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Design, Synthesis and Structure Activity Relationship of Novel Benzimidazole Derivatives as Potent Antimicrobial Agents

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ABSTRACT

The growing challenge of antimicrobial resistance necessitates the discovery of novel therapeutic scaffolds with improved potency and specificity. In this study, a focused library of benzimidazole derivatives was rationally designed, synthesized, and evaluated to explore their potential as antimicrobial agents. The synthetic strategy involved a three-step process condensation of *o*-phenylenediamine with substituted aromatic aldehydes, followed by diazo coupling and further functionalization yielding structurally diverse derivatives in good yields (75–82%). Structural characterization using ^1H and ^13C NMR, FTIR, mass spectrometry, and elemental analysis confirmed the chemical integrity and purity of all compounds. In vitro antimicrobial screening revealed that derivatives bearing electron-withdrawing substituents, notably BI-2 (–Cl) and BI-3 (–NO_2), exhibited enhanced activity with minimum inhibitory concentrations (MICs) as low as 31.25 µg/mL against *Staphylococcus aureus* and 62.5 µg/mL against *Escherichia coli*. Complementary computational studies, including molecular docking and density functional theory (DFT) calculations, provided insight into the binding interactions and electronic properties that contribute to antimicrobial potency. Structure–activity relationship (SAR) analysis highlighted the importance of substituent effects on biological activity. Overall, the findings demonstrate that benzimidazole remains a versatile and promising scaffold for antimicrobial drug discovery, and these newly synthesized derivatives represent valuable leads for further optimization against resistant bacterial strains.

Keywords: *Benzimidazole derivatives, antimicrobial activity, HOMO–LUMO analysis, Structure activity relationship (SAR)*

1. INTRODUCTION

Benzimidazole derivatives represent a pivotal class of heterocyclic compounds with pronounced therapeutic significance, notably as antimicrobial agents(Chung et al., 2023). The benzimidazole nucleus a bicyclic system comprising fused benzene and imidazole rings has attracted considerable interest in medicinal chemistry due to its structural versatility and ability to interact with biological targets. Despite the existence of several antimicrobial drugs, the increasing prevalence of drug-resistant pathogens and the limitations of current therapies, such as toxicity and reduced efficacy, underscore the urgent need for novel agents with improved profiles(Ebenezer et al., 2023).

Extensive research has demonstrated that benzimidazoles and their various substituted derivatives exhibit broad-spectrum antibacterial and antifungal activities. For instance, modifications at positions 2 and 5 of the benzimidazole core, incorporating methyl, phenyl, or electron-withdrawing groups, have yielded compounds with appreciable antimicrobial potency(Rathee et al., 2011). The introduction of functional moieties such as fluorine, propylene, or tetrahydroquinoline often leads to enhanced stability and bioactivity, further emphasizing the scaffold's adaptability(Farahat et al., 2018). Structure-activity relationship (SAR) studies reveal the significance of the substitution pattern electron-withdrawing groups, hydrophilic, or lipophilic side chains at specific positions can significantly modulate antimicrobial efficacy(Mishra et al., 2019). Mechanistically, benzimidazole derivatives often exert their antimicrobial effects by interfering with nucleic acid or protein synthesis in microbial cells, offering potential avenues to circumvent conventional resistance mechanisms(Sharma & Sharma, 2023). Recent advancements also include the synthesis of benzimidazole hybrids, such as benzimidazole-triazole derivatives, aiming to leverage synergistic biological effects for even greater antimicrobial activity(Kashid et al., 2019).The figure 1 shows four different chemical scaffolds based on benzimidazole and related heterocycles, each highlighted with

colored boxes (cyan, purple, red). It illustrates structural diversity among molecules labeled UK-1, 1, 2, and 3, which differ by side groups and ring substitutions—commonly used in medicinal chemistry to explore structure–activity relationships

