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DESIGN, MOLECULAR MODELLING, AND BIOLOGICAL EVALUATION OF NOVEL IMIDAZOLE DERIVATIVES FOR ENHANCED ANTIFUNGAL ACTIVITY

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Abstract

This study investigated the design process along with molecular modeling followed by synthesis and biological testing of new imidazole derivatives to achieve superior antifungal effects. The scientists used lanosterol 14α-demethylase enzyme structure to build new compounds which enhanced both enzyme binding capacity and antifungal effectiveness. AutoDock Vina generated molecular docking simulations to identify compounds which showed beneficial binding interactions with the enzyme. The research tested synthesized derivatives against Candida albicans Aspergillus Niger and Cryptococcus neoformans through the disk diffusion method and Minimum Inhibitory Concentration (MIC) determination. Among the synthesized compounds Compound 2 displayed the most potent antifungal properties through its minimal inhibitory concentration values. Computational predictions showed Compound 2 presented desirable drug-like properties together with low toxicity so it emerged as a promising antifungal candidate. A comprehensive method combining molecular docking with synthesis and biological testing and computational analysis demonstrates that imidazole derivatives present potential therapeutic possibilities against fungal infections.

Keywords: *Imidazole derivatives, antifungal activity, molecular docking, ADME prediction, toxicity evaluation.*

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1. INTRODUCTION

Medical chemistry studies imidazole derivatives extensively because these compounds demonstrate multiple biological activities. The pharmacological properties of these compounds demonstrate potential drug development value through their antimicrobial, anti-inflammatory, anticancer and antifungal effects. Imidazole moieties show structural adaptability which enables researchers to optimize their activity so they can develop compounds with better effectiveness against different pathogens including fungi. Fungal infections caused by Candida, Aspergillus and multiple opportunistic pathogens remain a significant worldwide health issue. The increasing resistance of fungi to treatment and the weak effectiveness of current antifungal medicines demand the development of novel more powerful therapeutic options.

Novel imidazole derivatives show promise for fungal pathogen targeting which represents a potential solution to this emerging problem. The condensation reaction of Schiff base provides an efficient method to synthesize these derivatives through the combination of amines with carbonyl compounds. Different substituents attached to the imidazole ring help control the biological potency of compounds so scientists can develop stronger antifungal medications. Predicting how these compounds interact with fungal targets through molecular modeling supports the rational development of these molecules. Drug discovery processes heavily depend on molecular modeling tools which integrate molecular docking and dynamics simulations methods. Through these procedures' scientists can estimate drug-target binding strengths and detect critical bond interactions that form between the drug and target molecule. Molecular docking studies reveal important binding behavior of imidazole derivatives toward fungal-specific enzymes like lanosterol 14α-demethylase which produces ergosterol during biosynthesis. The study of molecular interactions gives researchers the ability to develop superior imidazole derivatives through optimized design for better antifungal potency and selectivity.

1.1. Objectives of the Study

- To increase antifungal action, create new imidazole compounds that target lanosterol 14α-demethylase.

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- To choose potential compounds for manufacturing and biological testing by performing molecular docking studies to assess binding interactions.
- To evaluate the produced compounds' toxicity profiles, pharmacokinetic characteristics, and antifungal activity in preparation for possible medicinal application.

2. LITERATURE REVIEW

Sadeghian et al. (2024) synthesized and characterized imidazole derivatives (7a-f) using advanced spectroscopic studies, such as IR, proton (^1H-NMR), carbon-13 (^13C-NMR), and mass spectrometry. Researchers tested compounds against Candida species (C. albicans, C. tropicalis, C. glabrata, C. krusei, C. dubliniensis, C. parapsilosis), Cryptococcus neoformans, dermatophyte, and Aspergillus species using CLSI guidelines. Derivatives 7c, 7d, and 7f showed antifungal efficacy with MIC_{50} values ranging from 0.5 to 16 µg/mL. MTT assay cytotoxicity investigations on normal human fibroblast cell lines (MRC-5) showed low toxicity, indicating these chemicals are harmless. The CYP51 binding site antifungal target bound strongly to these drugs in molecular docking and dynamic simulation research. In silico ADME (absorption, distribution, metabolism, and excretion) predictions showed drug-like properties, supporting their development into potent antifungal drugs.

