

UDC: 547:615.28

DOI: <https://doi.org/10.30546/2521-6341.2026.01.944>

HYDRAZONE DERIVATIVES AS ANTIFUNGAL AGENTS: SYNTHESIS, BIOLOGICAL EVALUATION AND MOLECULAR DOCKING STUDIES

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ARTICLE INFO	ABSTRACT
Article history: Received:2025-10-30 Received in revised form:2025-11-10 Accepted:2025-12-15 Available online:2026-06-26 Keywords: hydrazine derivatives, antifungal agents, in silico analysis	Hydrazone derivatives are an important class of compounds known for their diverse biological activities, including antifungal properties. In the present study, six hydrazone derivatives were evaluated for their antifungal activity against <i>Candida albicans</i>, <i>Candida guilliermondii</i>, and <i>Candida tropicalis</i> using the agar well diffusion method. In addition, molecular docking studies were performed to investigate their interactions with <i>Candida albicans</i> lanosterol 14α-demethylase (CYP51, PDB ID: 5TZ1), a key enzyme involved in ergosterol biosynthesis. The biological results demonstrated that all tested compounds exhibited antifungal activity, although their effectiveness varied depending on the fungal species. Among the investigated derivatives, (E)-1-(4-methoxybenzylidene)-2-phenylhydrazine showed the strongest inhibitory effect, producing inhibition zones of 26.3 ± 1.0 mm, 26.0 ± 0.9 mm, and 27.0 ± 0.6 mm against <i>C. albicans</i>, <i>C. guilliermondii</i>, and <i>C. tropicalis</i>, respectively. Its activity was found to be 1.2–1.4 times higher than that of the reference drug fluconazole. <i>Candida albicans</i> exhibited the highest sensitivity toward all tested compounds. Molecular docking analysis revealed that the selected hydrazone derivatives were accommodated within the CYP51 active site and formed stabilizing interactions with key amino acid residues, including LYS358, LEU340, GLU336, GLU339, and GLU343. Compound I exhibited the most favorable docking score (-4.7 kcal/mol), while Compounds II and VI displayed comparable binding modes and interaction patterns. Hydrogen bonding, hydrophobic contacts, and π-mediated interactions contributed to ligand stabilization within the binding pocket. The combined experimental and computational findings suggest that hydrazone derivatives, particularly (E)-1-(4-methoxybenzylidene)-2-phenylhydrazine, represent promising scaffolds for the development of novel antifungal agents against <i>Candida</i> infections.

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1. INTRODUCTION

Hydrazones constitute an important class of nitrogen-containing organic compounds characterized by the presence of the azomethine moiety ($-\text{C}=\text{N}-\text{N}-$), which is generally formed through

the condensation of hydrazines or hydrazides with aldehydes and ketones [1-3]. The azomethine linkage imparts unique electronic properties to these molecules, while the presence of adjacent nitrogen atoms allows hydrazones to exhibit both nucleophilic and electrophilic behavior, making them highly versatile synthetic intermediates [3-4]. Furthermore, many hydrazone derivatives exist in keto–enol tautomeric forms, which significantly influence their reactivity, coordination ability, and biological activity [2, 3]. The most common synthetic route involves the reaction of substituted hydrazides or hydrazines with carbonyl compounds in alcoholic media such as ethanol or methanol, frequently in the presence of catalytic acetic acid, affording the target products in high yields under relatively mild reaction conditions [1,2]. This synthetic methodology is particularly attractive because of its operational simplicity, broad substrate scope, cost-effectiveness, and excellent tolerance toward a variety of functional groups. Moreover, the condensation approach enables straightforward structural modification of both reaction partners, providing rapid access to structurally diverse hydrazones for further biological and physicochemical investigations [1]. Owing to these advantages, hydrazones have emerged as valuable synthons for the preparation of numerous heterocyclic systems and functional materials, while also serving as important pharmacophores in medicinal chemistry. Indeed, a wide range of hydrazone derivatives have demonstrated antimicrobial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory, and enzyme-inhibitory activities, highlighting their significance in contemporary drug discovery and development [5-8]

