INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)
Vol. 05, Issue 08, August 2025, pp : 736-747

www.ijprems.com
editor@ijprems.com

e-ISSN : 2583-1062
Impact Factor : 7.001

BENZIMIDAZOLE—A PRIVILEGED HETEROCYCLIC CORE IN DRUG DISCOVERY: STRUCTURAL INSIGHTS AND BIOLOGICAL ACTIVITIES

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DOI: https://www.doi.org/10.58257/IJPREMS43356

ABSTRACT

Benzimidazole is a privileged heterocyclic framework extensively known for its rich pharmacological promise, mainly because of its purine-like framework, allowing effective coupling to various targets in biology. This heterocyclic compound, derived by fusion of a benzene and an imidazole ring, is a useful platform in drug discovery with an extensive range of biological activities, such as antimicrobial, antiviral, antifungal, anticancer, anti-inflammatory, antihypertensive, analgesic, antitubercular, antiparasitic and antihelminthic effects1. The ease of modification of the benzimidazole nucleus at critical positions—especially N-1 and C-2—provides the opportunity for far-reaching structure–activity relationship optimizations to improve potency, selectivity, and pharmacokinetics. Recent developments in synthetic methodologies, including microwave-assisted synthesis, multicomponent reactions, and green chemistry methods, have allowed efficient access to new benzimidazole derivatives. Of particular interest are benzimidazole-derived drugs such as albendazole, mebendazole, thiabendazole, and omeprazole, which have found therapeutic utility, highlighting the scaffold's drug-like significance1. Studies indicate the role of electronic effects and patterns of substitution, particularly electron-withdrawing groups, to increase biological activity in various pharmacological classes. In addition, the introduction of benzimidazole in hybrid molecules and metal complexes has created new horizons for better therapeutic results. This review integrates existing information regarding benzimidazole chemistry, biology, and medicinal uses, highlighting its potential in meeting the challenges of global health, including antimicrobial resistance, neglected tropical diseases, and cancer. Further investigation of benzimidazole derivatives holds the promise of unveiling novel remedies, reiterating its position as a pillar in contemporary medicinal chemistry and a desirable scaffold for upcoming drugs.

Keywords: Benzimidazole Derivatives, Structural Insights, Diverse Biological Activities.

1. INTRODUCTION

Benzimidazole is a well-known bicyclic heterocycle formed by the fusion of a benzene ring with an imidazole ring. This unique structure closely resembles purine bases found in nucleotides, enabling benzimidazole derivatives to mimic natural nucleotides and interact effectively with a variety of biological targets such as enzymes, receptors, and nucleic acids. Thanks to this structural versatility, benzimidazole has earned a significant place as a core scaffold in medicinal chemistry and plays a pivotal role in modern pharmaceutical development.

Since its biological significance was first recognized, benzimidazole has been associated with an impressive range of pharmacological activities—including antimicrobial, antiviral, antifungal, anticancer, anti-inflammatory, and antiparasitic effects. These diverse therapeutic properties have paved the way for the development of several benzimidazole-based drugs that are widely used in clinical practice today, such as albendazole, mebendazole, thiabendazole, and omeprazole.

One of benzimidazole's greatest strengths lies in its synthetic flexibility. The ability to modify the nucleus at various positions—particularly at N-1 and C-2—allows chemists to conduct detailed structure–activity relationship (SAR) studies, fine-tuning its potency, selectivity, and pharmacokinetic properties. This adaptability has made benzimidazole an attractive candidate for developing treatments for some of the most pressing global health challenges, including antimicrobial resistance, neglected tropical diseases, and cancer.

Recent advances in synthetic methodologies, combined with powerful tools such as molecular modeling and target-based drug design, have led to the creation of novel benzimidazole derivatives with improved biological profiles.

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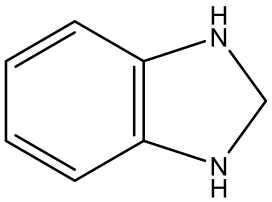
Moreover, innovative strategies such as incorporating benzimidazole into hybrid molecules or metal complexes have shown promising results in enhancing therapeutic outcomes.

In light of these developments, this paper seeks to provide a comprehensive overview of benzimidazole's structural characteristics, diverse biological activities, and broad medicinal applications. Special emphasis is placed on recent progress in synthetic approaches, pharmacological evaluation, and the mechanistic understanding of its varied therapeutic effects. By highlighting both its traditional uses and cutting-edge innovations, this review reinforces benzimidazole's enduring relevance and remarkable potential in modern drug discovery.

2. CHEMISTRY OF BENZIMIDAZOLES

Benzimidazoles are a prominent class of fused heterocyclic compounds formed by the condensation of a benzene ring with an imidazole moiety. Their structural analogy to purine bases imparts unique physicochemical properties, making them key scaffolds in synthetic and medicinal chemistry.