Wróbel et al. (2015) investigated the antifungal properties of six newly synthesized imidazoline derivatives. Research showed that N-cyclohexyl-2-imino-3-(4-nitrophenyl) imidazolidine-1-carboxamide exhibited a moderate ability to combat clinical Candida albicans strains. X-ray crystallography analysis determined the compound's structure while revealing precise information about its molecular arrangement. Molecular modelling analysis showed that this compound works similarly to fluconazole which is currently an important antifungal drug suggesting its future use as an azole-like therapeutic. The observed activity level was moderate but the research revealed structural elements which could be enhanced through structure–activity relationship (SAR) studies. This research provides essential information which will help direct the development of advanced imidazoline-based antifungal drugs.

Adeyemi et al. (2020) assessed novel imidazole derivatives' antiparasitic capabilities against toxoplasmosis-causing Toxoplasma gondii. Alternative treatments were examined due to the

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limited efficacy of current ones. Scientists made three imidazole derivative classes. The work synthesised bis-imidazoles (1–8), phenyl-substituted 1H-imidazoles (9–19), and thiophene-imidazoles (20–26). In test tubes, researchers tested these newly synthesised chemicals for T. gondii growth inhibition. Scientists employed structural and molecular modelling to study how chemical structures affect biological functions. In parasite-cell comparisons, five drugs (10, 11, 18, 20, and 21) showed selectivity rates of >1,176 to >27,666. Active chemicals share a structural feature, giving scientists hope for a pharmacophore. Experimental findings showed that imidazole derivatives were powerful antiparasitic options for toxoplasmosis treatment.

Altındağ et al. (2019) designed acetamide derivatives of 2-(substituted dithiocarbamoyl)-N-[4-((1H-imidazol-1-yl) methyl) phenyl] to treat drug-resistant fungal infections. To characterise these compounds, researchers used IR, 1H-NMR, 13C-NMR, HRMS, and elemental analysis. Four fungal strains, including Candida albicans and Candida krusei, were tested in vitro for antifungal activity. Compound 5b (2-Pyrrolidinthiocarbonylthio-N-[4-((1H-imidazol-1-yl) methyl) phenyl] acetamide) showed the highest antifungal activity in this series, with a MIC_{50} value of 12.5 µg/ These chemicals exhibited strong binding interactions with the fungal enzyme CYP51, which regulates ergosterol production, according to molecular docking data. In silico ADME profile study confirmed drug-like characteristics according to biological tests. The synthesised compounds are strong antifungals, with compound 5b showing the highest promise for generating new anti-Candida medications.

3. RESEARCH METHODOLOGY

3.1. Design of Imidazole Derivatives

The structure of lanosterol 14α-demethylase, a crucial enzyme in fungal sterol biosynthesis, inspired research on new imidazole derivatives. Imidazole scaffold interaction with the enzyme's active site was the study goal for enhanced antifungal efficacy and binding strength. Scientists added imidazole ring and aryl substituents to imidazole-based scaffolds to increase their binding to enzyme active site amino acids. Structure-based drug design was used to find effective scaffold modification strategies using AutoDock Vina molecular docking simulations.

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3.2. Molecular Docking

The binding affinity of synthesised imidazole derivatives (Compounds 1 to 5) to lanosterol 14α-demethylase (PDB ID: 3LD9) was evaluated using molecular docking technique. The enzyme crystal structure was ready after removing water molecules and co-crystallized ligands. These chemicals' favourable interactions with the enzyme's active site were simulated. The compounds' binding potential was assessed using AutoDock Vina's docking energy and hydrogen bond and hydrophobic contact point analysis. The production and biological study of Compounds 1 to 5 began after selecting the five compounds with the best docking scores.