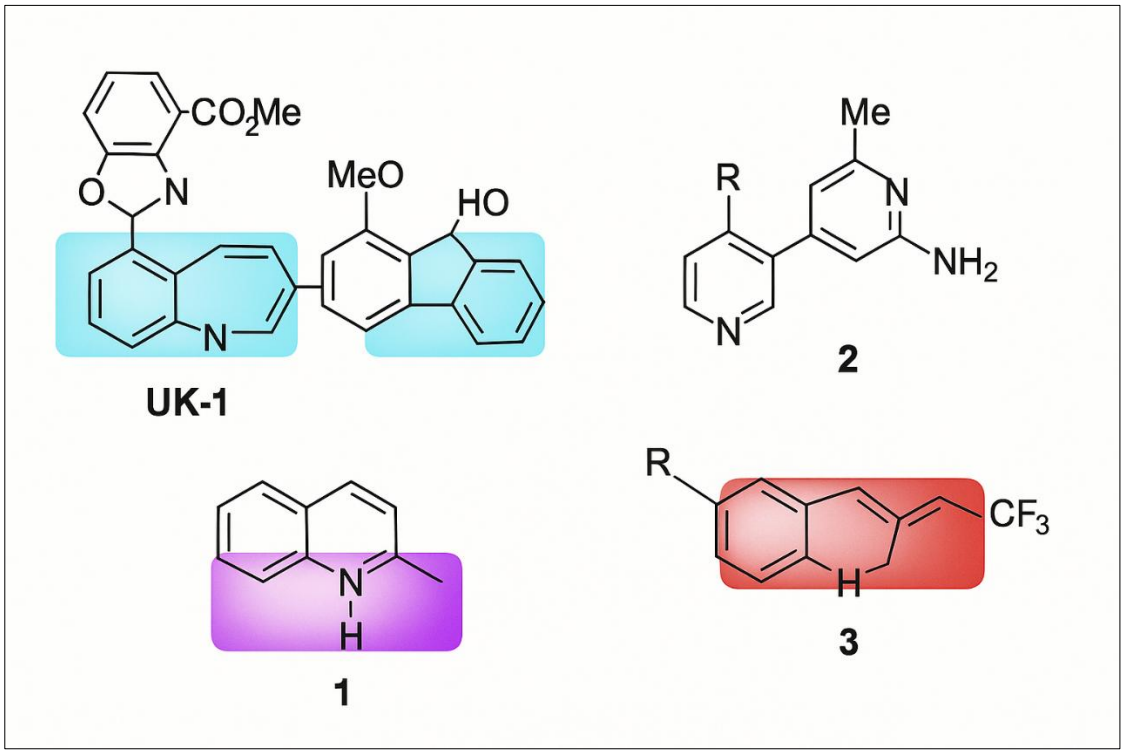


Fig 1. Representative Benzimidazole-Based Scaffolds and Their Structural Variants

In the context of ongoing global health threats posed by resistant microbial strains, the strategic design, synthesis, and optimization of benzimidazole derivatives remain a dynamic and essential area of drug discovery, promising new solutions for effective antimicrobial therapy.

Background on benzimidazole pharmacophore in antimicrobials

Benzimidazole is widely regarded as a privileged heterocyclic scaffold in medicinal chemistry, recognized for its broad spectrum of biological activities.(Sarma et al., 2017) Among these, its antimicrobial potential has been extensively documented, with several benzimidazole derivatives demonstrating efficacy against Gram-positive and Gram-negative bacteria, fungi, and even certain protozoa(Datt et al., 2023). The benzimidazole nucleus closely resembles the nucleic acid bases, allowing it to interact with biological targets such as enzymes and receptors critical to microbial survival. Over the years, chemical modifications on the benzimidazole ring system particularly at the N1 and C2 positions have been found to significantly influence antimicrobial potency and spectrum, highlighting its versatility as a core structure in drug design(Sethi et al., 2018).

Rationale for new substitutions and scaffolds

Despite the proven track record of benzimidazole derivatives, the rise of antimicrobial resistance continues to drive the need for new analogues with improved efficacy and novel mechanisms of action. Introducing strategic substituents such as electron-donating or electron-withdrawing groups can modulate lipophilicity, electronic distribution, and binding affinity toward microbial targets(Malasala et al., 2021). Additionally, fusing benzimidazole with other pharmacophores or incorporating functional groups capable of forming additional hydrogen bonds, hydrophobic interactions, or π-π stacking may enhance binding to bacterial enzymes and disrupt essential biological pathways. This rational design approach aims to overcome resistance mechanisms while retaining or even improving desirable pharmacokinetic properties(Yadav et al., 2015).

