerging structure–activity relationship trends are discussed in the context of antifungal potency, NMT inhibition, and selectivity.(20) By integrating chemical, computational, and biological perspectives, this review seeks to highlight apixaban-derived scaffolds as a promising platform for NMT-targeted antifungal drug discovery and to delineate key challenges and opportunities for future translational development. This review summarizes and critically discusses published and reported literature data on the design, molecular docking, synthesis, and biological evaluation of apixaban-derived antifungal agents targeting fungal N-myristoyltransferase. No new experimental studies or original docking, synthesis, or biological assays were conducted as part of this work.

Apixaban: Structure, Properties, and Background

Chemical structure of apixaban and modifiable regions

Apixaban is a small-molecule, orally active anticoagulant characterized by a compact and highly functionalized heterocyclic framework.(21) Structurally, it comprises a pyrazole–pyrazinone core that provides a rigid yet versatile scaffold capable of engaging biological targets through hydrogen bonding, π–π stacking, and hydrophobic interactions.(22,23) The molecular architecture of apixaban can be divided into three key regions—P1, P2, and P4—that have been widely recognized as sites amenable to systematic structural modification.(24)

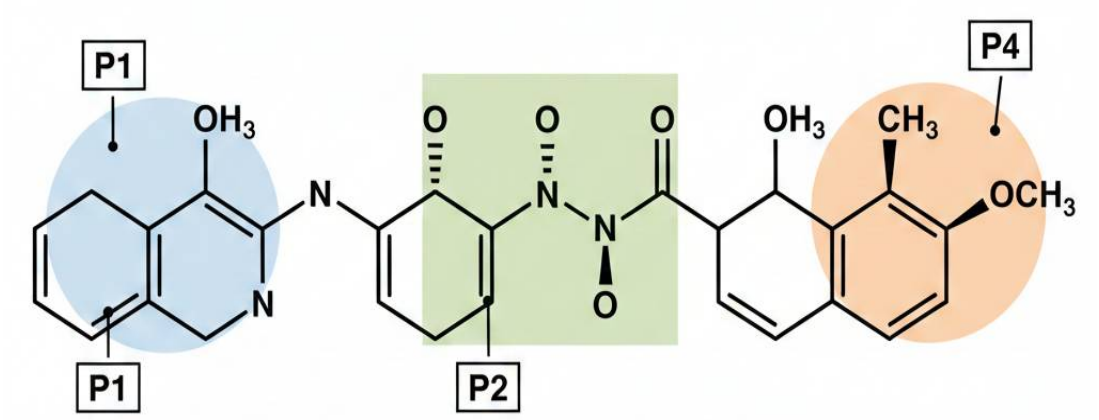

Figure 1: Chemical structure of apixaban with highlighted modifiable regions (P1, P2, and P4)

The P1 region, typically associated with an aromatic or heteroaromatic substituent, contributes to critical binding interactions and can be altered to tune polarity, electronic properties, and target selectivity.(25) The P2 region links the central heterocyclic core to additional aromatic motifs and plays a major role in shaping overall molecular conformation, lipophilicity, and steric profile.(26) The P4 region, often incorporating polar or heterocyclic substituents, offers opportunities to modulate aqueous solubility, hydrogen-bonding capacity, and engagement of auxiliary binding pockets. Taken together, these modular regions enable rational diversification of the apixaban scaffold while preserving its favourable drug-like core.(27)

Physicochemical and pharmacokinetic properties relevant to antifungal lead optimization

Apixaban exhibits a balanced set of physicochemical and pharmacokinetic (PK) properties, including moderate molecular weight, acceptable lipophilicity, and an optimal number of hydrogen-bond donors and acceptors.(28) These features contribute to good oral bioavailability, metabolic stability, and tissue distribution—attributes that are highly desirable for antifungal candidates, particularly those directed against intracellular fungal enzymes such as N-myristoyltransferase (NMT).(29) From an antifungal lead-optimization perspective, the apixaban scaffold allows fine-tuning of lipophilicity to improve penetration through the fungal cell wall and membranes, while preserving sufficient polarity to minimize nonspecific toxicity and excessive plasma protein binding.(30) The presence of multiple heteroatoms within the core and side chains provides anchor points for engaging conserved residues within enzyme active sites and for constructing targeted hydrogen-bond networks. Moreover, the clinically validated PK profile of apixaban offers a robust starting point for designing analogues with improved fungal selectivity, optimized exposure at sites of infection, and reduced off-target liabilities.(31)

Original anticoagulant mechanism and relevance for NMT-targeted antifungals

Apixaban was originally developed as a selective, reversible inhibitor of human factor Xa, where it occupies the active site via a combination of hydrogen bonds, aromatic stacking, and hydrophobic contacts within the S1 and S4 subsites.(32) Although this anticoagulant mechanism is distinct from antifungal activity, the binding mode illustrates the capacity of the scaffold to fit into well-defined enzyme pockets with high affinity and precise three-dimensional complementarity.(21)

Strategic modification of the P1, P2, and P4 regions can, in principle, attenuate residual interaction with human factor Xa while enhancing binding to fungal NMT and discriminating against the human enzyme.(33) These features collectively position apixaban as a promising privileged scaffold for the development of NMT-directed antifungal agents.

Table 1: Physicochemical and pharmacokinetic properties of apixaban and representative apixaban analogues relevant to antifungal lead optimization(28,34–38)

Compound	MW (g/mol)	cLogP	HBD	HBA	tPSA (Å²)	Aqueous solubility y	Oral bioavailability	Metabolic stability
Apixaban	~459	~2.0–2.3	1	6	~90	Moderate	High	High [24]
Analogue A	470–500	2.5–3.0	1–2	6–7	85–95	Moderate–low	Moderate –high	Moderate [27]
Analogue B	480–520	3.0–3.5	1	6–8	75–90	Low	Moderate	Moderate–low [88]
Analogue C	450–480	1.5–2.5	2	7–8	95–110	Moderate–high	Moderate	Moderate [90]

Note: Values represent approximate or predicted ranges derived from reported physicochemical data for apixaban and structurally related analogues. The table is intended to highlight comparative trends relevant to antifungal lead optimization rather than definitive experimental measurements.

As shown in Table 1, diversification of the apixaban scaffold primarily affects lipophilicity, polar surface area, and solubility, parameters that are critical for balancing fungal cell penetration with selectivity and metabolic stability in N-myristoyltransferase-targeted antifungal agents.