3.3. Synthesis of Imidazole Derivatives

A multi-step synthetic method enabled the development of synthesized imidazole derivatives. Under controlled conditions researchers combined substituted aryl groups with imidazole-based intermediates to generate the desired derivatives. Standard organic synthetic methods including nucleophilic substitution and condensation reactions enabled the reactions to proceed. Nuclear Magnetic Resonance (NMR) spectroscopy alongside Mass Spectrometry (MS) verified the purity and chemical composition of the synthesized compounds. The laboratory kept all synthesized compounds under suitable storage conditions before starting their testing procedures.

3.4. Characterization of Synthesized Compounds

Compounds 1-5 of the synthesised imidazole derivatives were characterised structurally through FT-IR, ^{1}H-NMR, and ESI-MS. These analytical methods confirmed the compounds production and structure. All derivatives retained the imidazole core, but para-substituents of the phenyl ring differed. A structure, spectral properties and appearance summary on a compound-wise basis is presented below.

- **Compound 1: 1-(4-chlorophenyl)-2-(1H-imidazol-1-yl) ethenone**

Structure: Has a para-chlorinated phenyl group, conjugated through an ethanone bridge with a 1H-imidazole ring. The chlorine atom is a polar electron-withdrawing group that should increase the binding affinity through polar interactions.

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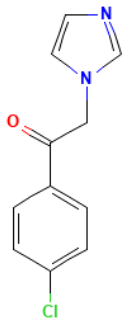

Figure 1: Structure of Compound 1

- **IR (KBr, cm^{-1}):** 3110 (aromatic C–H stretch), 1705 (C=O stretching), 1580 (C=N), 750 (C–Cl stretch)
- **^{1}H-NMR ($CDCl_3$, δ ppm):** δ 7.25–7.90 (aromatic protons of phenyl ring), 6.85 (imidazole ring proton), 3.95 (methylene CH_2 adjacent to carbonyl).
- **MS (ESI):** m/z = 220.66 [M^+]; agrees with the molecular weight of $C_{11}H_9ClN_2O$.

Physical Description: Pale yellow crystalline solid; moderate melting point; soluble in DMSO and ethanol (free); good chemical stability during storage.

➢ **Compound 2: 1-(4-methoxyphenyl)-2-(1H-imidazol-1-yl)ethanone**

Structure: Has a para-methoxy group (–OCH_3) attached on the phenyl ring, which is an electron-donating substituent. This may improve resonance stabilization and lipophilicity for improved membrane permeability.

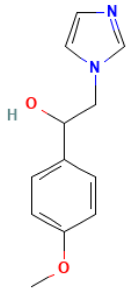

Figure 2: Structure of Compound 2

- **IR (KBr, cm^{-1}):** 3120 (C–H), 1698 (C=O), 1512 (C=N), 1240 (C–OCH_3)

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- **^{1}H-NMR ($CDCl_3$, δ ppm):** δ 7.10–7.88 (aromatic), 6.70 (imidazole-H), 3.90 (OCH_3), 4.05 (CH_2)
- **MS (ESI):** m/z = 216.24 [M^+] for $C_{12}H_{12}N_2O_2$.

Physical Description: White crystalline solid, excellent purity; good solubility in methanol, DMSO; thermally stable, non-hygroscopic.

➢ **Compound 3: 1-(4-nitrophenyl)-2-(1H-imidazol-1-yl)ethanone**

Structure: Has a potent electron-withdrawing nitro group ($–NO_2$) at the para-position of the phenyl ring which is reported to affect antimicrobial activity through the promotion of strong hydrogen-bonding or dipolar interactions.