The continuing emergence of multidrug-resistant pathogens has intensified the search for new bioactive molecules with improved efficacy and safety profiles. In this regard, hydrazone derivatives have attracted significant attention owing to their remarkable diversity of biological activities and their ability to serve as privileged scaffolds in medicinal chemistry [9]. Numerous studies have demonstrated that hydrazones exhibit a broad spectrum of pharmacological properties, including antimicrobial, antibacterial, antifungal, antiviral, antitubercular, anti-inflammatory, analgesic, antimalarial, anticonvulsant, anticancer, cardioprotective, and antiparasitic activities [10-12]. Furthermore, the hydrazone pharmacophore has been extensively utilized in the design of novel therapeutic agents because the azomethine ($-\text{NHN}=\text{CH}-$) linkage can interact efficiently with a variety of biological targets, while structural modifications around the hydrazone framework allow fine-tuning of biological responses [9, 13]. Among the various pharmacological applications of hydrazones, their antimicrobial properties have been investigated most extensively, reflecting the urgent need for new agents capable of combating resistant bacterial and fungal infections. Particularly, hydrazone derivatives have demonstrated promising antifungal activity against a range of clinically important fungal pathogens, including *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida tenuis*, *Cryptococcus neoformans*, *Aspergillus flavus*, and *Aspergillus niger* [13]. The antifungal potential of these compounds is often associated with the presence of the azomethine moiety and the possibility of introducing different electron-donating or electron-withdrawing substituents, which can significantly influence their interaction with fungal cellular targets. Consequently, hydrazones continue to represent a highly promising class of compounds for the development of novel antifungal agents aimed at overcoming the limitations of currently available therapies and addressing the growing challenge of fungal resistance.

Despite the considerable progress achieved in antifungal chemotherapy, the emergence of resistant fungal strains and the limited number of available therapeutic targets continue to present major clinical challenges. Consequently, the search for novel antifungal agents with

improved efficacy and safety profiles has become an important area of medicinal chemistry research. In recent years, molecular docking has emerged as a valuable computational tool for investigating ligand–target interactions and predicting the binding affinity of biologically active compounds toward specific fungal proteins [14]. By providing insights into the molecular basis of antifungal activity, docking studies facilitate the identification of key pharmacophoric features and support the rational design of more potent derivatives. Hydrazone-based compounds have attracted particular attention in this regard because their structural diversity, ease of functionalization, and ability to participate in hydrogen bonding and hydrophobic interactions make them suitable candidates for interaction with fungal enzymes and receptors. Several studies have reported that hydrazone derivatives exhibiting promising antifungal activity against *Candida albicans*, *Aspergillus niger*, and *Aspergillus flavus* also demonstrate favorable binding interactions with biologically relevant targets in molecular docking analyses, highlighting the usefulness of combining biological screening with computational approaches in the development of new antifungal agents [15–18].

Therefore, the present study focuses on the synthesis of novel hydrazone derivatives and the evaluation of their antifungal potential through molecular docking investigations. Particular attention was directed toward elucidating the relationship between structural features and predicted ligand–target interactions in order to identify promising antifungal candidates for further biological studies.

2. MATERIAL AND METHODS

2.1. Antifungal Activity

The antifungal activity of hydrazone derivatives: (E)-1-(4-methoxybenzylidene)-2-phenylhydrazine (I); (E)-1-(4-chlorobenzylidene)-2-(4-methoxyphenyl)hydrazine (II); (E)-1-(4-nitrobenzylidene)-2-phenylhydrazine (III); (E)-1-(4-chlorobenzylidene)-2-(4-nitrophenyl) hydrazine (IV); (E)-1-(4-chlorobenzylidene)-2-phenylhydrazine (V) and (E)-1-(4-chlorobenzylidene)-2-(p-tolyl)hydrazine (VI) were tested against conditionally pathogenic yeasts of the genus *Candida* (*C. albicans* BDU MI-44, *C. guilliermondii* BDU-217, and *C. tropicalis* BDU LK-30). All test cultures were obtained from the culture collection of the Microbiology and Virology Research Laboratory of Baku State University. The antifungal activity of this compound was tested *in vitro* using the agar well diffusion method [19]. One microliters of a fresh 24-hour culture suspension (4.0 McFarland) of each test strain were aseptically distributed over the surface of the agar medium. Then, 8-mm diameter wells were made in the agar, each filled with 150 microliters of a 0.1% solution of the test compound. Yeast cultures were incubated on Sabouraud dextrose agar (Liofilchem srl, Italy) at 30°C for 48 hours. The antifungal activity was assessed by measuring the diameter (in mm) of the inhibition zone formed around the wells after incubation. DMSO (solvent) was used as a negative control, and fluconazole (antibiotic) - as positive control.