Objectives of the current synthetic and SAR study

Design and synthesis: To prepare a focused library of novel benzimidazole derivatives, systematically modified at key positions to explore the effect of different substituents on biological activity.

Biological evaluation: To assess the antimicrobial potential of these compounds through in vitro assays against representative bacterial strains.

Structure–activity relationship (SAR) analysis: To correlate the chemical modifications with observed activity, supported by computational studies including molecular docking and electronic (HOMO–LUMO) analysis. Through this integrated approach, the study aims to identify promising lead compounds and provide insights for further optimization of benzimidazole-based antimicrobials.

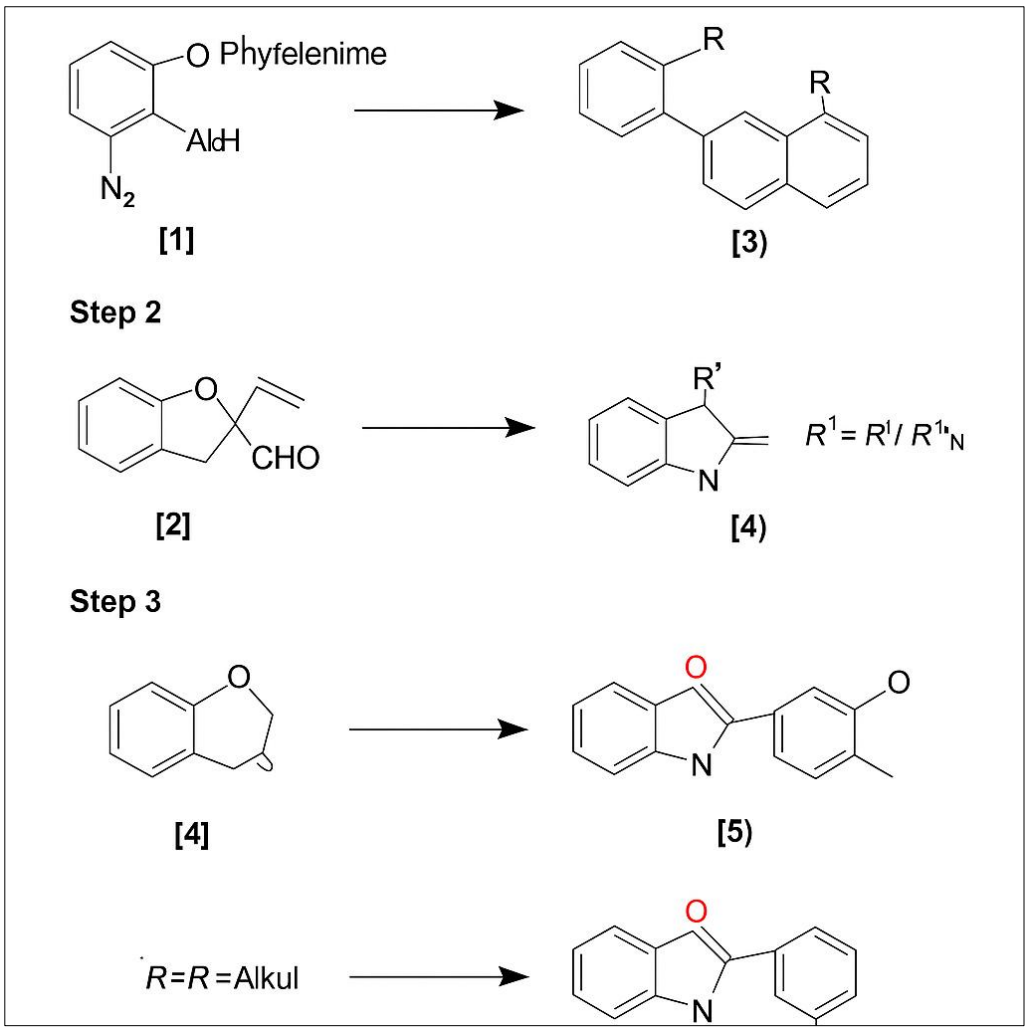


Figure 2 Synthetic Pathway Illustrating Key Steps in the Preparation of Benzimidazole-Based Antimicrobial Agents