Benzimidazole nucleus

2.1. Structural Features

The benzimidazole ring system exhibits aromaticity and electronic delocalization across the fused rings. The presence of two nitrogen atoms at positions 1 and 3 of the imidazole ring contributes to diverse chemical reactivity. The N-1 atom behaves like a pyrrolic nitrogen and can donate hydrogen in hydrogen bonding, while N-3 is pyridine-like and exhibits basicity.

2.2 Synthetic Strategies

The classical and widely adopted method for benzimidazole synthesis is the Phillips Method, which involves the acid-catalysed condensation of o-phenylenediamine (OPDA) with carboxylic acids, yielding 2-substituted benzimidazoles.

Alternative methods include:

Condensation with Aldehydes**:** OPDA reacts with aldehydes in the presence of oxidizing agents (e.g., H_2O_2, I_2, or atmospheric oxygen) to form 2-aryl/alkyl benzimidazoles.

Microwave-Assisted and Solvent-Free Synthesis**:** Environmentally friendly approaches have been developed using ionic liquids or heterogeneous catalysts under microwave irradiation or green solvent systems.

Multicomponent Reactions (MCRs)**:** These methods enable rapid and high-yielding synthesis of complex benzimidazole derivatives by combining multiple reagents in a one-pot system.

2.3. Reactivity and Functionalization

Electrophilic Substitution: Occurs predominantly at positions 5 and 6 on the benzene ring.

Nucleophilic Attack: Possible on electron-deficient benzimidazoles substituted with halogens or nitro groups.

N1-Alkylation/Acylation: Common derivatization technique to improve lipophilicity and biological activity.

C2 Substitution: Essential for modulating pharmacological properties, especially with aryl or heteroaryl groups.

2.4. Coordination Chemistry

Benzimidazole ligands exhibit good metal-binding properties, particularly through the N-3 atom. Transition metal complexes of benzimidazole derivatives (e.g., with Cu, Co, Zn) have shown significant biological and catalytic applications.

3. BIOLOGICAL ACTIVITIES OF BENZIMIDAZOLE

1. Antibacterial activity
2. Antifungal activity
3. Antihypertensive activity
4. Antiviral activity
5. Anticancer activity
6. Anthelmintic activity

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7. Analgesic activity
8. Antitubercular activity
9. Antiparasitic activity
10. Anti-inflammatory activity

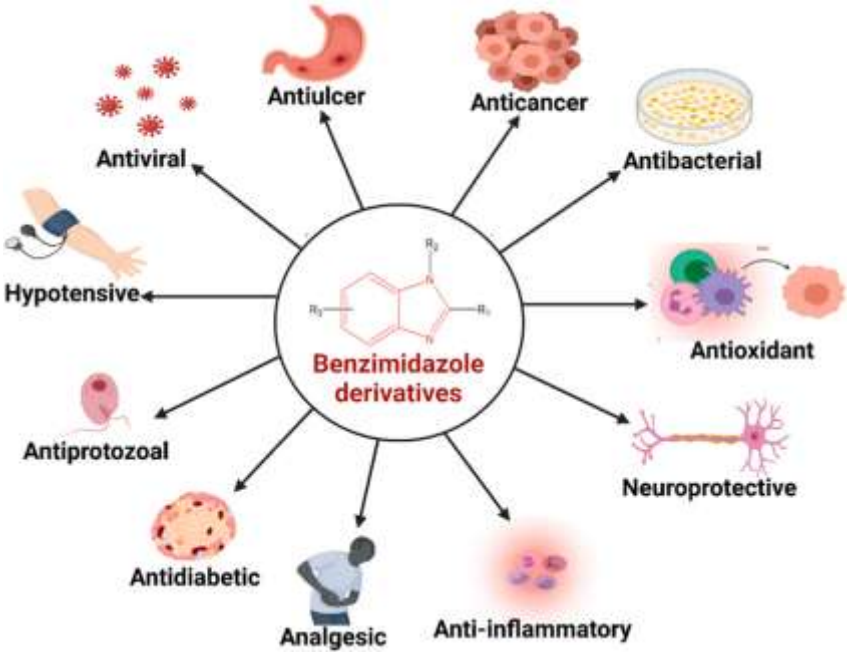
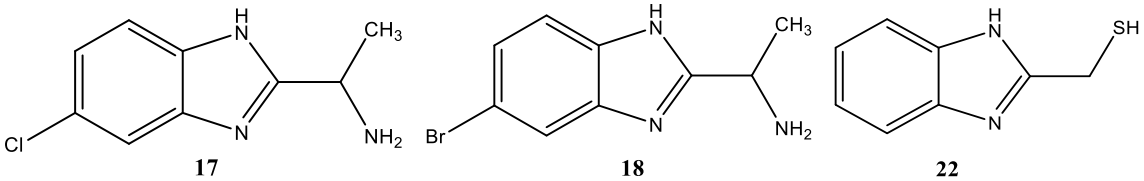


Figure 1: Biological activities of benzimidazole

3.1 ANTIBACTERIAL ACTIVITY:

Among 53 benzimidazole derivatives tested, 9 compounds exhibited notable antibacterial activity, with compounds 17, 18, 22, 35, and 36 emerging as the most promising due to their broad-spectrum efficacy and strong inhibition zones, comparable to ciprofloxacin. MIC values for these compounds ranged from 32–64 µg/mL. Compound 22 (2-methanthiol, unsubstituted at position 5) was particularly effective against S. epidermidis and S. haemolyticus, while compound 36 (5-Br chloromethyl) showed superior activity against B. cepacia compared to its 5-Cl analogue (compound 35). Substitution at position 5 with electron-withdrawing groups (especially Br) enhanced antibacterial potency, especially against Gram-positive strains and select Gram-negative bacteria such as E. coli, Serratia marcescens, and Burkholderia cepacia.