All the experiments were carried out in four replicates, and results are expressed as mean $\pm$ standard error. Statistical significance was evaluated using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. Differences were considered statistically significant at $p < 0.05$.

2.2. Molecular Docking Analysis

2.2.1. Ligand preparation

Proper ligand preparation, including structure standardization, hydrogen addition, geometry optimization, charge assignment, and rotatable bond definition, is essential for obtaining reproducible docking results. The SMILES codes of the investigated compounds were obtained using ChemDraw Professional 16.0. Ligand structures were generated and energy-minimized using Chem3D 16.0. Subsequently, the optimized ligands were prepared for docking in AutoDockTools 1.5.6 through the addition of hydrogen atoms, assignment of Gasteiger charges, and definition of rotatable bonds, followed by conversion into PDBQT format. Hydrogen atoms were added and Gasteiger charges were assigned during ligand preparation. However, exhaustive protonation-state and tautomer enumeration at physiological pH was not performed; therefore, the dominant prepared structures were used consistently throughout the docking workflow.

2.2.2. Protein preparation

Protein preparation is a critical step in docking workflows because missing atoms, incorrect protonation states, crystallographic waters, and unresolved residues may substantially influence predicted ligand binding. The crystal structure of *Candida albicans* lanosterol 14 α -demethylase (CYP51) complexed with an antifungal inhibitor (PDB ID: 5TZ1) [20] was retrieved from the RCSB Protein Data Bank. Prior to molecular docking studies, the protein structure was prepared using AutoDock Tools (ADT, version 1.5.6). All crystallographic water molecules and non-essential heteroatoms were removed from the protein structure. Polar hydrogen atoms were subsequently added, and Kollman charges were assigned to all amino acid residues. To avoid errors associated with metal parameterization during docking calculations, the iron atom of the heme prosthetic group was removed before receptor preparation. The prepared protein structure was then converted into the PDBQT format required for AutoDock Vina calculations. The resulting receptor model was used for all subsequent docking simulations. The docking grid was centered on the binding site of the co-crystallized ligand present in the 5TZ1 structure. Molecular docking calculations were performed using AutoDock Vina with an exhaustiveness value of 100 to ensure an extensive conformational search of the active site.

2.2.3. Docking grid definition and docking protocol

The co-crystallized ligand was extracted from the protein structure and used to identify the active-site region of *Candida albicans* lanosterol 14 α -demethylase (CYP51, PDB ID: 5TZ1). Molecular docking calculations were performed using AutoDock Vina. The docking grid was centered on the active-site cavity of the enzyme with grid center coordinates set to **x = 24.0, y = 22.0, and z = 24.0**. The dimensions of the docking box were defined as **22 × 22 × 22 Å**, ensuring complete coverage of the ligand-binding region. To improve the reliability of conformational sampling, the exhaustiveness parameter was set to **100**, while the number of output binding modes was fixed at **9**. The resulting ligand conformations were ranked according to their predicted binding affinities (kcal/mol), and the best-scoring poses were selected for further interaction analysis and visualization.

2.2.4. Docking validation

To validate the docking protocol, the co-crystallized ligand was redocked into the active site of DNA gyrase B. The superimposition of the crystallographic and redocked poses was analyzed using PyMOL, showing excellent agreement between the two conformations with an RMSD

value below 2.0 Å, thereby confirming the reliability and reproducibility of the docking procedure. Redocking of the co-crystallized ligand and RMSD analysis are commonly used to evaluate whether a docking protocol can reproduce the experimentally observed binding pose

2.2.5. Interaction analysis and methodological limitations

Protein–ligand interactions and binding conformations were analyzed and visualized using Discovery Studio 2021 Client and PyMOL. Therefore, the obtained docking scores primarily reflect ligand–protein interactions within the selected binding pocket and should be interpreted as preliminary estimates of binding potential rather than definitive evidence of inhibitory activity