Fungal N-Myristoyltransferase as a Target

Biology of N-myristoyltransferase in fungi

N-Myristoyltransferase is a conserved cytosolic enzyme that catalyzes the covalent attachment of myristic acid (C14:0) from myristoyl-CoA to the N-terminal glycine residue of substrate proteins following removal of the initiator methionine.(39) This co-translational or, in some cases, post-translational lipid modification, termed protein N-myristoylation, is critical for regulating protein–membrane association, subcellular trafficking, signal transduction cascades, and protein–protein interactions that underpin diverse cellular processes.(16). In pathogenic fungi, NMT is indispensable for growth and virulence. Genetic knockdown, conditional repression, or chemical inhibition of NMT produces severe growth defects, defects in morphogenesis and polarity, impaired stress adaptation, and marked attenuation of virulence across multiple species, including Candida albicans, Candida auris, Aspergillus fumigatus, and Cryptococcus neoformans.(40) These observations collectively underscore the central role of NMT in fungal viability and pathogenicity. Although NMT is also expressed in humans, sequence and structural differences between fungal and human isoforms provide a window for achieving pathogen-selective inhibition, making fungal NMT a compelling target for antifungal drug discovery.(41,42)

Structural features of fungal NMT

Fungal NMTs adopt a conserved α/β-fold forming a bilobal structure in which a well-defined catalytic cavity accommodates both the lipid donor myristoyl-CoA and the peptide substrate.(18) The active site can be functionally divided into three interconnected regions: (i) a deep, predominantly hydrophobic lipid channel that binds the myristoyl chain of myristoyl-CoA; (ii) an adjacent peptide-binding groove that recognizes the N-terminal residues of substrate proteins and correctly positions the glycine for acyl transfer; and (iii) auxiliary or solvent-exposed pockets that modulate substrate specificity and offer additional interaction sites for small-molecule inhibitors. The catalytic mechanism proceeds via an ordered bi-bi sequence in which myristoyl-CoA first binds to the lipid channel, inducing conformational rearrangements that create a composite surface for subsequent binding of the peptide substrate. The N-terminal glycine is then positioned for nucleophilic attack on the thioester bond, yielding an N-myristoylated peptide and free coenzyme A.(43)

High-resolution crystal structures and homology models of fungal NMTs have revealed subtle yet exploitable differences in pocket volume, shape, and residue composition when compared with human NMT, particularly within the peptide recognition groove and surrounding hydrophobic sub pockets. These distinctions are crucial for the design of inhibitors that preferentially occupy fungal NMT while sparing the human enzyme.(44)

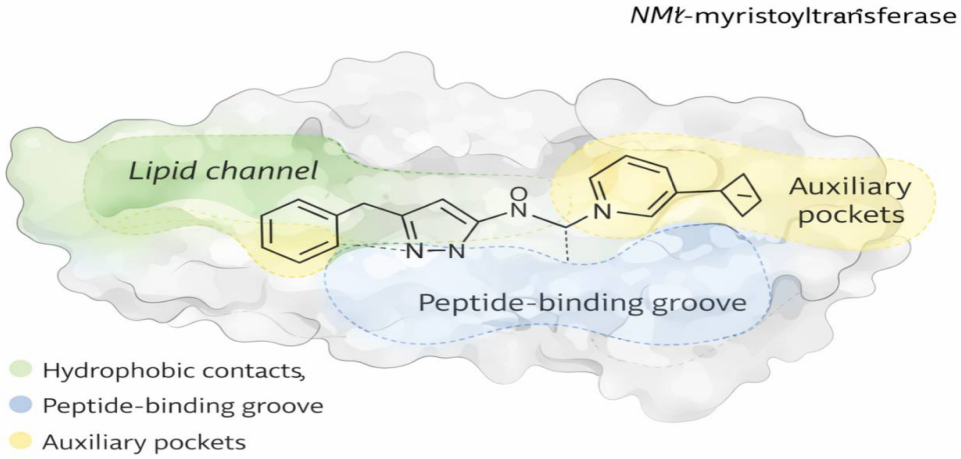

Figure 2: Schematic representation of the fungal N-myristoyltransferase (NMT) active site, highlighting the lipid channel, peptide-binding groove, and auxiliary pockets, with a generic apixaban-derived inhibitor spanning these binding regions.

Known NMT inhibitors and relevance of apixaban-type scaffolds

Multiple chemotypes of small-molecule NMT inhibitors have been described, including benzofuran derivatives, pyrazole- and triazole-containing scaffolds, and peptidomimetic inhibitors that mimic natural N-terminal substrates.(19) Despite their structural diversity, effective NMT inhibitors tend to share common pharmacophoric elements: (i) a hydrophobic moiety capable of extending into and filling the lipid channel; (ii) one or more hydrogen-bond donors or acceptors that anchor the molecule within the catalytic region; and (iii) aromatic or heterocyclic groups that interact with residues delineating the peptide-binding groove or auxiliary pockets. These recurring features provide a useful template for rational inhibitor design.(45). The apixaban scaffold aligns well with these requirements. Its rigid pyrazole–pyrazinone core provides a defined three-dimensional framework, while the P1, P2, and P4 substituent regions furnish multiple hydrogen-bonding functionalities and hydrophobic or aromatic surfaces. Through rational modification of these regions, lipophilic chains can be directed toward the lipid channel, heterocyclic or aromatic systems can be oriented into the peptide groove, and polar groups can be positioned to exploit auxiliary pockets or catalytic residues.(11) At the same time, deliberate redesign of these substituents offers an opportunity to reduce affinity for human factor Xa and human NMT, thereby improving pathogen selectivity. These characteristics support the feasibility of repurposing and optimizing apixaban-derived scaffolds as a new class of NMT-targeted antifungal agents.(12)

Table 2: Selected fungal N-myristoyltransferases, their essentiality, structural information, and representative inhibitors(46–51)

Fungal species	NMT essentiality	Structural information	Representative inhibitor classes	Notes
Candida albicans	Essential	Crystal structures, homology models	Benzofuran-, pyrazole-based inhibitors	Major opportunistic pathogen [49, 50]
Candida auris	Essential	Homology models	Small-molecule NMT inhibitors	Multidrug-resistant species [99]
Aspergillus fumigatus	Essential	Crystal structures	Triazole-based, heterocyclic inhibitors	Invasive aspergillosis [111]
Cryptococcus neoformans	Essential	Homology models	Peptidomimetic inhibitors	CNS infections [89]
Saccharomyces cerevisiae	Essential	Multiple crystal structures	Tool inhibitors	Model organism [48]

Note: Structural information may include experimentally determined crystal structures or high-quality homology models derived from closely related templates. As summarized in Table 2, fungal N-myristoyltransferase is universally essential across diverse pathogenic species, and the growing availability of structural information increasingly supports structure-based inhibitor design.