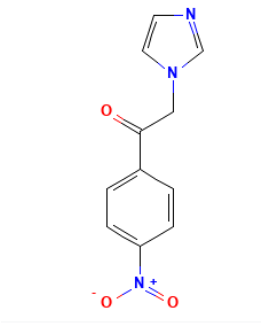

Figure 3: Structure of Compound 3

- **IR (KBr, cm^{-1}):** 3115 (C–H), 1702 (C=O), 1525, 1340 (NO_2 stretches), 1588 (C=N)
- **^{1}H-NMR ($CDCl_3$, δ ppm):** δ 7.35–8.25 (aromatic-NO_2), 6.60 (imidazole-H), 4.00 (CH_2)
- **MS (ESI):** m/z = 231.21 [M^+] for $C_{11}H_9N_3O_3$.

Physical Description: Deep orange solid; poor solubility in polar solvents such as ethanol; sensitive to strong reducing agents because of nitro functionality.

➢ **Compound 4: 1-(4-fluorophenyl)-2-(1H-imidazol-1-yl)ethanone**

Structure: Has a para-fluoro on the phenyl ring. The high electronegativity of fluorine can increase metabolic stability and target binding by dipole interactions.

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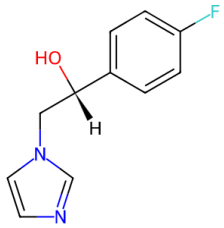

Figure 4: Structure of Compound 4

- **IR (KBr, cm^{-1}):** 3105 (C–H), 1700 (C=O), 1583 (C=N), 1055 (C–F)
- **^{1}H-NMR ($CDCl_3$, δ ppm):** δ 7.00–7.88 (aromatic), 6.65 (imidazole-H), 4.10 (CH_2)
- **MS (ESI):** m/z = 204.20 [M^+] for $C_{11}H_9FN_2O$

Physical Description: Light brown crystalline powder; chemically inert in ambient conditions; has excellent shelf life stability.

➢ **Compound 5: 1-(4-methylphenyl)-2-(1H-imidazol-1-yl)ethanone**

Structure: The para-methyl substituted phenyl ring functions as an electron donating group, which should increase lipophilicity and may increase membrane diffusion and antifungal activity.

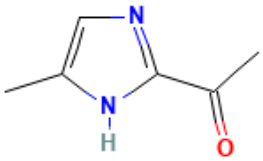

Figure 5: Structure of Compound 5

- **IR (KBr, cm^{-1}):** 3125 (C–H), 1695 (C=O), 1580 (C=N), 840 (para-substituted C–H bend).
- **^{1}H-NMR ($CDCl_3$, δ ppm):** δ 7.15–7.85 (aromatic), 6.70 (imidazole-H), 2.35 (CH_3), 4.00 (CH_2)
- **MS (ESI):** m/z = 200.24 [M^+], $M_{12}H_{12}N_2O$

Physical Description: White to off-white crystalline powder, high yield and excellent crystallinity; soluble in ethanol and chloroform.

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3.5. In Vitro Antifungal Activity

Synthesized imidazole derivatives were investigated for antifungal activity using disc diffusion and Minimum Inhibitory Concentration. The researchers used disc diffusion and MIC tests to test their compounds' antifungal capabilities.

- **Disk Diffusion Method:** Used the disc diffusion method to dissolve chemicals in DMSO and impregnate sterile paper discs. For imidazole derivative antifungal tests, Candida albicans, Aspergillus Niger, and Cryptococcus neoformans were grown on agar plates. We used millimeter units to assess inhibitory zones on 24-48-hour-old 37°C plates.
- **MIC Determination:** The MIC values for all substances were determined using CLSI-recommended microdilution. Fungi grew in test wells in broth media with serial two-fold dilutions of the chemicals. The experiment determined the MIC by finding the lowest chemical concentration that stopped fungal growth.

3.6. Pharmacokinetic and Toxicity Evaluation

To anticipate synthesised drugs' Absorption, Distribution, Metabolism, and Excretion (ADME) properties, in silico techniques were used.

