IJPP

International Journal of Food Safety and Public Health
Vol. 12 (2), pp. 01-04, September, 2025
ISSN: 2756-3693

Full Length Article

Recent Advances in Indole-Based Heterocyclic Compounds as Antibacterial and Antifungal Agents: Synthetic Strategies, Structure–Activity Relationships and Therapeutic Perspectives

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Accepted 08 September 2025

Abstract
Antimicrobial resistance (AMR) has emerged as one of the greatest challenges to global healthcare, significantly reducing the effectiveness of existing antibacterial and antifungal drugs. The increasing prevalence of multidrug-resistant bacteria and pathogenic fungi has accelerated the search for novel therapeutic agents with improved efficacy and safety. Among the various heterocyclic scaffolds explored in medicinal chemistry, the indole nucleus has gained considerable attention because of its unique structural characteristics, ease of functionalization, and broad spectrum of biological activities. Indole-based heterocyclic compounds have demonstrated remarkable antibacterial and antifungal properties by targeting multiple microbial pathways, including DNA replication, cell-wall synthesis, membrane integrity, and ergosterol biosynthesis. Recent advances in synthetic chemistry, molecular hybridization, molecular docking, and computational drug design have facilitated the development of potent indole derivatives with enhanced pharmacological profiles. This review summarizes the chemistry of indole, major synthetic approaches, antimicrobial activities, structure–activity relationships (SAR), molecular docking studies, ADMET considerations, and future prospects for indole-based antimicrobial agents.

Keywords: *Indole, Heterocyclic compounds, Antibacterial activity, Antifungal activity, Medicinal chemistry, Structure–Activity Relationship, Molecular docking.*

1. Introduction

The rapid emergence of antimicrobial resistance (AMR) has become a serious global health concern. Excessive and inappropriate use of antibiotics and antifungal drugs has led to resistant microorganisms that are increasingly difficult to treat. Common bacterial pathogens such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, together with fungal pathogens including *Candida albicans*, *Candida auris*, and *Aspergillus fumigatus*, are responsible for a large proportion of hospital-acquired infections worldwide.

The discovery of new antimicrobial agents has therefore become an important priority. Heterocyclic compounds occupy a central position in medicinal chemistry because nitrogen, oxygen, and sulfur-containing rings exhibit diverse biological activities. Among these, indole is regarded as a privileged scaffold due to its remarkable ability to bind multiple biological targets.

The indole nucleus consists of a benzene ring fused with a pyrrole ring, producing a planar aromatic bicyclic system. This structure enables hydrogen bonding, π–π stacking, hydrophobic interactions, and van der Waals forces with biological macromolecules. Consequently, indole derivatives exhibit antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, antioxidant, and antimalarial activities.

Natural molecules such as tryptophan, serotonin, melatonin, vinblastine, vincristine, and reserpine further demonstrate the biological importance of the indole scaffold. Their therapeutic success has inspired the synthesis of numerous indole-containing heterocyclic compounds for antimicrobial drug discovery.

2. Chemistry of Indole

Indole (C_8H_7N) is an aromatic bicyclic heterocycle comprising a six-membered benzene ring fused with a five-membered pyrrole ring. The aromatic system contains ten π-electrons, satisfying Hückel's rule and conferring exceptional stability.

The C-3 position of the indole ring possesses the highest electron density and therefore undergoes

International Journal of Food Safety and Public Health
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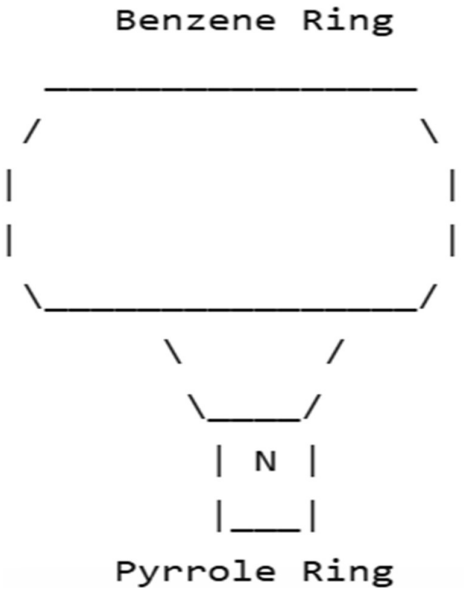
electrophilic substitution most readily. The nitrogen atom contributes to aromaticity while also participating in hydrogen bonding, making indole derivatives effective ligands for enzyme active sites.

