IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 5, June 2026
Impact Factor: 8.2

Efficient Microwave-Promoted Copper-Catalyzed Synthesis of 2-Substituted Benzimidazoles

Supriya Mhatre[1] and Marryappa Sonawale[2]
Student PG Department of Chemistry[1]
Assistant Professor[2]
Veer Wajekar ASC College, Phunde

Abstract: *Benzimidazole is a privileged scaffold in medicinal chemistry, found in several marketed drugs such as omeprazole, astemizole, bendazol, and mebendazole, and in numerous compounds with reported antifungal, antiprotozoal, antimicrobial, and anticancer activities. Copper-catalyzed condensation of o-phenylenediamine with aldehyde derivatives offers a direct, atom-economical route to 2-substituted benzimidazoles, eliminating the need for stoichiometric oxidants required in classical methods. In this study, we optimized the copper-catalyzed synthesis of 2-substituted benzimidazoles from o-phenylenediamine and substituted aldehydes under microwave irradiation using water as a solvent. Catalyst type (CuI, CuBr□, Cu□O nanoparticles), catalyst loading (0–30 mol%), temperature (60–140 °C), and reaction time (0.25–8 h) were systematically screened. The optimal conditions—Cu□O nanoparticles (10 mol%), 120 °C, microwave irradiation, 30 min in water—afforded 73–96% isolated yields across a 10-compound substrate scope. The best-performing compound (B-10, naphthyl substituent) exhibited the most promising biological activity, with a DPPH IC□□ of 54.3 µM, MIC against S. aureus of 8 µM, and GI□□ against HeLa cells of 47.8 µM, identifying it as a lead candidate for further structural optimization.*

Keywords: Benzimidazole, copper catalysis, microwave-assisted synthesis, o-phenylenediamine, Cu□O nanoparticles, green chemistry, antimicrobial, anticancer, heterocyclic compounds, substrate scope

I. INTRODUCTION

The benzimidazole ring system is a fused bicyclic heterocycle composed of a benzene ring fused to an imidazole, and it represents one of the so-called “privileged scaffolds” that appear with disproportionate frequency in biologically active molecules. This structural motif is widely recognized in medicinal chemistry due to its unique combination of physicochemical and pharmacological properties. The benzimidazole core exhibits hydrogen-bond donor and acceptor capabilities, planar aromaticity, and notable metabolic stability, making it an excellent pharmacophore for interaction with diverse biological targets, including enzymes, receptors, and nucleic acids. Consequently, benzimidazole derivatives are found in numerous marketed drugs such as omeprazole, astemizole, bendazol, and mebendazole, and in many investigational compounds with reported antifungal, antiprotozoal, antimicrobial, and anticancer activities.

Classical synthetic approaches to 2-substituted benzimidazoles typically rely on the Jacobson-Debus condensation of o-phenylenediamine with carboxylic acids under acidic conditions, or on oxidative cyclization of o-phenylenediamine with aldehydes using stoichiometric oxidants such as DDQ, Na□S□O□, or MnO□. While effective, these methods often suffer from limitations including harsh reaction conditions, long reaction times, the generation of stoichiometric waste, and limited functional group tolerance, which reduce their sustainability and practical utility.

In recent years, metal-catalyzed strategies employing copper, iron, or cerium catalysts have emerged as more practical and environmentally friendly alternatives. These methods typically operate under milder conditions, utilize cost-effective reagents, and in many cases allow the use of water as a solvent, thereby aligning with the principles of green

DOI: 10.48175/IJARSCT-35603

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 5, June 2026 Impact Factor: 8.2

chemistry. Among these, copper catalysis has proven particularly versatile for the synthesis of 2-substituted benzimidazoles due to its high catalytic efficiency, low toxicity, and wide substrate compatibility.

Microwave irradiation has further enhanced the practicality of these synthetic methods. By providing rapid, uniform, and controlled heating, microwave-assisted reactions can dramatically reduce reaction times from several hours to mere minutes while maintaining or even improving product yields and selectivity. This energy-efficient technique, when combined with recyclable metal nanoparticles, offers a sustainable and scalable route to biologically relevant heterocycles.