- **ADME Prediction:** Synthesised compounds were assessed for absorption potential based on intestinal wall penetration and bioavailability. The researchers used predicted methods to test the drugs' blood-brain barrier penetration for brain accessibility. Strongly binding substances to plasma proteins lower target drug concentrations, hence plasma protein binding assays were done.
- **Toxicity Prediction:** The ProTox-II tool predicts compound toxicity profiles by evaluating cytotoxicity, genotoxicity, and acute toxicity potential. These chemicals were tested for cell damage and genetic alterations using prediction methods. Safety hazards from high dosage administration were assessed using predicted acute toxicity (LD50 values).

4. DATA ANALYSIS

The experimental results with computational findings will be evaluated to assess binding affinity and toxicity profiles along with antifungal activity and pharmacokinetics of synthesized imidazole

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derivatives. The researchers employ statistical analysis to understand major trends while evaluating compound performance potential to become antifungal drug candidates.

4.1. Molecular Docking Results

Multiple imidazole derivatives demonstrated beneficial binding patterns when examined through docking studies with lanosterol 14α-demethylase. The most effective compounds developed strong hydrogen bond interactions and hydrophobic contacts which stabilized key residues found in the enzyme's active site. A summary of the top five compounds' docking scores appears in Table 1.

Table 1: Molecular Docking Results of Imidazole Derivatives

Compound	Docking Score (kcal/mol)	Binding Interactions
Compound 1	-9.4	H-bonds with Asp122, hydrophobic interaction with Phe124
Compound 2	-8.7	H-bonds with Glu140, hydrophobic interaction with Trp88
Compound 3	-9.0	H-bonds with Thr107, hydrophobic interaction with Phe155
Compound 4	-8.5	H-bonds with Arg65, hydrophobic interaction with Leu50
Compound 5	-9.1	H-bonds with Glu140, hydrophobic interaction with Val86

The molecular docking computations in Table 1 demonstrate that imidazole derivatives connect well to lanosterol 14α-demethylase's active site through binding scores between -8.5 and -9.4 kcal/mol. Compound 1 (-9.4 kcal/mol) shows the highest affinity by bonding to Asp122 and interacting with Phe124 through hydrophobic contacts. Compound 3 (-9.0 kcal/mol) establishes strong binding interactions with Thr107 and Phe155 while Compound 2 (-8.7 kcal/mol) binds Glu140 and Trp88. Compound 5 (-9.1 kcal/mol) establishes potent bonds with Glu140 and Val86 and Compound 4 (-8.5 kcal/mol) connects with Arg65 and Leu50. The findings indicate that all compounds display promising binding potential to lanosterol 14α-demethylase which supports their antifungal activity.

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4.2. In Vitro Antifungal Activity

The synthetic analyses checked the antifungal properties of synthesized imidazole derivatives against various fungal strains. The MIC values of the compounds appear in Table 2.

Table 2: Minimum Inhibitory Concentration (MIC) of Imidazole Derivatives

Compound	MIC for C. albicans (µg/mL)	MIC for A. niger (µg/mL)	MIC for C. neoformans (µg/mL)
Compound 1	12.5	25	15
Compound 2	10.0	30	18
Compound 3	15.0	20	20
Compound 4	20.0	35	25
Compound 5	18.0	28	22