3. RESULTS AND DISCUSSION

3.1. Antifungal activity

It was found that hydrazine (I) has a similarly high inhibitory effect against yeasts of the genus *Candida* (Table). Hydrazine (II) showed maximum antifungal activity against *C. albicans*, and its activity was 1.3 and 1.5 times higher than that against *C. guilliermondii* and *C. tropicalis*, respectively. Hydrazine III, IV, V and VI showed maximum activity against *C. albicans*, and this activity was 1.3–2.0 and 1.4–2.0 times higher than that against *C. guilliermondii* and *C. tropicalis*, respectively. It should be noted that *C. albicans* showed high sensitivity to all the studied substances and was 1.1–1.4 times higher than that against the antibiotic fluconazole. *C. guilliermondii* and *C. tropicalis* fungi showed high sensitivity to substances I and II, and low sensitivity to substances III – VI. In any case, the studied yeast species had high sensitivity to substance I, and their sensitivity was 1.4, 1.3 and 1.2 times higher than the sensitivity to the antibiotic fluconazole, respectively.

Table. Antifungal activity of hydrazine derivatives

Test Cultures	Compounds and diameter of inhibition zone (mm), M±m						
	I	II	III	IV	V	VI	Fluconazole
<i>Candida albicans</i>	26.3±1.0	25.3±1.2	26.0±1.2	20.0±0.9	26.0±1.2	20.0±0.8	18.0±0.8
<i>Candida guilliermondii</i>	26.0±0.9	20.0±0.9	14.0±0.6	14.0±0.7	13.0±0.4	13.4±0.4	20.0±0.6
<i>Candida tropicalis</i>	27.0±0.6	17.0±0.7	14.0±0.5	14.0±0.6	13.0±0.5	13.0±0.5	22.0±1.0

- I. (E)-1-(4-methoxybenzylidene)-2-phenylhydrazine
- II. (E)-1-(4-chlorobenzylidene)-2-(4-methoxyphenyl)hydrazine
- III. (E)-1-(4-nitrobenzylidene)-2-phenylhydrazine
- IV. (E)-1-(4-chlorobenzylidene)-2-(4-nitrophenyl)hydrazine
- V. (E)-1-(4-chlorobenzylidene)-2-phenylhydrazine
- VI. (E)-1-(4-chlorobenzylidene)-2-(p-tolyl)hydrazine

3.2. Molecular Docking Analysis of Compound 1, 2 and 6 against Lanosterol 14α-Demethylase (5TZ1)

Compound 1 exhibited the highest binding affinity among the investigated derivatives, with a docking score of −4.7 kcal/mol. Analysis of the binding mode revealed the formation of a hydrogen bond between the hydrazone nitrogen atom and LYS358, while additional π -alkyl and

π -anion interactions were established with LEU340 and GLU336, respectively. The presence of multiple stabilizing contacts suggests that the hydrazone linker and aromatic fragments contribute significantly to ligand recognition within the CYP51 active site.

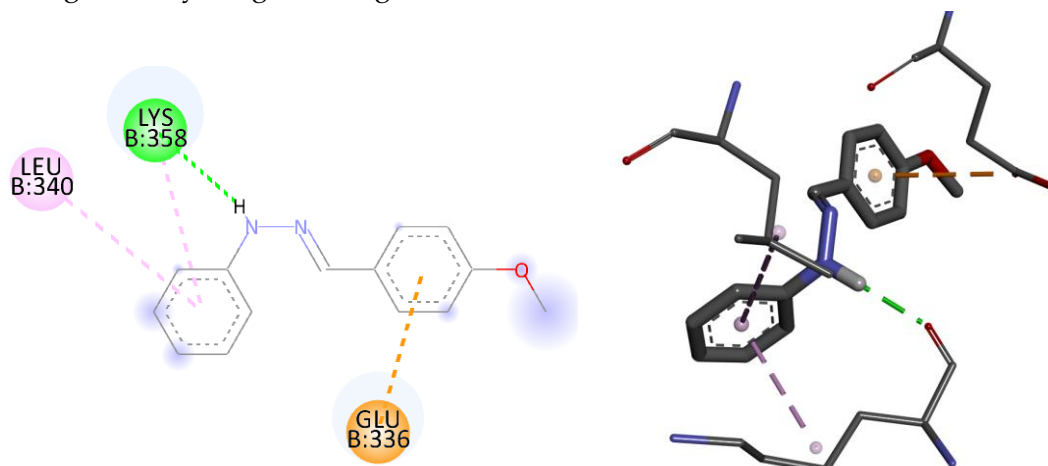


Figure 1. Docking interaction profile of Compound 1 with *Candida albicans* lanosterol 14 α -demethylase (CYP51, PDB ID: 5TZ1): (A) 2D interaction map highlighting key amino acid residues involved in ligand binding; (B) 3D representation of the binding mode within the active site.