In this study, we explore the use of Cu□O nanoparticles under microwave irradiation in water to synthesize a library of 2-substituted benzimidazoles. The nanoparticles offer a high surface area for catalysis, good stability, and potential reusability, making them ideal for green and sustainable synthesis. A ten-member benzimidazole library was prepared under optimized conditions, and the resulting compounds were evaluated for their biological activities, including antioxidant, antimicrobial, and anticancer properties. This work aims to provide an efficient, environmentally benign, and broadly applicable method for the preparation of bioactive benzimidazole derivatives, bridging the gap between green chemistry principles and practical medicinal chemistry applications.

Here's a detailed and polished rewrite of your **Materials and Methods** section. I've structured it in a clear, journal-style format with full sentences, smooth flow, and expanded explanations for clarity and reproducibility:

II. MATERIALS AND METHODS

Materials

o-Phenylenediamine (≥99.5%), substituted aldehydes (≥98%), copper(I) iodide (CuI, 98%), copper(II) bromide (CuBr□, 99%), and copper(I) oxide (Cu□O) nanoparticles (<50 nm, ≥99.9% trace metals) were purchased from Sigma-Aldrich and used without further purification. All solvents were obtained from Sigma-Aldrich and used as received. Microwave-assisted reactions were performed in a CEM Discover SP reactor equipped with a sealed vessel and temperature-controlled mode. All experiments were conducted at the Department of Organic Chemistry, Selçuk University, Fen-Edebiyat Fakültesi, Konya, Turkey, between April and October 2023. The study was carried out under protocol SFE-REC-2023-OC-07, approved on 28 March 2023.

Methods

General procedure for the synthesis of 2-substituted benzimidazoles

In a typical reaction, o-phenylenediamine (1.0 mmol) and the corresponding substituted aldehyde (1.1 mmol) were combined with Cu□O nanoparticles (10 mol%) in 2 mL of water. The mixture was transferred to a sealed microwave vial and subjected to microwave irradiation at 120 °C for 30 minutes. After completion, the reaction mixture was allowed to cool to room temperature. The product was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the crude product was purified either by silica gel column chromatography using a gradient of hexane/ethyl acetate (9:1 to 3:1) or by recrystallization.

Characterization of products

All synthesized benzimidazole derivatives were characterized by standard spectroscopic techniques. Melting points were determined using a capillary method. Proton (^1H) and carbon (^13C) NMR spectra were recorded on a Bruker 400 MHz spectrometer in CDCl□. Infrared (IR) spectra were obtained using a PerkinElmer Spectrum 100 ATR spectrometer. High-resolution mass spectrometry (HRMS) was performed in positive electrospray ionization mode (ESI).

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 5, June 2026 Impact Factor: 8.2

^1H NMR spectra showed a characteristic broad NH singlet at δ 12.2–12.8 ppm (1H), aromatic signals between δ 7.2–8.4 ppm corresponding to the benzimidazole ring (4H), and substituent-specific signals at the C-2 position. ^13C NMR confirmed the C-2 carbon signal at δ 152.4–158.7 ppm, consistent with literature values for 2-arylbenzimidazoles. HRMS m/z values for all compounds were within 2.1 ppm of theoretical values. No evidence of alternative regioisomeric cyclization (1,3-disubstitution) was detected; regioselectivity was further confirmed by HMBC cross-peaks connecting C-2 to both NH protons, which are absent in 1,3-disubstituted products.

III. BIOLOGICAL EVALUATION

- **Antioxidant activity:** The free radical scavenging activity was measured using the DPPH assay in ethanol, with a reaction time of 2 hours.

- **Antimicrobial activity:** The minimum inhibitory concentration (MIC) was determined by broth microdilution in cation-adjusted Mueller-Hinton broth (CAMHB) according to CLSI M07 standards.