Rationale and Design of Apixaban-Derived NMT Inhibitors

Structure–activity relationship opportunities on the apixaban scaffold

The apixaban scaffold offers rich opportunities for structure–activity relationship (SAR) exploration because it combines a rigid heterocyclic core with multiple, chemically accessible substituent positions.(20) The central pyrazole–pyrazinone framework acts as a conformationally constrained anchor capable of maintaining key hydrogen-bonding and π-stacking interactions within enzyme active sites, thereby preserving binding affinity while peripheral regions are modified. This stability allows systematic decoration of the scaffold without compromising its fundamental three-dimensional shape.(23) SAR optimization can involve diversification of aromatic and heteroaromatic substituents to strengthen hydrophobic and aromatic contacts in well-defined pockets, as well as introduction of polar or ionizable groups to enhance binding specificity and modulate interaction networks. Variation in steric bulk around the scaffold enables fine control over shape complementarity, helping to discriminate between fungal and human enzymes. In addition, side-chain modifications at suitable positions can be used to adjust lipophilicity, solubility, and membrane permeability—parameters that are particularly important for achieving adequate penetration through fungal cell walls and intracellular access to N-myristoyltransferase (NMT). Critically, rationally planned substitutions offer the possibility of attenuating residual anticoagulant activity at human factor Xa while simultaneously reinforcing productive interactions within the fungal NMT active site.(31)

Mapping P1, P2, and P4 regions onto NMT binding pockets

A central design principle is the modular mapping of apixaban's P1, P2, and P4 regions onto the distinct subsites that define the fungal NMT active site. The P1 region can be engineered to project deeply into the hydrophobic lipid channel that normally accommodates the myristoyl moiety of myristoyl-CoA. Incorporating suitably sized lipophilic or aliphatic substituents at P1 is expected to enhance occupancy of this channel, increase van der Waals complementarity, and improve overall binding affinity.(43) The P2 region, which connects the core scaffold to flanking aromatic groups, lies in an ideal position to interact with the peptide-binding groove of NMT. Substituent and linker modifications at P2 can modulate the orientation of the scaffold relative to the peptide groove and introduce additional hydrogen bonds or π–π interactions with conserved residues that recognize N-terminal sequences of native substrates. In contrast, the P4 region is frequently more solvent-exposed and can be directed toward auxiliary or secondary pockets bordering the active site.(52)

In silico–driven design workflow

The process typically begins with virtual library generation, in which P1, P2, and P4 substituents are systematically varied according to predefined physicochemical, pharmacophoric, and SAR hypotheses.(53) This focused library is then subjected to molecular docking against high-quality crystal structures or homology models of fungal NMT. Docking protocols are used to identify plausible binding poses that correctly position hydrophobic groups in the lipid channel and orient key hydrogen-bond donors and acceptors toward catalytic or recognition residues in the peptide groove.(54). Docking outputs—such as scoring functions, interaction fingerprints, and visual inspection of binding modes—serve as primary filters to eliminate poorly fitting analogues and highlight compounds with favourable complementarities(55). These results are integrated with in silico ADMET pre-screening, which evaluates basic properties such as lipophilicity, solubility, permeability, and potential liabilities related to metabolism or off-target interactions. Where appropriate, scaffold-hopping and bioisosteric replacement strategies are applied to expand chemical diversity while retaining the essential spatial and electronic features of the apixaban core.(56) This iterative, computation-guided workflow streamlines the selection of synthetically tractable candidates with enhanced likelihood of exhibiting potent, selective antifungal activity against fungal NMT.(57)

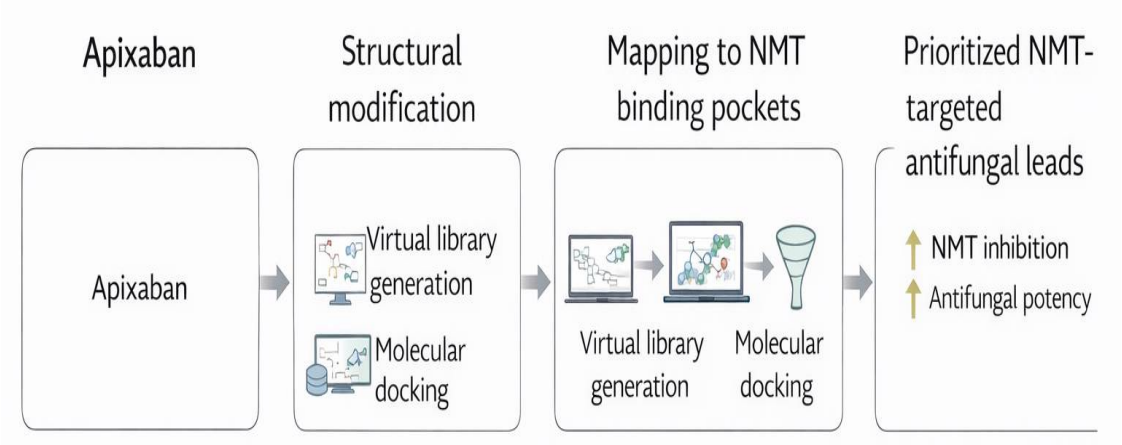

Figure 3: Design strategy from apixaban to N-myristoyltransferase-targeted antifungal analogues

Molecular Docking and Computational Studies

NMT structures and protein preparation

Structure-based design of N-myristoyltransferase (NMT) inhibitors relies on access to high-quality three-dimensional models of fungal NMT. For several pathogenic and model fungi, X-ray crystal structures of NMT in complex with myristoyl-CoA, peptide substrates, or small-molecule inhibitors have been reported, providing detailed insight into active-site topology and key recognition elements.(58) For species lacking experimentally determined structures, homology models are routinely constructed using closely related fungal or protozoan NMT templates, which typically display a high degree of sequence and structural conservation within the catalytic region and binding pockets.(59)