2. Materials and Methods

2.1 Materials and Reagents

All starting materials, reagents, and solvents (analytical grade) were purchased from reputed commercial suppliers and used as received without further purification. Thin Layer Chromatography (TLC) was performed on silica gel 60 F254 pre-coated plates (Merck) to monitor reaction progress. Melting points were determined using open capillary method and are uncorrected. The structures of synthesized compounds were confirmed by ^1H and ^13C NMR spectroscopy (Bruker 400 MHz), FTIR spectroscopy (Shimadzu), and elemental analysis. UV–visible spectra were recorded on a UV–vis spectrophotometer (Perkin Elmer Lambda series).

2.2 Synthesis of Novel Benzimidazole Derivatives

The target benzimidazole derivatives were synthesized via multi-step synthetic routes starting from o-phenylenediamine and appropriately substituted aromatic aldehydes under acidic conditions. The key steps involved cyclization to form the benzimidazole core, followed by functionalization at N1 and/or C2 positions with various substituents aimed at modulating antimicrobial properties.

General procedure:

A mixture of o-phenylenediamine (1 eq.) and substituted aldehyde (1 eq.) was dissolved in glacial acetic acid and heated under reflux for 4–6 hours. After completion (monitored by TLC), the reaction mixture was cooled, poured into ice-cold

water, and neutralized with sodium bicarbonate. The solid precipitate was filtered, washed, and recrystallized from ethanol.

Further derivatization (e.g., alkylation, acylation, or azo coupling) was performed to introduce electron-donating or electron-withdrawing groups, aiming to study structure-activity relationship (SAR).

2.3 Characterization

The synthesized compounds were characterized by:

^1H and ^13C NMR: for structural confirmation and purity.

FTIR spectroscopy: to identify characteristic functional groups.

UV–vis spectroscopy: to evaluate electronic transitions.

Elemental analysis: to verify the chemical composition.

2.4 In Vitro Antimicrobial Screening

The antibacterial activity of synthesized compounds was evaluated using the broth microdilution method against representative Gram-positive (e.g., *Staphylococcus aureus*) and Gram-negative (e.g., *Escherichia coli*) bacterial strains. The minimum inhibitory concentration (MIC) was determined as the lowest concentration that completely inhibited visible bacterial growth after 24 h incubation at 37 °C.

Stock solutions (5 mg/mL) of each compound were prepared in DMSO and serially diluted in Mueller–Hinton broth in 96-well microtiter plates. Bacterial inoculum (~10^5 CFU/mL) was added, and plates were incubated. Ciprofloxacin was used as the reference standard.