General Structure of Indole



The physicochemical properties of indole—including moderate lipophilicity, aromaticity, and structural flexibility—facilitate membrane permeability and interaction with microbial targets.

3. Synthetic Approaches

Numerous synthetic methodologies have been developed for the preparation of indole derivatives.

Fischer Indole Synthesis

The Fischer indole synthesis remains the most widely used method. It involves the acid-catalyzed cyclization of phenylhydrazones derived from aldehydes or ketones to produce substituted indoles. The method is economical, versatile, and suitable for large-scale synthesis.

Other Classical Methods

Other important synthetic routes include:

- Madelung synthesis
- Bartoli synthesis
- Larock cyclization
- Transition-metal-catalyzed coupling reactions

Modern Synthetic Techniques

Contemporary medicinal chemistry increasingly employs:

- Microwave-assisted synthesis
- Ultrasound-assisted synthesis
- Multicomponent reactions
- Green chemistry approaches
- Solvent-free synthesis
- Recyclable catalysts

These methods reduce reaction time, improve yields, minimize solvent consumption, and support environmentally sustainable synthesis.

4. Molecular Hybridization

Molecular hybridization combines two pharmacologically active scaffolds into a single molecule, often resulting in improved biological activity and reduced resistance development.

Common hybrids include:

- Indole–Triazole
- Indole–Oxadiazole
- Indole–Thiazole
- Indole–Pyrazole
- Indole–Benzimidazole
- Indole–Imidazole
- Indole–Pyrimidine

These hybrid molecules frequently exhibit greater antimicrobial activity than either pharmacophore alone due to complementary interactions with multiple biological targets.

5. Antibacterial Activity

Indole-based heterocyclic compounds have demonstrated broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria.

Gram-Positive Bacteria

Reported active organisms include:

- *Staphylococcus aureus*
- Methicillin-resistant *S. aureus* (MRSA)
- *Bacillus subtilis*
- *Enterococcus faecalis*

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Halogen-substituted indole derivatives containing fluorine, chlorine, bromine, or trifluoromethyl groups often display enhanced antibacterial potency because these substituents improve lipophilicity and bacterial cell penetration.

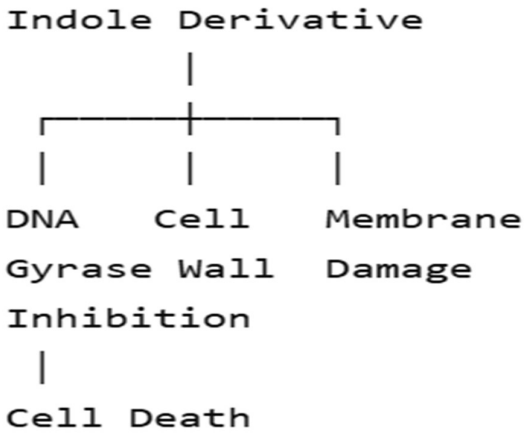
Gram-Negative Bacteria

Effective activity has also been reported against:

- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*

Indole–oxadiazole and indole–triazole hybrids have shown particularly promising results by inhibiting bacterial DNA replication and cell-wall biosynthesis.

Mechanisms of Antibacterial Action



Major mechanisms include:

- DNA gyrase inhibition
- Topoisomerase IV inhibition
- Mur enzyme inhibition
- Cell-wall disruption
- Membrane destabilization
- Reactive oxygen species generation

6. Antifungal Activity

Fungal infections have increased substantially because of immunosuppression, cancer chemotherapy, diabetes, and organ transplantation. Common pathogens include *Candida albicans*, *Candida auris*, *Aspergillus fumigatus*, and *Aspergillus niger*.