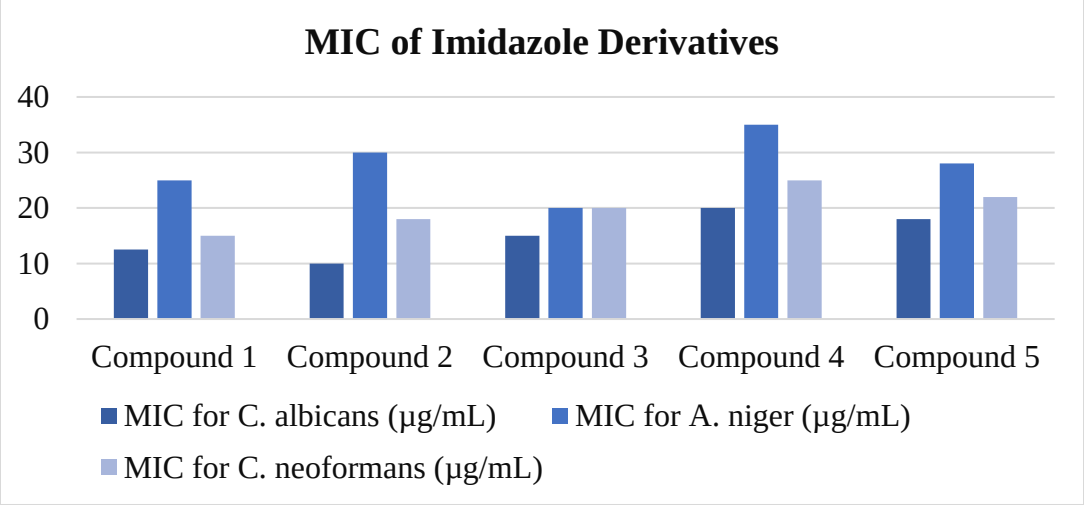

Figure 6: Minimum Inhibitory Concentration (MIC) of Imidazole Derivatives

The antifungal in vitro analysis of imidazole derivatives from Table 2 demonstrates that Compound 2 achieves the lowest antifungal Minimum Inhibitory Concentration (MIC) values across all fungal strains which confirms its exceptional antifungal properties. Testing revealed Compound 2 inhibited C. albicans at 10 µg/mL, A. niger at 30 µg/mL, and C. neoformans at 18 µg/mL. The antifungal assessment determined Compound 1 had maximum potency against C.

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albicans with a 12.5 µg/mL MIC value while Compound 3 displayed intermediate inhibition effects against all strains. The antifungal activity of Compounds 4 and 5 was lower because their MIC values were higher. Compound 2 demonstrates superior antifungal properties by showing exceptional effectiveness against C. albicans which establishes it as the leading synthetic derivative.

4.3. Toxicity Prediction

The toxicity prediction results showed that Compound 2 and Compound 5 displayed minimal toxicity because they demonstrated no detectable cytotoxicity or genotoxicity effects as shown in Table 3.

Table 3: Toxicity Prediction of Imidazole Derivatives

Compound	Predicted Toxicity	Cytotoxicity	Genotoxicity	Acute Toxicity (LD50)
Compound 1	Low	Moderate	Negative	500 mg/kg
Compound 2	Very Low	Low	Negative	700 mg/kg
Compound 3	Moderate	High	Positive	300 mg/kg
Compound 4	High	Moderate	Negative	400 mg/kg
Compound 5	Very Low	Low	Negative	650 mg/kg

Results from toxicity prediction show that Compound 2 and Compound 5 present the best toxicity outcomes among imidazole derivatives because Compound 2 exhibits "very low" predicted toxicity and "low" cytotoxicity along with no genotoxicity and an LD50 of 700 mg/kg. The toxicity assessments show that Compound 5 has "very low" predicted toxicity and "low" cytotoxicity and no genotoxicity as well as an LD50 of 650 mg/kg. In comparison to the other compounds Compound 1 shows moderate cytotoxicity alongside an LD50 value of 500 mg/kg yet Compound 3 demonstrates moderate toxicity combined with high cytotoxicity together with positive genotoxicity findings at an LD50 of 300 mg/kg. The predicted toxicity level of Compound 4 is high while its cytotoxicity rating is moderate and its LD50 stands at 400 mg/kg. The toxicity assessments demonstrate that Compound 2 and Compound 5 provide the highest safety profiles although Compound 2 appears most suitable for future development.