Compound 2 showed a binding affinity of -4.5 kcal/mol and interacted primarily with residues LYS358, LEU340, GLU336, GLU339, and GLU343. Compared with Compound 1, a larger number of amino acid residues participated in ligand stabilization, although the calculated binding affinity was slightly lower. The interaction pattern indicates that both aromatic rings contribute to the accommodation of the ligand within the binding cavity.

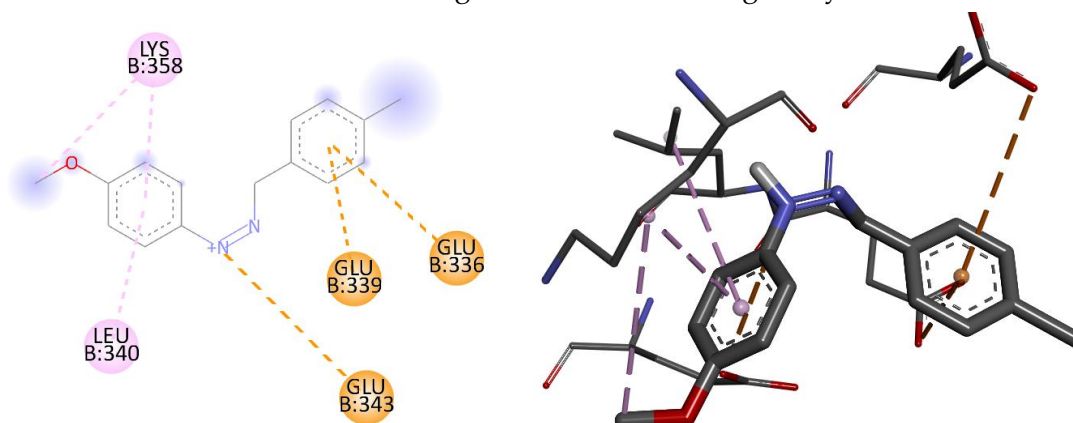


Figure 2. Docking interaction profile of Compound 2 with *Candida albicans* lanosterol 14 α -demethylase (CYP51, PDB ID: 5TZ1): (A) 2D interaction map showing the principal ligand-residue contacts; (B) 3D visualization of the docked conformation in the enzyme binding pocket.

Compound 6 displayed a docking orientation characterized by a conventional hydrogen bond with LYS358 together with hydrophobic interactions involving LEU340 and π -mediated contacts with GLU336 and GLU343. The interaction profile was similar to that observed for Compound 1, highlighting the importance of the hydrazone scaffold in maintaining favorable contacts within the active site of lanosterol 14 α -demethylase.