Indole-containing antifungal agents primarily act by inhibiting ergosterol biosynthesis, disrupting fungal membranes, or interfering with cell-wall synthesis.

Indole–triazole and indole–imidazole hybrids have shown significant activity against Candida species by inhibiting the CYP51 enzyme responsible for ergosterol production.

Proposed Mechanism

Indole Derivative
|
CYP51 Inhibition
|
Reduced Ergosterol
|
Membrane Damage
|
Fungal Cell Death

7. Structure–Activity Relationship (SAR)

SAR studies reveal that antimicrobial activity is strongly influenced by structural modifications on the indole nucleus.

Electron-Withdrawing Groups

Substituents such as:

- Fluorine
- Chlorine
- Bromine
- Nitro
- Trifluoromethyl

generally enhance antimicrobial potency by increasing lipophilicity and strengthening enzyme binding.

Electron-Donating Groups

Methoxy, methyl, and hydroxyl substituents may improve hydrogen bonding and antioxidant properties, although their effects depend on substitution position.

Hybrid Pharmacophores

Hybridization with triazole, oxadiazole, benzimidazole, or thiazole frequently produces compounds with broader antimicrobial spectra and lower MIC values than simple indole derivatives.

8. Molecular Docking and ADMET Studies

Computational techniques have become valuable tools in antimicrobial drug discovery.

Molecular Docking

Docking predicts ligand–protein interactions before synthesis. Common software includes AutoDock, Glide, Discovery Studio, and MOE.

Major microbial targets include:

- DNA gyrase
- Topoisomerase IV
- MurB enzyme
- Dihydrofolate reductase
- CYP51
- β-Glucan synthase

Strong hydrogen bonding, π–π stacking, and hydrophobic interactions generally correlate with improved biological activity.

ADMET Evaluation

Successful antimicrobial candidates require acceptable pharmacokinetic properties.

Important parameters include:

- Oral absorption
- Membrane permeability
- Metabolic stability
- Controlled excretion
- Low toxicity

Computational platforms such as SwissADME, pkCSM, and ProTox-II assist in early evaluation of drug-likeness and toxicity, reducing the risk of late-stage failure.

9. Future Perspectives

Future development of indole-based antimicrobial agents is expected to focus on:

- Artificial intelligence-assisted drug discovery
- Green synthetic methodologies
- Nanotechnology-based drug delivery
- Multitarget molecular hybridization
- Structure-guided lead optimization
- Combination therapy with existing antibiotics
- Improved bioavailability and reduced toxicity

The integration of synthetic chemistry, computational biology, microbiology, and pharmaceutical sciences will accelerate the development of clinically useful indole derivatives.

10. Conclusion

Indole-containing heterocyclic compounds represent one of the most promising classes of antimicrobial molecules in modern medicinal chemistry. Their structural versatility, synthetic accessibility, and ability to interact with multiple biological targets have led to the development of numerous antibacterial and antifungal agents with encouraging biological activity. Molecular hybridization strategies involving triazoles, oxadiazoles, thiazoles, pyrazoles, and benzimidazoles have consistently enhanced antimicrobial potency while offering opportunities to overcome emerging drug resistance.

Structure–activity relationship studies indicate that electron-withdrawing substituents and rational pharmacophore hybridization significantly improve biological activity. Computational techniques such as molecular docking and ADMET prediction further support the efficient identification of promising lead compounds. Although relatively few indole-based antimicrobial agents have reached clinical practice, continued advances in synthetic methodologies, computational drug design, and nanotechnology are expected to facilitate the development of safer and more effective therapeutics. Future research should emphasize multidisciplinary approaches integrating medicinal chemistry, microbiology, pharmacology, and artificial intelligence to combat the growing threat of antimicrobial resistance.

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