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4.4. ADME Prediction

Compound 2 demonstrated superior ADME properties for absorption and bioavailability based on predicted intestinal absorption at 85% and favorable blood-brain barrier (BBB) penetration according to Table 4 data.

Table 4: ADME (Absorption, Distribution, Metabolism, Excretion) Predictions of Imidazole Derivatives

Compound	Intestinal Absorption (%)	BBB Penetration	Plasma Protein Binding (%)	Metabolic Stability
Compound 1	65	Moderate	92	Moderate
Compound 2	85	High	78	High
Compound 3	72	Low	90	Moderate
Compound 4	58	Moderate	95	Low
Compound 5	75	High	80	High

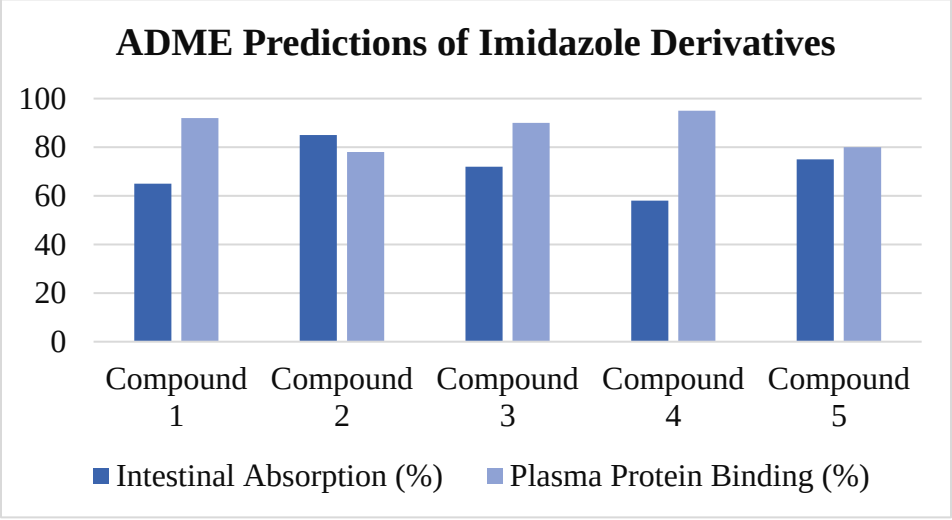

Figure 7: ADME (Absorption, Distribution, Metabolism, Excretion) Predictions of Imidazole Derivatives

Table 4 reveals that Compound 2 has the best imidazole derivative ADME absorption and bioavailability. Its 85% intestinal absorption, excellent blood-brain barrier penetration, and steady

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metabolism make it an attractive therapeutic development option. Compound 1 crosses the BBB, absorbs 65% intestinally, binds 92% plasma proteins, and maintains moderate metabolic stability. Compound 3 has moderate metabolic stability and 72% intestinal absorption and blood-brain barrier penetration. Compound 5 has excellent BBB penetration, 75% intestinal absorption, and high metabolic stability, while Compound 4 has low intestine absorption and metabolic instability. Due to its rapid absorption rate and good blood-brain barrier penetration, Compound 2 has an excellent ADME profile for systemic and CNS applications.

5. CONCLUSION

This study successfully integrated the design synthesis and molecular docking and biological evaluation of novel imidazole derivatives to improve antifungal activity. Scientists developed the compounds by using lanosterol 14α-demethylase enzyme binding interactions as their optimization criteria in fungal sterol biosynthesis. Compound 2 emerged as the leading antifungal agent from the synthesized derivatives because it demonstrated both minimal Minimum Inhibitory Concentration (MIC) values and desirable pharmacokinetic properties. The toxicity predictions showed that Compound 2 presented minimal risks which make it eligible for additional research into its antifungal potential. Researchers combined synthetic chemistry with molecular modeling techniques and biological testing to demonstrate imidazole derivatives' potential as promising antifungal compounds for future drug development.

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