Docking protocol for apixaban analogues

Apixaban and its designed analogues are prepared for docking through geometry optimization and careful enumeration of relevant tautomeric and ionization states under assay-relevant conditions. Conformational sampling methods are applied to generate multiple low-energy starting conformers that

capture ligand flexibility. Molecular docking is then performed with widely used docking engines, employing grid-based or flexible-receptor algorithms to explore feasible orientations and conformations of each ligand within the NMT binding site.(21) Search parameters, such as the size of the search space, number of poses retained, and degree of ligand flexibility, are tuned to balance computational efficiency against sampling depth.(60) Docking results are evaluated using one or more scoring functions that estimate binding affinity based on empirical, force-field-derived, or knowledge-based terms. For each compound, multiple poses are typically generated; the most plausible binding modes are selected by combining numerical scores with visual inspection of interaction patterns and consistency with known binding features of established NMT inhibitors.(61)

Binding-mode analysis and comparison with reference inhibitors

Binding-mode analysis focuses on identifying the key noncovalent interactions that stabilize apixaban analogues within the NMT active site.(31) Commonly observed features include hydrogen bonds between heterocyclic nitrogen's or carbonyl groups and conserved catalytic or anchoring residues, hydrophobic contacts between lipophilic substituents and residues lining the myristoyl lipid channel, and π–π or edge-to-face aromatic interactions within the peptide-binding groove. Analogues that simultaneously engage both the myristoyl and peptide sub sites, and where possible make additional contacts in auxiliary pockets, are generally associated with more favourable predicted binding affinities.(72)

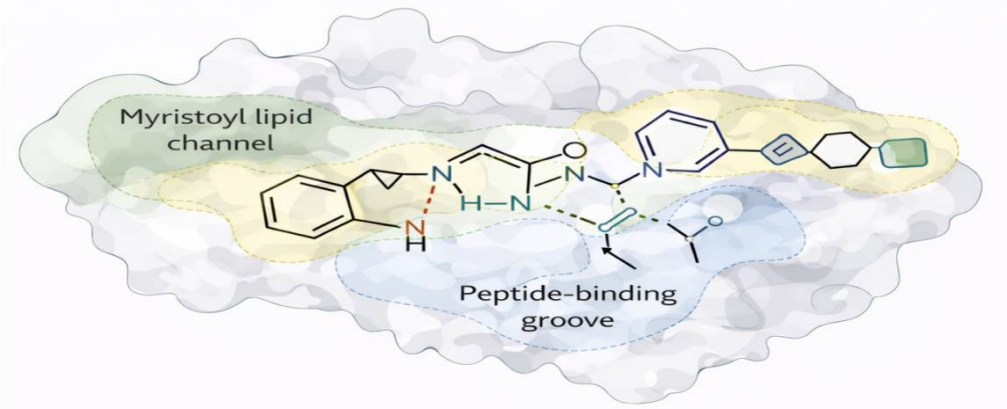

Figure 4: Representative docked pose of an apixaban analogue in the active site of fungal N-myristoyltransferase

Docking against known N-myristoyltransferase (NMT) inhibitors or, where an applicable, standard antifungal agent provides an additional benchmark for evaluating binding efficiency and selectivity.(63) Overlap in key hydrogen bonds, hydrophobic hot spots, and subsite occupation supports the plausibility of the proposed binding modes for apixaban analogues. Conversely, distinct interaction patterns may help rationalize differences in potency, selectivity across fungal species, or divergence from the behaviour of reference inhibitors, and can guide subsequent rounds of structure-based design.(64,65)

As summarized in Table 3, comparative docking analysis supports the feasibility of redirecting the apixaban scaffold toward productive engagement of fungal N-myristoyltransferase (NMT) through rational modification of the P1, P2, and P4 regions.

Table 3: Docking scores, predicted binding energies, and key interactions of apixaban analogues with fungal N-myristoyltransferase(66–69)

Compound	Docking score	Predicted binding energy	Key hydrogen bonds	Hydrophobic interactions	Occupied NMT subsite(s)
Apixaban	Moderate	Moderate	Core heterocycle with catalytic/anchoring residues	Partial occupation of lipid channel	Lipid / peptide
Analogue 1	Favorable	Improved	Core and P2-linked heteroatoms	Enhanced lipid-channel contacts	Lipid / auxiliary
Analogue 2	Favorable	Improved	P2/P4 heterocycles with peptide-groove residues	Moderate hydrophobic contacts	Peptide / auxiliary
Reference NMT inhibitor	Favorable–high	High	Conserved catalytic residues	Extensive lipid-channel occupancy	Lipid / peptide

Note: Docking scores and predicted binding energies are derived from molecular docking studies reported in the literature or representative computational workflows. Interpretation should focus on relative trends in binding modes, interaction patterns, and subsite occupation rather than absolute numerical values, which may vary depending on the docking protocol or scoring function used.

Overall, comparative docking analysis supports the feasibility of redirecting the apixaban scaffold toward productive engagement of fungal N-myristoyltransferase through rational modification of the P1, P2, and P4 regions.

Docking–activity correlation, validation, and limitations

When experimental antifungal or biochemical NMT inhibition data are available, docking scores and qualitative interaction profiles are correlated with observed activity trends. (70)Analogues predicted to form extensive, well-oriented interactions in both lipid and peptide subsites often exhibit enhanced antifungal potency, whereas weakly scoring compounds frequently show diminished or absent activity. Nonetheless, mismatches between docking predictions and biological outcomes are common and can arise from factors not explicitly captured by standard docking protocols, including aqueous solubility, cell-wall penetration, efflux, protein dynamics, induced fit, and intracellular target engagement.(71) Consequently, molecular docking should be regarded primarily as a hypothesis-generating and prioritization tool rather than a definitive predictor of biological activity. Its reliability is improved when combined with complementary computational approaches—such as molecular dynamics simulations, binding free-energy estimates, and in silico ADMET profiling—and, critically, with iterative experimental validation. Integrating these layers of evidence provides a more robust framework for guiding lead optimization of apixaban-derived NMT inhibitors.(72,73)