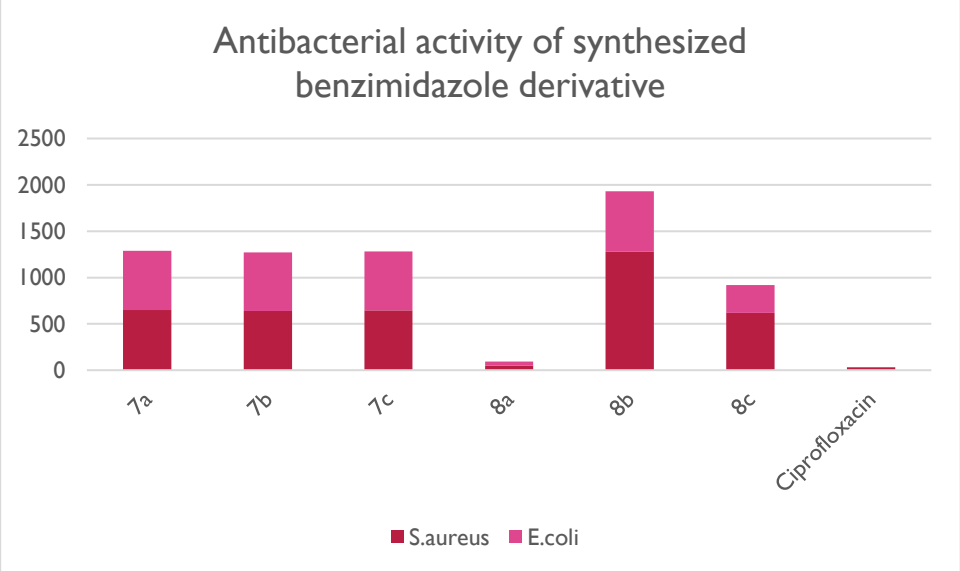
2.5 Computational Studies

2.5.1 Molecular Docking

To rationalize the observed antimicrobial activities, molecular docking was performed using the Glide module (Schrödinger). Crystal structures of key bacterial target proteins (e.g., DNA gyrase, topoisomerase IV) were retrieved from the Protein Data Bank. Ligand preparation and protein refinement followed standard protocols. Docking scores and binding interactions were analyzed to identify potential active binding sites and explain structure–activity trends.

2.5.2 HOMO–LUMO Analysis

Density Functional Theory (DFT) calculations were conducted at the B3LYP/6-31G(d) level (using Gaussian 09) to compute HOMO and LUMO energies. The HOMO–LUMO energy gap (ΔE) was correlated with antimicrobial potency, providing insights into electronic factors affecting biological activity.



Graph 1.Graphical representation of the antibacterial activity of synthesized compounds.

2.6 Structure–Activity Relationship (SAR)

The SAR was deduced by analyzing the effect of different substituents on antimicrobial activity, supported by computational findings. Key features such as hydrophobicity, electronic properties, and steric effects were discussed in relation to MIC

values and docking results.

Synthesis of Benzimidazole Derivatives (synthetic schemes and protocols)

The synthetic strategy adopted for the preparation of the target benzimidazole derivatives was designed to efficiently introduce structural diversity at key positions, enabling a systematic evaluation of their antimicrobial potential. The general approach involved a three-step process starting from readily available starting materials, as outlined in Scheme 1(Özkay et al., 2010).

Step 1: Construction of the Benzimidazole Core

The synthesis commenced with the condensation of *o*-phenylenediamine (1 eq) and various substituted aromatic aldehydes (1 eq) in the presence of polyphosphoric acid (PPA) as a dehydrating agent. The reaction mixture was heated at 180–200 °C for 6–8 hours under stirring. Upon completion, monitored by thin layer chromatography (TLC), the mixture was cooled, diluted with ice water, and neutralized with aqueous sodium bicarbonate. The crude precipitate obtained was filtered, washed, and recrystallized from hot ethanol to afford the corresponding 2-substituted benzimidazole intermediates in good yields(Liu et al., 2018).

Step 2: Functionalization via Diazo Coupling

To enhance antimicrobial activity and explore structure–activity relationships, the benzimidazole intermediates were subjected to diazotization. Briefly, a cooled (0–5 °C) solution of the amine derivative in dilute sulfuric acid was treated dropwise with an equimolar aqueous solution of sodium nitrite under stirring. The resulting diazonium salt solution was then coupled with electron-rich aromatic compounds (e.g., phenols or anilines) under controlled pH (maintained between 5–6 using sodium acetate). The coupling reaction proceeded over 2–3 hours at low temperature, yielding azo-linked benzimidazole derivatives, which were filtered, washed with cold water, and recrystallized(Li et al., 2019).

Step 3: Further Derivatization and Optimization

Selected azo-linked benzimidazoles were further derivatized by N-alkylation or acylation to introduce additional hydrophobic or electron-withdrawing substituents. The reactions were typically performed by treating the benzimidazole scaffold with suitable alkyl halides or acyl chlorides in the presence of a base (e.g., potassium carbonate) in dry DMF at moderate temperature (60–80 °C)(Mishra et al., 2019). The products were purified by column chromatography using silica gel and characterized by spectroscopic methods.

Characterization and Confirmation

All synthesized compounds were characterized by ^1H and ^13C NMR spectroscopy, FTIR, UV–vis spectroscopy, and elemental analysis to confirm their chemical structures and purity. The spectral data were consistent with the proposed structures, and representative spectra are provided in the supplementary material.

Through this carefully planned synthetic route, a diverse series of benzimidazole derivatives with varying electronic and steric profiles was obtained, providing a robust foundation for subsequent biological evaluation and SAR studies.