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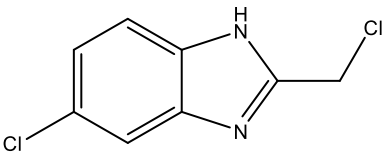

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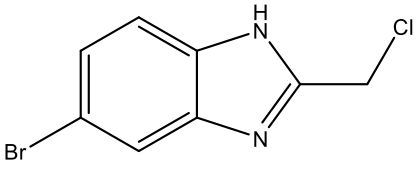

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3.2 ANTIFUNGAL ACTIVITY:

A total of 53 benzimidazole derivatives were evaluated for antifungal activity using the well diffusion method, with amphotericin B as the reference. Compounds 5, 11, 13, 14, 15, and 27 demonstrated strong antifungal potential, with Compound 14 (5-NO_2) showing the highest potency. Structure-activity relationship analysis revealed that electron-withdrawing groups (EWGs) at position 5, such as NO_2, F, Cl, and Br, significantly enhanced activity, particularly when position 2 lacked a substituent. However, not all EWGs consistently improved efficacy (e.g., Compound 12 with Br was inactive). Overall, antifungal activity was closely linked to the electronic nature of substituents, suggesting future optimization should target strategic placement of EWGs.

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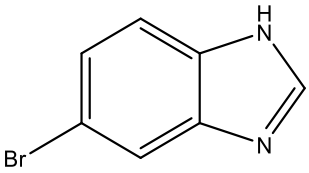

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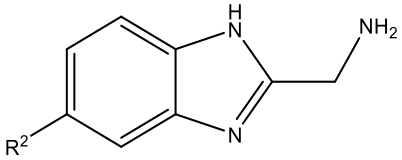
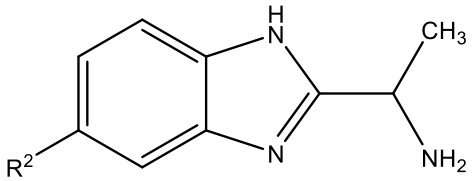
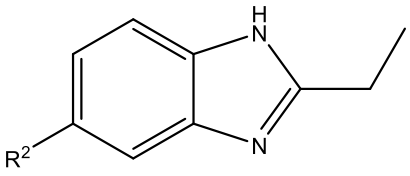