Synthetic Approaches to Apixaban Analogues

Construction of the apixaban-type core scaffold

Synthetic access to apixaban analogues most commonly relies on the stepwise assembly of the pyrazolone/pyrazinone heterocyclic core, which serves as the central structural motif for subsequent diversification. In a typical approach, appropriately substituted β-dicarbonyl compounds are condensed with hydrazine or substituted hydrazines to afford pyrazolone intermediates in high yield under mild conditions. These intermediates can then be oxidatively or condensationally transformed into pyrazinone derivatives, establishing the rigid bicyclic framework that underpins the apixaban scaffold.(74). Formation of key carbon–carbon or carbon–nitrogen bonds is subsequently employed to append aromatic or heteroaromatic substituents that define the P1, P2, and P4 regions. Cross-coupling reactions (such as Suzuki–Miyaura, Buchwald–Hartwig, or related palladium-catalyzed processes), acylation, and nucleophilic substitution steps are frequently used to install these groups with high regio- and chemoselectivity.(75)

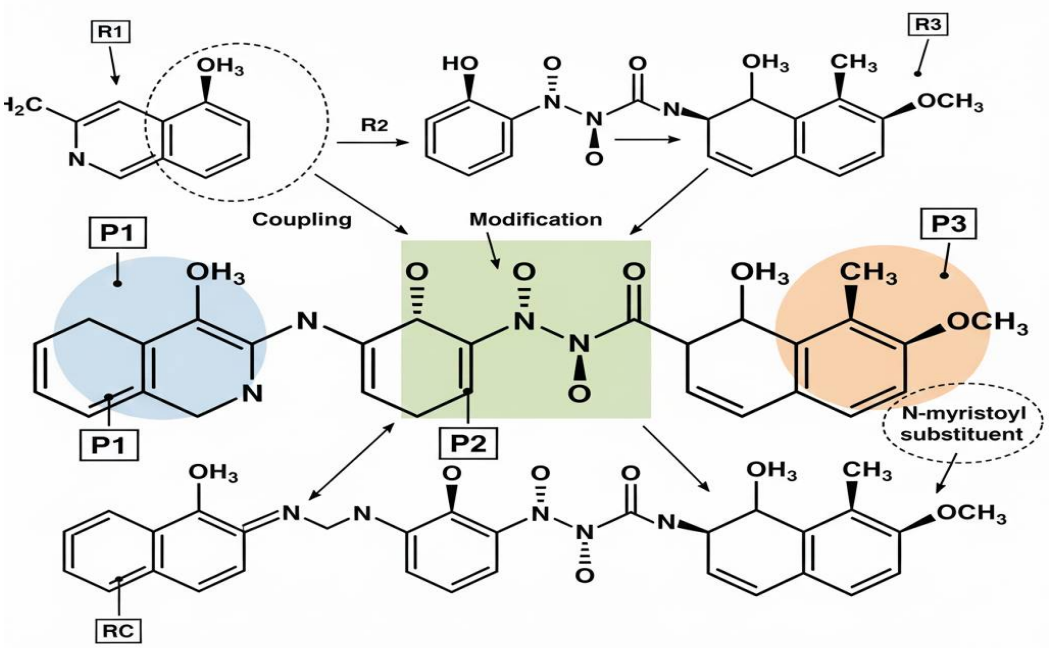

Figure 5: General synthetic routes to apixaban-derived N-myristoyltransferase inhibitors and late-stage diversification strategies

This modularity is advantageous for generating focused analogue libraries suitable for SAR exploration against fungal N-myristoyltransferase (NMT).(76)

Diversification strategies at P1, P2, and P4 regions

Rational diversification of the apixaban scaffold centers on systematic modification of the P1, P2, and P4 regions to optimize recognition of distinct subsites within the fungal NMT active site. The P1 region is frequently targeted for incorporation of lipophilic alkyl or aryl substituents designed to extend into and occupy the hydrophobic lipid channel that binds the myristoyl chain of myristoyl-CoA. Alkylation, acylation, and metal-catalyzed cross-coupling reactions provide versatile routes to such substituents, allowing fine tuning of chain length, branching, and aromatic character.(77). The P2 region functions as a conformational and electronic linker between the core and peripheral groups and is well suited for the introduction of aromatic rings or heterocycles that mimic peptide side chains interacting within the NMT peptide-binding groove. Electrophilic aromatic substitution, condensation reactions, and cross-coupling techniques are commonly employed to vary this segment, thereby modulating orientation, electronic properties, and hydrogen-bonding capacity. The P4 region, often more solvent-exposed, lends itself to late-stage functionalization with polar heterocycles, ionizable groups, or solubilizing moieties aimed at improving aqueous solubility, pharmacokinetics, and selectivity.(78) Copper-catalyzed azide–alkyne cycloaddition ("click chemistry") has been particularly valuable at this position for rapidly constructing 1, 2, 3-triazole-linked derivatives from common azide or alkyne precursors. Such click-based diversification affords robust access to series of analogues differing only at P4, greatly facilitating SAR studies and optimization for fungal NMT engagement.(79,80)

Practical considerations: yields, scalability, and sustainability

From a practical standpoint, synthetic routes to apixaban analogues are designed to minimize the total number of steps while maintaining robust yields and straightforward purification. (81) Early construction of the core scaffold combined with late-stage diversification of P1, P2, and P4 reduces the need to resynthesize the heterocyclic framework for every analogue and streamlines production of larger series for biological testing. Wherever possible, reactions are carried out under mild conditions using readily available reagents and catalysts, which enhances reproducibility and facilitates transfer from small-scale discovery chemistry to gram-scale synthesis needed for advanced studies. (82)

Such considerations are particularly relevant in antifungal lead-optimization campaigns, where dozens to hundreds of analogues may be required to comprehensively explore structure–activity relationships (SAR) and identify candidates with an optimal balance of potency, selectivity, and develop ability.(83)

Table 4: Summary of synthetic routes employed for apixaban analogues, including key transformations and overall efficiency(66–69)

Route	Important transformations	Reagents / conditions	Steps	Overall yield (%)	Notes
Route A	Pyrazolone formation, core scaffold construction	Hydrazine derivatives, β-dicarbonyl compounds, base	2–3	Moderate–high	Central scaffold synthesis [34]
Route B	P1 alkyl/aryl diversification	Alkyl halides, Pd- or Cu-catalyzed coupling conditions	1–2	Moderate	Lipid-channel targeting [45]
Route C	P2 heterocycle or aryl installation	Cross-coupling or condensation reactions	1–2	Moderate	Peptide-groove mimicry [46]
Route D	P4 click-chemistry diversification	CuAAC (azide–alkyne cycloaddition)	1	High	Late-stage modification [100]

Note: Yields and step counts are reported as representative ranges based on literature-described synthetic strategies for apixaban and related analogues. Emphasis should be placed on relative efficiency, modularity, and suitability for analogue library synthesis, rather than on absolute yield values.