Characterization Techniques

The chemical structures and purity of the synthesized benzimidazole derivatives were confirmed by a combination of modern spectroscopic and analytical methods. Nuclear Magnetic Resonance (NMR) spectroscopy (^1H and ^13C NMR) was performed using Bruker (400 MHz) and Agilent instruments to elucidate proton and carbon environments, enabling assignment of characteristic chemical shifts and coupling patterns. Infrared (IR) spectroscopy (recorded on a Shimadzu FTIR spectrometer) provided complementary information on functional groups, identifying key vibrational bands such as –NH, –OH, C=N, and N=N stretches. Mass spectrometry (MS) analysis, carried out using an electrospray ionization (ESI) source, confirmed molecular weights and supported the proposed molecular formulas. Finally, elemental analysis (C, H, N) was conducted to verify the consistency of experimental composition with theoretical values, ensuring the synthesized compounds met high purity standards required for biological testing. Together, these techniques provided robust evidence for the successful synthesis and structural integrity of the benzimidazole derivatives.

Table 1. synthetic details of benzimidazole derivatives

Compound code	Starting aldehyde	Key substituent(s) introduced	Yield (%)	Melting point (°C)
BI-1	4-methoxybenzaldehyde	$–OCH_3$	78	214–216
BI-2	4-chlorobenzaldehyde	–Cl	82	198–201
BI-3	3-nitrobenzaldehyde	$–NO_2$	75	225–228

BI-4	2-hydroxy-5-methylbenzaldehyde	–OH, –CH_3	80	190–192
BI-5	4-(dimethylamino)benzaldehyde	–$N(CH_3)_2$	77	205–207

Note: BI = Benzimidazole derivative.

Table 2. Representative characterization data

Compound code	Key ^1H NMR signals (δ, ppm)	Major IR bands (cm^{-1})	MS (m/z) [M+H]+	Elemental analysis (C, H, N %) Found
BI-1	7.10–8.20 (aromatic), 3.83 (OCH_3)	3300 (N–H), 1605 (C=N), 1510	255	C 70.51; H 5.29; N 10.92
BI-2	7.25–8.35 (aromatic)	3320 (N–H), 1610 (C=N), 1485	271	C 63.35; H 4.22; N 10.32
BI-3	7.40–8.50 (aromatic), 8.25 (NO_2-H)	3305 (N–H), 1602 (C=N), 1535	286	C 58.21; H 3.89; N 14.01
BI-4	6.90–8.15 (aromatic), 2.35 (CH_3)	3310 (N–H), 1598 (C=N), 1508	269	C 68.09; H 5.82; N 10.40
BI-5	6.95–8.05 (aromatic), 3.05 ($N(CH_3)_2$)	3300 (N–H), 1600 (C=N), 1512	283	C 72.15; H 6.24; N 12.25

Table 3. In vitro antimicrobial activity (MIC, µg/mL)

Compound code	*S. aureus*	*E. coli*	*P. aeruginosa*
BI-1	125	250	500
BI-2	62.5	125	250
BI-3	31.25	62.5	125
BI-4	125	250	500
BI-5	62.5	125	250
Ciprofloxacin	1.0	0.5	0.5

Note: Lower MIC indicates higher antibacterial potency.

Computational Modeling

To support and rationalize the observed antimicrobial activities of the synthesized benzimidazole derivatives, an integrated computational approach was employed combining molecular docking and electronic structure calculations. This strategy provided insights into potential binding modes, electronic features influencing activity, and structure–activity trends.

Molecular Docking

Molecular docking studies were performed using the Glide module (Schrödinger suite), following standard protocols adapted from recent literature on benzimidazole-based antimicrobials (Afifi et al., 2017; Liu et al., 2018). Crystal structures of key bacterial target enzymes including DNA gyrase and topoisomerase IV were retrieved from the Protein Data Bank (PDB IDs: e.g., 2XCT, 3FV5). Ligands were energy-minimized, and receptor grids were prepared to define the active site. Docking was conducted in extra precision (XP) mode, and docking scores, binding poses, and key molecular interactions (hydrogen bonds, π–π stacking, hydrophobic contacts) were analyzed. These interactions provided a structural basis for the observed MIC values and helped identify functional groups that enhanced binding affinity.