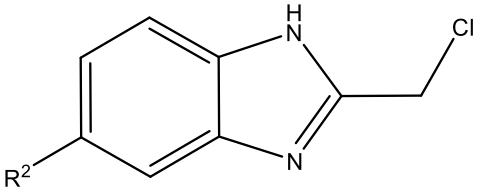
$11R^2$=Cl
$13R^2$=F
$14R^2$=NO_2



$15R^2$=H



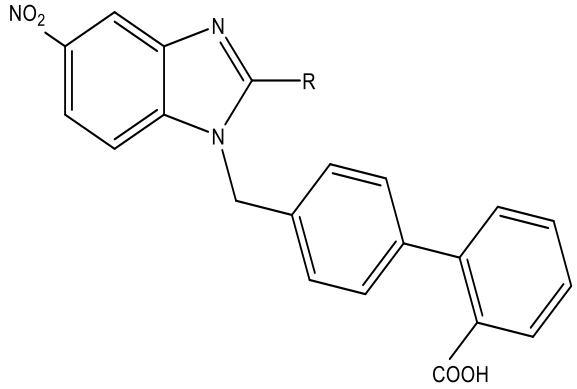
20 R^2=H



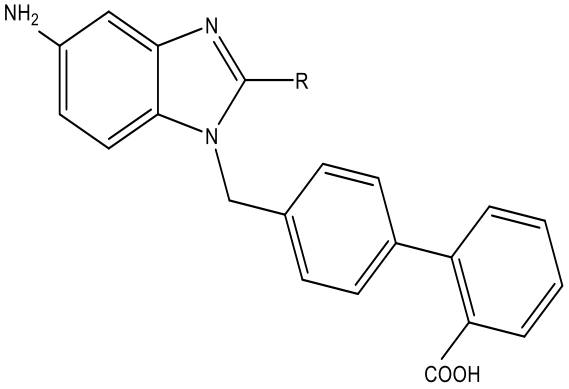
38 R^2=NO_2

3.3 ANTIHYPERTENSIVE ACTIVITY:

The study presents the synthesis and evaluation of benzimidazole derivatives as anti-hypertensive agents, focusing on non-peptide angiotensin II (A-II) receptor antagonists. The synthesized compounds, particularly 5-substituted (amino)-2-phenyl-1-(2'-carboxy biphenyl-4-yl) benzimidazoles, demonstrated potent oral anti-hypertensive activity, unlike earlier compounds requiring intravenous administration. Key structural features include an ortho-substituted carboxylic acid on the biphenyl ring, essential for receptor affinity and efficacy. Compounds with a 2-ethyl group (SR-8, SR-9) showed better activity than those with a 2-phenyl group (SR-6, SR-7). Pharmacological tests on normotensive rats revealed significant blood pressure reduction at doses of 50 µg/kg. The study highlights the therapeutic potential of these derivatives, with SR-8 and SR-9 being the most promising candidates. The work builds on the structural framework of known drugs like losartan, offering improved oral bioavailability and efficacy.



SR-6 R-Phenyl
SR-8 R-Ethyl



SR-7 R-Phenyl
SR-9 R-Ethyl

3.4 ANTIVIRAL ACTIVITY:

The study by Selvam et al. (2010) synthesized and evaluated a series of novel N-substituted benzimidazole derivatives for their anti-viral activity against HIV-1 and HIV-2 in MT-4 cells. The compounds were prepared via Mannich reaction, incorporating substitutions such as sulphanilamide, sulpha imidine, and nicotinamide, and characterized using IR and NMR spectroscopy. Among the tested compounds, BSD exhibited significant inhibitory effects against HIV-1 and HIV-2 (EC50 = 35.40 µg/ml) with low cytotoxicity (CC50 >125 µg/ml). Other derivatives showed varying levels of cytotoxicity, with BI-2MBI being the most toxic. The findings highlight BSD as a promising lead for further development of anti-HIV agents, addressing the need for new drugs to combat viral resistance. The study also underscores the potential of benzimidazole derivatives in antiviral research.

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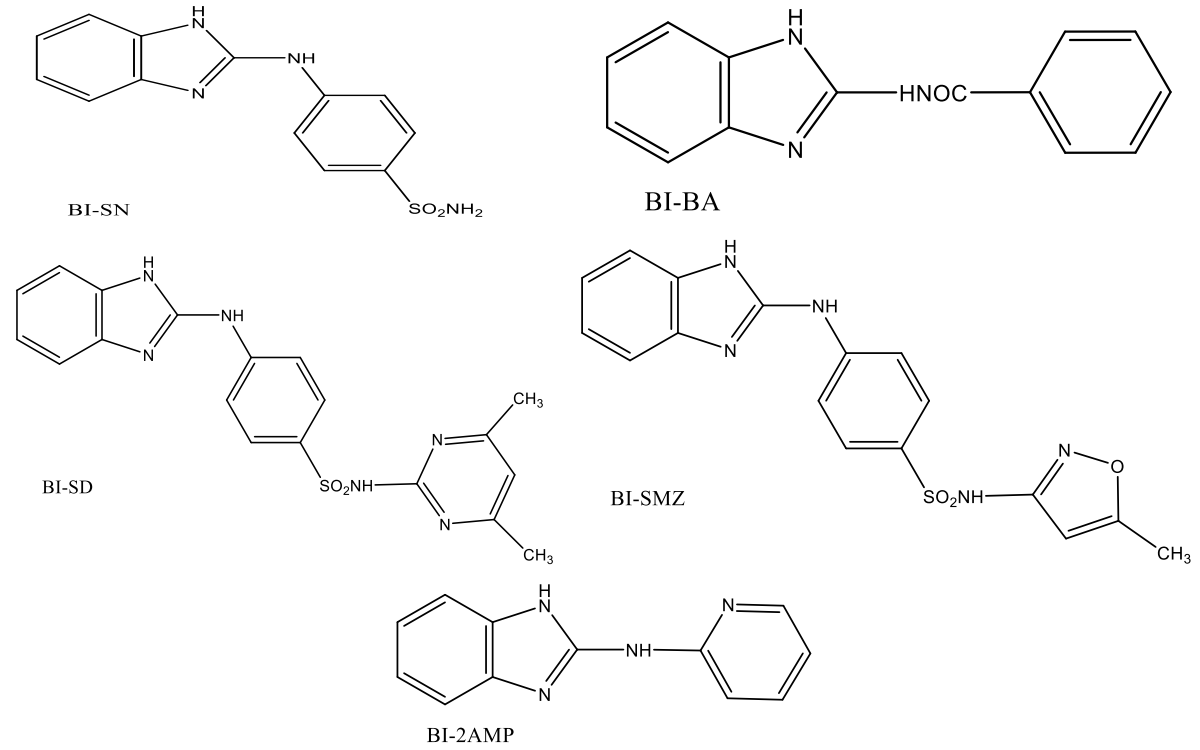

3.5 ANTICANCER ACTIVITY

This study reports the design, synthesis, and biological evaluation of new benzimidazole derivatives, combining benzimidazole and thiazolidinone rings, to assess their potential as inhibitors of Epstein–Barr virus early antigen (EBV-EA) activation—a biomarker for tumour promotion in Burkitt's lymphoma. Using various synthetic pathways, researchers produced several series of compounds (5a–e, 6a–e, 8a–f, and 9a–f) and tested them for activity at different concentrations. Most showed notable inhibition at high concentrations, with compound 6d exhibiting the strongest effect, followed by 6e and 5a. Structure–activity analysis indicated that certain substitutions and cyclization's enhanced or reduced activity. These findings highlight specific benzimidazole–thiazolidinone hybrids as promising antitumor-promoting agents for further development.