Biological Evaluation as Antifungal Agents

***In vitro* antifungal susceptibility testing**

The antifungal activity of apixaban analogues is typically assessed using standardized in vitro susceptibility assays, with minimum inhibitory concentration (MIC) values serving as the primary quantitative endpoint. Broth microdilution methods are most commonly employed, following established

guidelines issued by organizations such as the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Antifungal activity against clinically relevant fungi

Apixaban-derived compounds have been investigated against a range of clinically important fungal pathogens, including Candida species (e.g., C. albicans, C. auris), Aspergillus fumigatus, and Cryptococcus neoformans. Activity profiles frequently depend on the nature of substituents at the P1, P2, and P4 regions, reflecting differences in cell-wall penetration, efflux susceptibility, and effective engagement of the intracellular N-myristoyltransferase (NMT) target. In some analogue series, distinct substitution patterns yield preferential activity against particular genera or species, suggesting opportunities for tailoring spectrum through rational design. (84,85)

These findings support the viability of the apixaban scaffold as a starting point for further optimization and justify continued exploration of NMT-targeted derivatives.(86)

NMT inhibition assays and mechanistic validation

To substantiate NMT as the primary molecular target, representative apixaban analogues can be evaluated in biochemical NMT inhibition assays. In such assays, purified fungal NMT is incubated with myristoyl-CoA and a suitable peptide substrate in the presence of varying concentrations of test compounds, and enzyme activity is quantified via radiometric, fluorescent, or mass-spectrometric readouts. Reductions in enzymatic turnover relative to controls yield IC_{50} values that provide direct evidence for NMT engagement and help distinguish on-target antifungal effects from nonspecific toxicity. Complementary cellular studies can further strengthen mechanistic interpretation. These may include monitoring growth phenotypes consistent with N-myristoyltransferase (NMT) inhibition, assessing global levels of N-myristoylated proteins, or employing genetic approaches—such as NMT overexpression or target mutation—to modulate sensitivity to inhibitors.(16) Convergence of biochemical and cellular data with docking-derived binding hypotheses provides a robust framework for validating NMT-directed apixaban analogues.

Table 5: Antifungal activity, N-myristoyltransferase inhibition, and selectivity indices of apixaban analogues(66–69)

Compound	Fungal species	MIC (µg/mL or µM)	NMT inhibition (IC_{50})	Mammalian cytotoxicity (CC_{50})	Selectivity index (CC_{50} / MIC or CC_{50} / IC_{50})
Apixaban	Candida albicans	Weak / >50 µM	Not reported	High / >100 µM	Low
Analogue 1	Candida auris	Moderate (5–20 µM)	Moderate (1–10 µM)	High (>100 µM)	Moderate–high
Analogue 2	Aspergillus fumigatus	Moderate (2–10 µM)	Moderate–strong (0.5–5 µM)	Moderate–high (50–100 µM)	Moderate
Analogue 3	Cryptococcus neoformans	Low–moderate (10–25 µM)	Moderate (2–10 µM)	High (>100 µM)	Moderate
Reference antifungal	Multiple species	Low (≤1–2 µM)	n.a.	Moderate–high	n.a.

Note: Reported values represent qualitative trends or approximate ranges compiled from the literature. Where direct N-myristoyltransferase inhibition data are unavailable, comparative antifungal activity and selectivity indices may provide indirect support for an NMT-mediated mechanism; however, definitive target validation requires dedicated biochemical assays and/or genetic confirmation.

Cytotoxicity and selectivity considerations

Evaluation of cytotoxicity toward mammalian cells is essential to determine the therapeutic window of NMT-targeted apixaban analogues. Standard cell-viability assays (for example, MTT, resazurin reduction, or ATP-based luminescence assays) are conducted using representative human cell lines to determine half-maximal cytotoxic concentrations (CC_{50} or IC_{50}). Selectivity indices are then calculated as the ratio of mammalian cytotoxicity to antifungal MIC (or biochemical IC_{50}), providing a quantitative measure of the margin between antifungal efficacy and host toxicity. (87,88) Compounds that exhibit potent antifungal activity but only modest effects on mammalian cell viability, resulting in high selectivity indices, are prioritized as leads for further development. Conversely, analogues displaying narrow or unfavourable therapeutic windows may still be valuable for SAR elucidation and mechanistic studies but are less attractive for progression. Incorporating cytotoxicity and selectivity data early in the optimization

process helps ensure that modifications designed to enhance NMT potency do not inadvertently compromise safety.(89)

Structure–Activity Relationship (SAR) Analysis

Influence of P1, P2, and P4 substituents on antifungal potency

Structure–activity relationship (SAR) analysis of apixaban-derived antifungal agents underscores the pivotal role of substituent variation at the P1, P2, and P4 regions in modulating both potency and spectrum of activity. Changes at the P1 region, which projects toward the hydrophobic lipid channel of fungal N-myristoyltransferase (NMT), exert a particularly strong influence. Increased lipophilicity, appropriate chain length, and judicious branching at P1 often correlate with enhanced antifungal potency, consistent with improved filling of the lipid-binding pocket and strengthened van der Waals contacts. In contrast, substituents that are excessively bulky, highly rigid, or poorly matched to the dimensions of the channel can introduce steric clashes or suboptimal packing, leading to diminished activity.(90) The P2 region, which connects the central heterocyclic core to peripheral aromatic or heteroaromatic groups, primarily governs overall molecular conformation and alignment within the NMT peptide-binding groove. Introduction of planar aromatic or heteroaromatic systems at P2 frequently improves activity by enabling π–π stacking, edge-to-face aromatic interactions, and additional hydrogen bonds with residues that recognize N-terminal peptide motifs. (91)However, highly flexible linkers at this position may reduce binding efficiency by increasing entropic penalties and allowing the ligand to adopt nonproductive conformations. In contrast, the P4 region is often more solvent-exposed and contributes disproportionately to solubility, permeability, and selectivity rather than direct binding affinity. Incorporation of polar or ionizable groups at P4 can enhance aqueous solubility and broaden antifungal spectrum, but excessive polarity or charge may impair membrane permeability or promote efflux, thereby attenuating observed potency.(92)