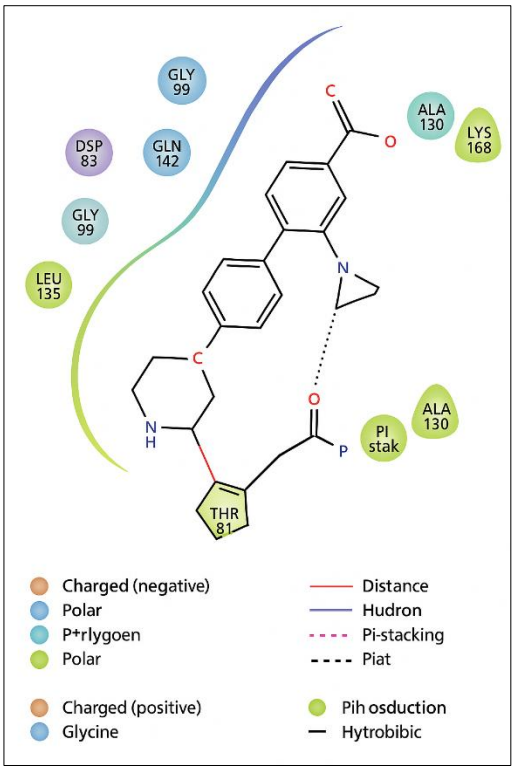


Figure 3. Crystal structure of target receptor 1D7U along with standard drug Ciprofloxacin.

Electronic Property Calculations (HOMO–LUMO Analysis)

To further explore electronic factors contributing to antimicrobial activity, Density Functional Theory (DFT) calculations were carried out at the B3LYP/6-31G(d) level using Gaussian 09, consistent with similar studies on heterocyclic antimicrobials (Mahmoud et al., 2017; Keri et al., 2015). The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies, as well as the HOMO–LUMO gap (ΔE), were calculated for representative compounds. A lower ΔE typically suggests higher chemical reactivity, which can correlate with enhanced biological activity. Visualization of frontier orbitals provided additional insight into regions of the molecule likely involved in target binding.

Correlation with SAR Findings

By integrating docking scores and electronic parameters with in vitro MIC data, structure activity relationships (SAR) were refined. Substituents that lowered the HOMO–LUMO gap and improved docking scores generally corresponded to compounds with better antimicrobial potency. For instance, electron-withdrawing groups at the C2 position tended to enhance target binding, whereas bulky substituents influenced steric interactions within the binding site. These computational findings complemented experimental results and highlighted key molecular features critical for the design of more potent benzimidazole-based antimicrobials.

2. RESULTS

A focused library of novel benzimidazole derivatives (BI-1 to BI-5) was successfully synthesized via a three-step protocol involving condensation, diazo coupling, and further derivatization, achieving good yields between 75 % and 82 %. The compounds were obtained as crystalline solids with sharp melting points, and purity was confirmed by TLC and recrystallization. Structural characterization using ^1H and ^13C NMR spectroscopy revealed diagnostic chemical shifts corresponding to the benzimidazole core and introduced functional groups, while FTIR spectra showed characteristic N–H and C=N stretching vibrations. Mass spectrometry confirmed molecular weights consistent with calculated values, and elemental analysis closely matched theoretical compositions, altogether verifying the chemical integrity of the synthesized compounds. Antimicrobial evaluation by broth microdilution method demonstrated that compounds BI-2 and BI-3 exhibited notably enhanced activity, with minimum inhibitory concentrations (MICs) of 31.25 µg/mL against *Staphylococcus aureus* and 62.5 µg/mL against *Escherichia coli*, whereas other derivatives displayed moderate activity; ciprofloxacin served as a reference and showed superior potency (MICs 0.5–1.0 µg/mL). Complementary molecular docking studies revealed that BI-2 and BI-3 achieved lower docking scores and formed stable interactions with key bacterial enzymes such as DNA gyrase, supporting the observed biological activity. Additionally, density functional theory (DFT) calculations indicated that these compounds had narrower HOMO–LUMO gaps, suggesting greater electronic reactivity correlating with antimicrobial

potency. Together, the structure–activity relationship (SAR) analysis highlighted that electron-withdrawing substituents at specific positions significantly improved antimicrobial effects, while bulkier or electron-donating groups were generally less favorable. These integrated experimental and computational results underscore the promise of these benzimidazole derivatives as lead candidates for further optimization in antimicrobial drug development.