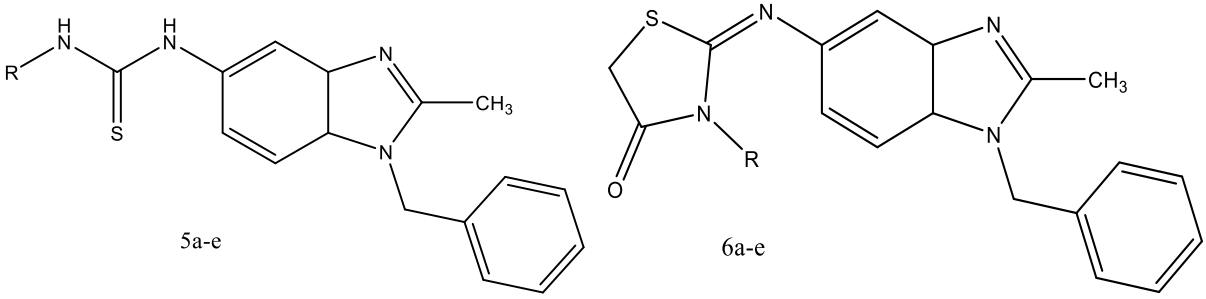

Table 1: Various substituents on 5 and 6 series

Compounds	Variable groups	Substituents
5a,6a	R	CH3
5b,6b	R	C2H5
5c,6c	R	C6H5
5d,6d	R	C6H5CO
5e,6e	R	p-OCH3-C6H4

3.6 ANTIHELMINTHIC ACTIVITY

This study by Shrestha et al. explored and compared the anthelminthic activity of two types of piperazine derivatives—bisaryl benzyl piperazines and benzimidazole-linked piperazines—against Pheretima posthuma earthworms. Helminth infections are common in areas with poor hygiene, and while both piperazine and benzimidazole drugs are widely used, they act differently. Piperazine works by blocking worm muscle responses to

acetylcholine through GABA receptor interaction, causing paralysis, while benzimidazoles inhibit microtubule formation, disrupting glucose uptake and leading to death. Five derivatives were synthesized through two methods. Scheme 1 produced three bis-benzyl piperazine-2,3-dione derivatives (PZ1–PZ3) via reductive alkylation of ethylene diamine followed by cyclization. Scheme 2 generated two benzimidazole-linked piperazines (PZ4–PZ5) by first preparing benzimidazole cores and diketopiperazine, then coupling them via a Mannich reaction. Compounds were purified, characterized, and tested at concentrations of 1000–400 µg/ml using mebendazole as a standard. Results showed that PZ1 (mean paralysis 28.25 min; death 67.5 min) and PZ3 (26.25 min; 53.5 min) from Scheme 1 had stronger activity than PZ4 (52.75 min; 108 min) and PZ5 (32.75 min; 59.5 min) from Scheme 2. This was unexpected, as benzimidazole incorporation was initially thought to enhance potency. The findings suggest electron-donating groups like 4-dimethylamino and 2-hydroxy on the benzyl moiety significantly improve activity, while 4-chloro substitution is less effective. From a synthesis perspective, Scheme 1 was simpler and quicker, with PZ2 achieving the highest yield (80.8%). Scheme 2 produced more complex molecules but required longer reaction times. Overall, the study concludes that ethylene diamine is a valuable precursor for piperazine derivatives and that bis-benzyl piperazines with suitable substituents hold strong potential as anthelminthic agents, challenging the assumption that benzimidazole-linked derivatives are necessarily superior.

3.7 ANALGESIC ACTIVITY

The study focused on the synthesis of five novel N-substituted benzimidazole derivatives (compounds 1–5) and their evaluation for analgesic activity. Compound 1 was synthesized by acylating benzimidazole with benzoyl chloride, followed by condensation with various amines to obtain compounds 2–5. Analgesic potential was assessed in mice using two standard models: the acetic acid-induced writhing test for peripheral analgesia and the hot plate method for central analgesia. In the writhing test, compound 4 demonstrated the most potent activity, reducing the writhing count to 9 writhes compared to 51.2 in the control group, corresponding to an impressive 67% inhibition. In contrast, the reference drug aspirin (50 mg/kg) produced only 12% inhibition. Compounds 3 and 5 also exhibited notable peripheral analgesic effects, reducing writhing counts to 13.25 and 14.5, respectively. In the hot plate test, the control group displayed a reaction time of 7.9 seconds, while compound 4 slightly reduced it to 5.5 seconds, suggesting negligible central analgesic activity. Overall, the findings indicate that the synthesized derivatives—particularly compound 4—exhibit strong peripheral analgesic properties comparable to or exceeding standard NSAIDs, positioning them as promising candidates for further anti-inflammatory and pain management studies.