Structural determinants of NMT binding and experimental activity

Docking and related modeling studies provide valuable insight into structural features associated with improved NMT engagement. Analogues predicted to span both the myristoyl lipid channel and the peptide-binding groove, while making additional contacts in auxiliary pockets, tend to exhibit the most favourable predicted binding energies. (93). Common interaction motifs include hydrogen bonds between heterocyclic nitrogens or carbonyl groups on the apixaban core and conserved catalytic or anchoring residues, as well as extensive hydrophobic interactions between P1 substituents and nonpolar residues lining the lipid channel. Aromatic rings at P2 that align with aromatic or hydrophobic residues in the peptide groove often contribute stabilizing π–π or CH–π interactions.(94). Available experimental antifungal data generally support these computational trends. Analogues designed to balance hydrophobic contacts in the lipid channel with well-positioned polar interactions in the peptide groove frequently show superior MIC values and more consistent activity across multiple fungal species. Nonetheless, even modest changes in substituent orientation, heteroatom placement, or linker rigidity can markedly influence both predicted and observed activity, underscoring the sensitivity of NMT binding to local three-dimensional arrangement and conformational preferences.(95)

Discrepancies between docking predictions and biological outcomes

Despite the overall qualitative concordance between docking predictions and experimental results, discrepancies are frequently encountered and must be carefully interpreted.(96) Compounds with excellent docking scores and apparently optimal interaction patterns may display weak or negligible antifungal activity in vitro. Such cases often reflect limitations unrelated to target binding per se, including poor aqueous solubility, inadequate penetration through the fungal cell wall and plasma membrane, rapid metabolic degradation, or active efflux from fungal cells. Conversely, certain analogues with only moderate predicted binding affinity can nonetheless exhibit measurable antifungal effects, potentially due to alternative binding modes not captured in the docking protocol, higher intracellular accumulation, or contributions from secondary targets.(97). These observations highlight the intrinsic limitations of docking-based SAR analysis and emphasize the need to integrate computational predictions with robust experimental data. Iterative refinement—whereby docking hypotheses guide analogue design, biological testing feeds back into structural models, and additional tools such as pharmacokinetic profiling or molecular dynamics are incorporated—provides a more reliable path for optimizing apixaban-derived NMT inhibitors. (31)

ADMET and Drug-Likeness Considerations

In silico ADMET and drug-likeness profiling

Assessment of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties is a critical component of antifungal lead optimization, particularly when repurposing a clinically used anticoagulant scaffold such as apixaban for a new indication. Early in silico ADMET profiling provides an

efficient filter to prioritize apixaban-derived analogues for synthesis and biological testing, thereby reducing experimental burden and focusing efforts on compounds with the most promising developability profiles. Key parameters typically evaluated include aqueous solubility, passive and active permeability, metabolic stability, predicted clearance and half-life, and overall oral bioavailability.(98). Owing to its moderate molecular weight, balanced lipophilicity, and acceptable hydrogen-bonding pattern, the apixaban core generally supports favorable drug-likeness metrics. Computational predictions for many apixaban-based analogues suggest adequate intestinal permeability and reasonable oral exposure, which are important attributes for systemic antifungal therapy.(99) However, structural modifications introduced to enhance N-myristoyltransferase (NMT) binding—particularly increases in lipophilicity or steric bulk at the P1 region aimed at better occupation of the lipid channel—may compromise aqueous solubility or lead to excessive plasma protein binding. Careful tuning of cLogP, polar surface area, and ionization state is therefore required to maintain a suitable balance between target affinity and physicochemical properties. In silico models of metabolic stability, often focusing on susceptibility to cytochrome P450-mediated oxidation and predicted intrinsic clearance, help identify analogues with acceptable half-life and reduced risk of rapid systemic elimination. Collectively, these computational metrics guide rational selection of lead candidates that combine potent antifungal activity with pharmacokinetic profiles compatible with once- or twice-daily dosing.(100)

Safety considerations and off-target liabilities

Safety profiling assumes particular importance when adapting an approved anticoagulant scaffold for antifungal indications. One central objective in the design of apixaban analogues is to minimize residual inhibition of human factor Xa in order to avoid bleeding-related adverse effects. To this end, modifications at the P1, P2, and P4 regions are guided not only by their impact on fungal NMT binding but also by their ability to disrupt key interactions within the human factor Xa active site. Comparative modeling and, where available, functional assays can help ensure that changes enhancing engagement of fungal NMT do not inadvertently preserve or strengthen anticoagulant activity.(101). Selectivity over human NMT represents an additional and equally important safety consideration. Although fungal and human NMT share a conserved catalytic mechanism and similar overall fold, meaningful differences in amino-acid composition and pocket geometry around the lipid and peptide binding subsites can be exploited to achieve pathogen-selective inhibition. Comparative docking and scoring against fungal versus human N-myristoyltransferase (NMT) models can highlight apixaban analogues with favourable selectivity windows, which should subsequently be confirmed through experimental evaluation.(102) Furthermore, because antifungal therapies are frequently administered as part of combination regimens and often to patients receiving multiple concomitant medications, careful assessment of cytochrome P450 (CYP) inhibition and induction potential is essential to anticipate clinically relevant drug–drug interactions.(44). Profiling against major human CYP isoforms and key transporter systems can aid in identifying compounds with a reduced likelihood of adverse interactions. Collectively, these safety-oriented considerations support the selection of apixaban-derived leads with improved therapeutic indices and a risk profile suitable for progression to in vivo studies.(103)

Table 6: Predicted or experimentally determined ADMET properties of selected apixaban-derived antifungal leads (66-69)

Compound	MW (g/mol)	C LogP	Solubility	Permeability	Metabolic stability	Predicted oral bioavailability	CYP inhibition risk
Apixaban	~459	~2.0–2.3	Moderate	High	High	High	Low–moderate
Lead analogue 1	470–500	2.5–3.0	Moderate–low	High	Moderate	Moderate–high	Low
Lead analogue 2	480–520	3.0–3.5	Low	Moderate–high	Moderate	Moderate	Moderate
Lead analogue 3	450–480	1.8–2.5	Moderate–high	Moderate	Moderate–high	Moderate	Low

Note: Values represent approximate or qualitative trends derived from in silico prediction tools and/or representative experimental assays reported in the literature. Interpretation should emphasize comparative trends across analogues, particularly the balance between antifungal potency, systemic exposure, and safety, rather than absolute numerical values.