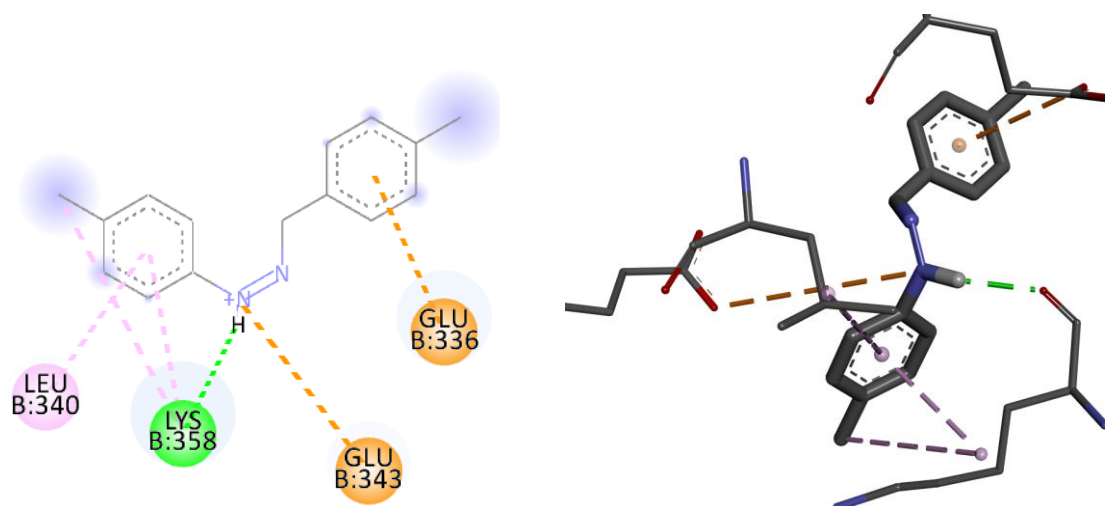


Figure 3. Docking interaction profile of Compound 6 with *Candida albicans* lanosterol 14 α -demethylase (CYP51, PDB ID: 5TZ1): (A) 2D interaction diagram illustrating the main non-covalent interactions; (B) 3D binding mode of the ligand within the active site of CYP51.

3.3. Comparative Analysis of Docking Results

Comparative analysis of the docking results revealed that all investigated hydrazone derivatives occupied a similar region within the active site of lanosterol 14 α -demethylase (CYP51). In all cases, LYS358 appeared as the most important residue, participating either in hydrogen-bond formation or hydrophobic stabilization. LEU340 was also frequently involved in ligand recognition through π -alkyl interactions. Furthermore, acidic residues such as GLU336, GLU339, and GLU343 contributed to ligand stabilization through π -type interactions.

Among the investigated compounds, Compound 1 exhibited the most favorable binding affinity (-4.7 kcal/mol), whereas Compounds 2 and 6 showed slightly lower docking scores. Despite these differences, the interaction profiles of all derivatives indicate that the hydrazone linkage and aromatic substituents play a crucial role in molecular recognition within the CYP51 binding cavity. The relatively similar docking energies suggest that structural modifications mainly affect the interaction pattern rather than the overall binding mode.

Although the docking scores were lower than that reported for the co-crystallized inhibitor oteseconazole, the ability of the synthesized compounds to establish multiple stabilizing interactions with key active-site residues supports their potential as antifungal candidates. These findings provide a theoretical basis for further biological evaluation and molecular dynamics investigations.

hydrophobic, and π -mediated interactions within the enzyme binding pocket. Among the docked compounds, Compound 1 exhibited the most favorable binding affinity, while Compounds 2 and 6 also demonstrated comparable interaction profiles.

Overall, the combined biological and computational findings suggest that hydrazone derivatives represent promising candidates for the development of new antifungal agents. The observed antifungal activity, together with their ability to interact with a biologically relevant fungal target, supports further optimization and in-depth investigations, including molecular dynamics simulations and in vivo studies.

4. CONCLUSION

In this study, a series of hydrazone derivatives were evaluated for their antifungal potential against *Candida* species and their interactions with *Candida albicans* lanosterol 14 α -demethylase (CYP51) were investigated using molecular docking analysis. The biological results demonstrated that the synthesized compounds exhibited varying degrees of antifungal activity against the tested fungal strains. Among them, **(E)-1-(4-methoxybenzylidene)-2-phenylhydrazine** showed the highest antifungal activity against all tested *Candida* species, displaying inhibitory effects that were 1.2–1.4 times greater than those of fluconazole.

Molecular docking studies revealed that the investigated compounds were able to occupy the active site of CYP51 and establish stabilizing interactions with key amino acid residues, including LYS358, LEU340, GLU336, GLU339, and GLU343. The docking results indicated that the hydrazone scaffold plays an important role in ligand recognition through hydrogen-bonding, hydrophobic, and π -mediated interactions within the enzyme binding pocket. Among the docked compounds, Compound 1 exhibited the most favorable binding affinity, while Compounds 2 and 6 also demonstrated comparable interaction profiles.

Overall, the combined biological and computational findings suggest that hydrazone derivatives represent promising candidates for the development of new antifungal agents. The observed antifungal activity, together with their ability to interact with a biologically relevant fungal target, supports further optimization and in-depth investigations, including molecular dynamics simulations and in vivo studies.

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