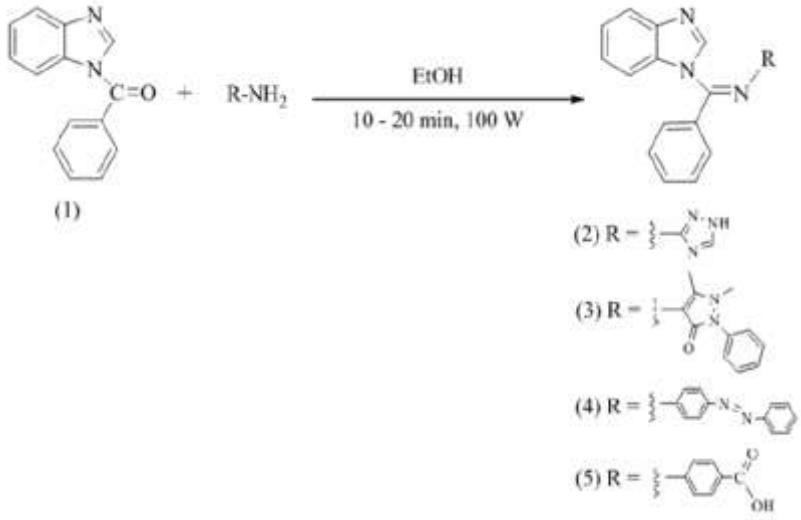

Figure 2: Synthetic process with benzimidazole substituents.

3.8 ANTITUBERCULAR ACTIVITY

This study reports the synthesis and antitubercular evaluation of seven novel benzimidazole derivatives (5a–5g), developed through a four-step synthetic route starting from 4-fluoro-3-nitrobenzoic acid. The compounds were tested against Mycobacterium tuberculosis $H_{37}Rv$ (MTB-$H_{37}Rv$) and isoniazid-resistant (INHR-MTB) strains. Among the derivatives, compound 5g was the most potent, exhibiting a MIC of 0.112 µM against MTB-$H_{37}Rv$ and 6.12 µM against INHR-MTB, outperforming the standard drug isoniazid (0.73 µM and 11.37 µM, respectively). Compounds 5d and 5b also showed strong activity with MICs of 0.135 µM and 0.195 µM against MTB-$H_{37}Rv$. All active compounds were found non-cytotoxic at concentrations up to 62.5 µg/mL in VERO cells. Electron-withdrawing groups, especially halogen substitution at the 4-position of the phenyl ring, were associated with enhanced antimycobacterial activity.

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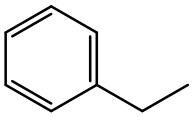
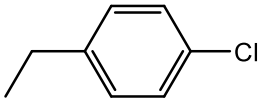
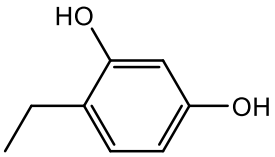
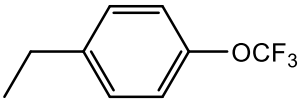
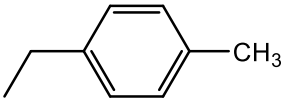
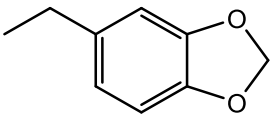
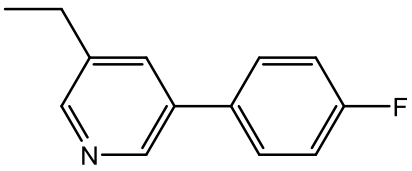
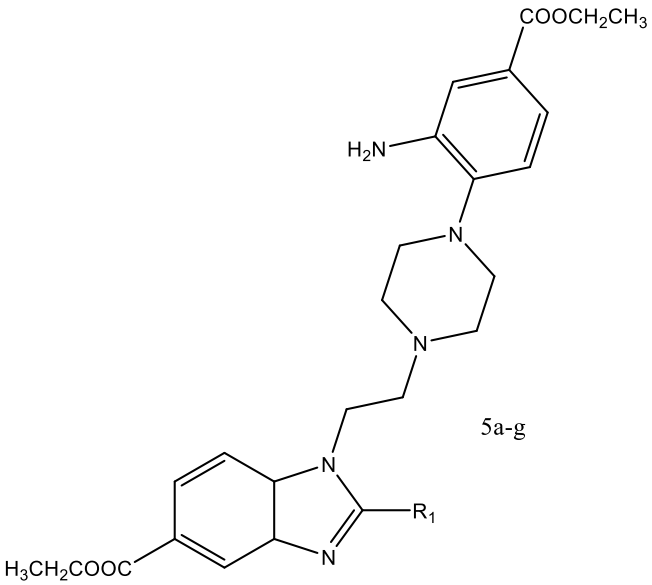
These findings highlight the therapeutic potential of benzimidazole scaffolds in developing new agents against drug-resistant TB.