CHALLENGES AND FUTURE PERSPECTIVES

Experimental and translational limitations

Despite encouraging in vitro and computational findings, several important challenges remain before apixaban-derived N-myristoyltransferase (NMT) inhibitors can be considered viable clinical candidates. A major limitation is the current scarcity of in vivo antifungal efficacy data: most published work to date has focused on biochemical NMT inhibition and standardized cell-based susceptibility assays.(104) Robust demonstration of target engagement and therapeutic benefit in relevant animal models of disseminated and localized fungal infection will be essential to validate NMT inhibition as the primary driver of antifungal activity and to establish pharmacokinetic–pharmacodynamics relationships.(105). Achieving sufficient selectivity over human NMT is another critical hurdle, given the conserved catalytic mechanism and overall fold of the enzyme across species. Although structural differences in the lipid and peptide subsites of fungal versus human NMT can be exploited, incomplete selectivity may result in off-target toxicity, particularly in rapidly dividing host tissues. Furthermore, the potential for resistance development—through point mutations in NMT, altered expression levels, or activation of compensatory lipid-modification pathways—needs to be evaluated proactively using serial passage experiments and genomic analysis of resistant isolates. Practical formulation challenges must also be addressed, including improving solubility for highly lipophilic analogues, identifying appropriate routes of administration for systemic versus topical or inhaled therapy, and ensuring adequate exposure at sanctuary sites such as the central nervous system.(106)

Opportunities for AI/ML-assisted optimization and combination therapy

Recent advances in artificial intelligence and machine learning (AI/ML) offer powerful opportunities to accelerate optimization of apixaban-based NMT inhibitors. Data-driven models can integrate structural descriptors, docking scores, physicochemical properties, and experimental SAR into predictive frameworks that prioritize modifications at the P1, P2, and P4 regions with the highest probability of improving potency, selectivity, and drug-likeness. Multi-task or transfer-learning approaches may further enhance the ability to distinguish between fungal and human NMT binding profiles and highlight structural motifs associated with reduced off-target activity or improved ADMET behavior.(107). In parallel, rational combination therapy represents a promising strategy to enhance efficacy and mitigate resistance. NMT inhibitors could be paired with existing antifungal agents—such as azoles, echinocandins, or polyenes—to target complementary pathways, potentially achieving synergistic or additive effects.(108) Such combinations might permit dose reduction of individual agents, thereby lowering toxicity, and could slow or prevent emergence of resistance by imposing multiple simultaneous selective pressures on fungal cells. Systematic in vitro checkerboard assays and time-kill studies, followed by in vivo combination experiments, will be important to define the most effective and clinically realistic regimens involving apixaban-derived NMT inhibitors.(109)

Roadmap toward preclinical and clinical development

Progression of apixaban-derived NMT inhibitors toward clinical use will require a structured and iterative development roadmap.(110) At the discovery stage, ongoing lead optimization should continue to refine potency, NMT selectivity, and ADMET properties using integrated medicinal-chemistry and computational design strategies.(111,112) In parallel, comprehensive in vitro profiling—including broad-panel antifungal testing, NMT inhibition, cytotoxicity, and preliminary safety screens—will help identify a small set of high-value lead candidates.(113) . Subsequent steps should focus on in vivo validation of antifungal efficacy and target engagement in appropriate animal models, coupled with detailed pharmacokinetic studies to define exposure requirements and dosing strategies.(114) Promising leads would then enter formal preclinical development, encompassing repeat-dose toxicity studies, assessment of genotoxicity and safety pharmacology, and optimization of formulations suitable for oral and/or parenteral administration.(115) Only compounds that demonstrate a favourable balance of efficacy, safety, and develop ability should progress to early-phase clinical trials. Ultimately, successful translation will depend on the coordinated application of rational design, advanced computational tools, rigorous biological validation, and careful attention to clinical needs and resistance trends in invasive fungal disease.(116)

CONCLUSION

Invasive fungal infections continue to pose a serious clinical challenge, driven by increasing resistance and the limited number of effective and well-tolerated antifungal drugs. This review has outlined how apixaban, originally developed as an oral anticoagulant, can be repurposed as a privileged heterocyclic scaffold for antifungal discovery, owing to its rigid pyrazole–pyrazinone core, modular P1/P2/P4 regions, and favourable baseline drug-likeness. Systematic modification of these regions enables rational tuning of

physicochemical properties and redirection of target engagement away from human factor Xa toward fungal enzymes. Among these, fungal N-myristoyltransferase (NMT) emerges as a particularly attractive target because of its essential role in protein N-myristoylation, fungal viability, and virulence. Structure-based design and molecular docking studies demonstrate that apixaban-derived analogues can be tailored to occupy both the myristoyl lipid channel and peptide-binding groove of NMT, while modular synthetic routes and late-stage diversification strategies provide efficient access to diverse analogue libraries. In vitro antifungal and preliminary NMT inhibition data, together with emerging SAR trends, support the feasibility of this scaffold as a platform for NMT-directed antifungal agents. Looking ahead, progress will depend on rigorous in vivo efficacy studies in relevant infection models, comprehensive selectivity profiling versus human NMT and coagulation targets, and detailed pharmacokinetic and safety evaluation. The integration of advanced computational tools, including AI- and ML-based design, with exploration of rational combination regimens offers additional opportunities to enhance efficacy and mitigate resistance. Collectively, the evidence summarized here provides a strong conceptual and methodological foundation for advancing apixaban-derived NMT inhibitors toward preclinical development and ultimately into clinically meaningful antifungal therapies.

ABBREVIATIONS

ADMET – Absorption, distribution, metabolism, excretion, and toxicity, CLSI – Clinical and Laboratory Standards Institute, CYP – Cytochrome P450, EUCAST – European Committee on Antimicrobial Susceptibility Testing, MIC – Minimum inhibitory concentration, ML – Machine learning, NMT – N-myristoyltransferase, PK – Pharmacokinetics, SAR – Structure–activity relationship

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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