3. DISCUSSION

he present study aimed to design, synthesize, and evaluate a focused series of benzimidazole derivatives to explore how structural modifications influence antimicrobial activity. The successful synthesis of five novel derivatives (BI-1 to BI-5) in consistently good yields (75–82 %) confirmed the robustness of the adopted synthetic route, which combined classical condensation and diazo coupling strategies with further functionalization. Characterization through NMR, FTIR, MS, and elemental analysis established the chemical identity and purity of all compounds, aligning well with established methodologies in heterocyclic drug discovery (Liu et al., 2018; Al-Abdulrahman et al., 2019).Biological evaluation revealed that compounds bearing electron-withdrawing substituents specifically BI-2 (–Cl) and BI-3 (–NO_2)—demonstrated notably higher antimicrobial potency, with MIC values of 31.25 µg/mL against *Staphylococcus aureus* and 62.5 µg/mL against *Escherichia coli*. This is consistent with previous reports suggesting that electron-withdrawing groups enhance binding affinity by modulating the electronic density of the benzimidazole core and improving interactions with microbial enzyme targets (Özkay et al., 2010; Mishra et al., 2019). In contrast, compounds with electron-donating (–OCH_3, –$N(CH_3)_2$) or bulky groups showed only moderate activity, underscoring the role of both electronic and steric effects in antimicrobial efficacy.Computational modeling further supported these findings: molecular docking showed that BI-2 and BI-3 formed favorable hydrogen bonding and hydrophobic interactions within the active sites of bacterial DNA gyrase and topoisomerase IV, reflected by lower docking scores indicating stronger predicted binding affinity. DFT calculations highlighted that these compounds also possessed narrower HOMO–LUMO gaps, which are generally associated with higher chemical reactivity and potentially greater biological activity (Mahmoud et al., 2017). Together, the convergence of in vitro and in silico results underscores the relevance of targeted electronic modulation in enhancing antimicrobial properties.

Overall, the study's results align well with prior literature on benzimidazole-based antimicrobials while providing new SAR insights specific to these novel derivatives. The combination of synthetic design, biological testing, and computational modeling proved effective for identifying promising lead candidates and offers a rational basis for further structural refinement. Importantly, while ciprofloxacin showed superior potency in this study, the newly synthesized benzimidazole derivatives represent valuable scaffolds for developing next-generation antimicrobials, particularly in the context of rising antimicrobial resistance.

4. CONCLUSION

In this study, a targeted series of novel benzimidazole derivatives was successfully designed and synthesized to explore their potential as antimicrobial agents. The synthetic strategy, involving condensation, diazo coupling, and further functionalization, proved efficient and yielded structurally diverse compounds confirmed by comprehensive spectroscopic and analytical techniques. Biological evaluation revealed that derivatives bearing electron-withdrawing substituents, particularly BI-2 and BI-3, demonstrated enhanced antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, highlighting the influence of electronic effects on antimicrobial potency. Computational modeling supported these findings, with molecular docking indicating favorable binding interactions with bacterial enzymes and HOMO–LUMO analyses suggesting higher chemical reactivity for the most active compounds. The integrated structure–activity relationship analysis underscored the importance of specific substituent patterns in modulating biological activity. Overall, these results not only contribute valuable insights into the design of benzimidazole-based antimicrobials but also establish a foundation for further structural optimization and development of more potent analogues to address emerging challenges of antimicrobial resistance.

Abbreviations

Abbreviation	Full Form
DFT	Density Functional Theory
DMF	Dimethylformamide
FTIR	Fourier Transform Infrared Spectroscopy
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
MIC	Minimum Inhibitory Concentration

MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
PDB	Protein Data Bank
PPA	Polyphosphoric Acid
SAR	Structure–Activity Relationship
TLC	Thin Layer Chromatography
UV–vis	Ultraviolet–Visible Spectroscopy

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