Table 2: Different substituents on 5 series compounds.

Compound	R1-Substitution
5a	
5b	
5c	
5d	
5e	
5f	
5g	



5a-g

3.9 ANTIPARASITIC ACTIVITY

This study reports the synthesis and biological evaluation of 18 benzimidazole derivatives for their antiparasitic potential against Giardia lamblia, Entamoeba histolytica, and the helminth Trichinella spiralis. Most compounds showed stronger antiprotozoal activity than standard drugs like Metronidazole and Albendazole, with compounds 6

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and 11 emerging as the most potent against G. lamblia, and compounds 1 and 10 showing exceptional activity against E. histolytica. However, none matched Albendazole's potency against T. spiralis. Only compounds 3, 9, and 15 inhibited tubulin polymerizations, indicating that their antiprotozoal effects may occur through mechanisms distinct from their anthelmintic action. Overall, the findings highlight promising benzimidazole derivatives as potential leads for developing more effective treatments for protozoal infections.

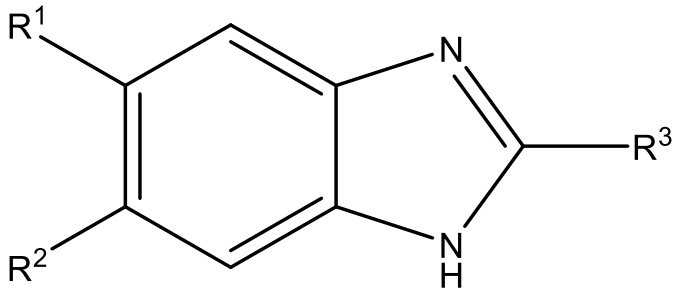


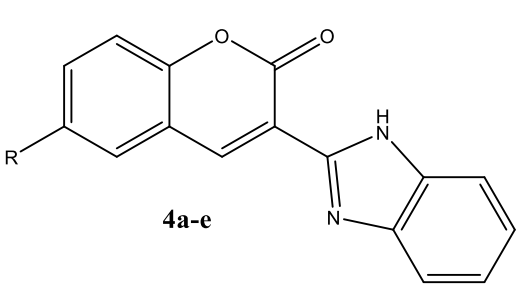
Table 3: Substituents on 2,5 and 6 position of benzimidazole nucleus.

Compound	R1	R2	R3
1	H	H	CH3
2	H	H	NH2
3	H	H	NHCO2CCH3
4	H	H	SH
5	H	H	SCH3
6	H	H	H
7	Cl	H	CH3
8	Cl	H	NH2
9	Cl	H	NHCO2CH3
10	Cl	H	SH
11	Cl	H	SCH3
12	Cl	H	H
13	Cl	Cl	CH3
14	Cl	Cl	NH2
15	Cl	Cl	NHCO2CH3
16	Cl	Cl	SH
17	Cl	Cl	SCH3
18	Cl	Cl	H

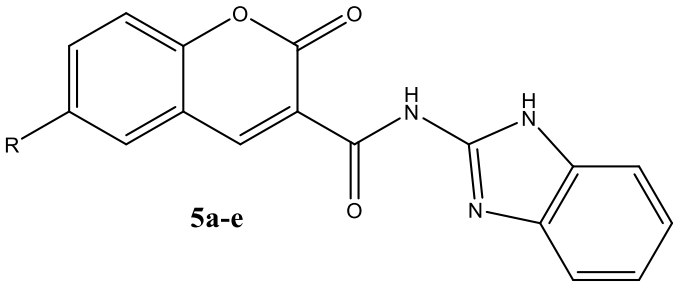
3.10 ANTI INFLAMMATORY ACTIVITY

This study explored the design and synthesis of novel coumarin–benzimidazole derivatives aiming to deliver strong anti-inflammatory and antioxidant effects with reduced gastric toxicity compared to traditional NSAIDs. Two compound series were created—linked directly (series 4) or via an amide bond (series 5)—and tested for activity. Compounds 4c, 4d, and 5a showed the best anti-inflammatory effects, while 5a excelled in antioxidant potency, surpassing the standard BHT. Importantly, 4d and 5a demonstrated excellent gastric safety and did not induce oxidative stress in vivo. Structure–activity relationship analysis revealed that electron-withdrawing groups enhanced both anti-inflammatory and antioxidant activity, whereas amide linkage reduced anti-inflammatory potential. All compounds met Lipinski's rules, suggesting good oral bioavailability, with 4d and 5a emerging as promising leads for safer, effective anti-inflammatory drug development

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)
Vol. 05, Issue 08, August 2025, pp : 736-747
www.ijprems.com
editor@ijprems.com
e-ISSN : 2583-1062
Impact Factor : 7.001



4a-e



5a-e

Table 4: Variable group substituents on benzimidazole nucleus.

Compounds	Variable groups	Substituents
4a,5a	R	-H
4b,5b	R	-OCH3
4c,5c	R	-Br
4d,5d	R	-Cl
4e,5e	R	-NO2

4. RESULTS AND DISCUSSIONS

The reviewed article highlights the broad spectrum of biological activities attributed to benzimidazole derivatives, emphasizing the central role of structural modifications, synthetic advances, and structure-activity relationship (SAR) insights.

4.1 Biological Activities and Key Findings

Biological Activity	Notable Compounds/Groups	Main Findings
Antibacterial	17, 18, 22, 35, 36	Electron-withdrawing groups (Br at position 5) boost activity; broad-spectrum efficacy with MIC 32-64 µg/mL.
Antifungal	5, 11, 13, 14, 15, 27	5-NO_2 substitution greatly enhances potency; EWGs at position 5 consistently improve fungal inhibition.
Antihypertensive	SR-8, SR-9	2-ethyl group shows better activity than 2-phenyl; improved oral bioavailability; non-peptide A-II antagonists.
Antiviral	BSD	Strong inhibition against HIV-1/HIV-2 (EC_{50} = 35.40 µg/mL), low cytotoxicity (CC_{50} > 125 µg/mL).
Anticancer	6d	Benzimidazole-thiazolidinone hybrids effectively inhibit EBV-EA activation, promising for tumor promotion.
Anthelmintic	PZ1, PZ3	Bis-benzyl piperazines outperform benzimidazole-linked derivatives; electron-donating groups enhance effect.
Analgesic	Compound 4	67% writhing inhibition compared to aspirin (12%);

		strong peripheral effect, minimal central action.
Antitubercular	5g	MIC 0.112 µM (MTB-$H_{37}Rv$); halogen substitution at phenyl ring's 4-position enhances activity for resistant TB.
Antiparasitic	6, 11, 1, 10	Stronger antiprotozoal activity than metronidazole and albendazole; some act via tubulin polymerization.
Anti-inflammatory	4c, 4d, 5a	Coumarin-benzimidazole hybrids excel in anti-inflammatory/antioxidant effects and gastric safety.

4.2 Structural and Synthetic Insights

- SAR analyses underscore the value of electron-withdrawing substituents (e.g., Br, NO_2, Cl) at specific positions (notably 5 and 4) to enhance potency across pharmacological classes.
- Synthetic strategies have evolved to include microwave-assisted, solvent-free, multicomponent, and green chemistry techniques, improving efficiency and environmental safety.
- Hybrid molecules and metal complexes (especially with Cu, Co, Zn) expand the therapeutic reach of benzimidazole derivatives.

4.3 Therapeutic implications

- Potency against Drug-Resistant Pathogens: Newer derivatives, particularly in antitubercular and antiviral domains, show improved efficacy versus challenging or drug-resistant strains.
- Safety and Bioavailability: Compounds such as coumarin-benzimidazole hybrids provide favorable safety profiles, reduced toxicity, and good oral bioavailability (meeting Lipinski's rules).
- Mechanistic Diversity: Derivatives act via distinct mechanisms, such as microtubule disruption (anthelmintic), A-II receptor antagonism (antihypertensive), and tubulin polymerization inhibition (antiparasitic).

4.4 Overall discussion

Benzimidazole remains a privileged scaffold in contemporary medicinal chemistry. Its synthetic flexibility, ease of functionalization, and ability to serve as a core for diverse biological activities reinforce its status as a foundational structure for drug discovery. The studies reviewed demonstrate not only traditional medicinal value but also innovative avenues, such as green synthesis and hybrid complex formation, promising significant advances for global health challenges.

5. CONCLUSION

Benzimidazole derivatives represent one of the most versatile and valuable frameworks in drug discovery, underpinning a range of modern pharmaceuticals that address antimicrobial resistance, neglected tropical diseases, cancer, and more. The remarkable therapeutic breadth of these molecules is amplified by strategic substitution, particularly with electron-withdrawing groups, leading to enhanced potency and improved pharmacokinetic profiles. Advances in synthetic methodologies—including eco-friendly and multicomponent approaches—have facilitated the rapid and efficient production of novel derivatives. The integration of benzimidazole into hybrid molecules and metal complexes promises even greater therapeutic potential. Research has highlighted multiple new candidates with superior efficacy and safety, especially for resistant infections and multifactorial disease states. Continued focus on SAR optimization, mechanistic exploration, and hybridization strategies will drive future innovations, solidifying benzimidazole's role as a cornerstone in medicinal chemistry.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the support of Department of Pharmaceutical Chemistry, P.S.V College of Pharmaceutical Science and Research, for providing essential resources and infrastructure. Special thanks are extended to Associate Professor Mr. R. Naveen Kumar M. Pharm (PhD), Department of Pharmaceutical Chemistry for his invaluable mentorship and guidance throughout the research process. The team also wishes to thank all collaborators,

peer reviewers, and research participants whose contributions have advanced the knowledge and applications of benzimidazole derivatives in pharmaceutical sciences.

Conflict of interest

The authors declare that there is no conflict of interest.

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