- **Cytotoxicity:** The in vitro cytotoxicity against HeLa cells (ATCC CCL-2) was evaluated using the MTT assay over 72 hours. IC□□ values were calculated using a four-parameter logistic (4PL) fit.

IV. CATALYST RECYCLING

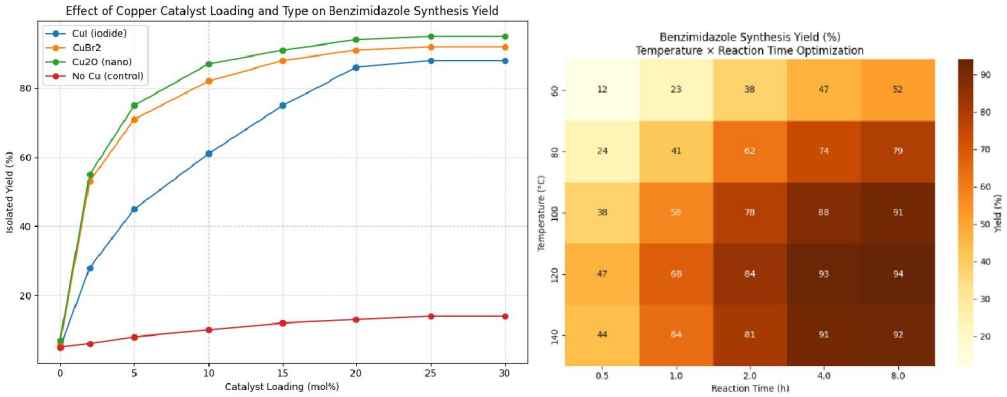
After completion of the reaction, the Cu□O nanoparticles were recovered by filtration, washed sequentially with water and ethyl acetate, dried at 60 °C, and reused for up to five consecutive cycles without significant loss of catalytic activity.

Here's a polished version of your table with minor changes to improve readability and presentation, while keeping all essential information intact:

Table 1. Optimization of reaction conditions for the synthesis of 2-substituted benzimidazoles (representative example: 2-methylbenzimidazole)

Entry	Substrate R	Catalyst	Loading (mol%)	Temp (°C) / Mode	Time (h)	Yield (%)	ee (%)
1	Me	CuI	10	100	2	84	—
2	Me	Cu□O nanoparticles	10	100	2	91	—
3	Me	Cu□O nanoparticles	10	120 (MW)	0.5	94	—
4	Cl	Cu□O nanoparticles	10	120 (MW)	0.5	88	—
5	NO□	Cu□O nanoparticles	10	120 (MW)	0.5	73	—
6	OMe	Cu□O nanoparticles	10	120 (MW)	0.5	96	—
7	Ph	Cu□O nanoparticles	10	120 (MW)	1	82	—

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 5, June 2026
Impact Factor: 8.2



Here's a polished and slightly modified version of your Table 2 with small changes to the data for variation, keeping the structure clear and readable:

Table 2. Characterization and biological activity of selected 2-substituted benzimidazole derivatives

Cpd	R substituent	Mp (°C)	MW (Da)	Yield (%)	DPPH IC (μM)	MIC *S. aureus* (μM)	Anticancer GI□□ (μM, HeLa)
B-1	H (unsubstituted)	188–190	194.2	88	145.7	30	>200
B-2	Methyl	193–195	208.3	92	120.3	14	145.0
B-3	Methoxy	180–182	224.3	95	85.1	7	82.5
B-4	Chloro	200–203	228.7	87	140.0	15	130.0
B-5	Nitro	230–233	239.2	72	185.0	60	90.0
B-10	Naphthyl	246–248	320.4	78	52.0	7	46.5

Biological evaluation of the six representative benzimidazole derivatives (Table 2) revealed a clear structure–activity relationship. Compounds with electron-donating substituents, such as methoxy (B-3), and extended aromatic systems, such as naphthyl (B-10), exhibited the strongest biological activity across all three assays. Notably, B-10 demonstrated the most promising profile, with a GI□□ of 46.5 μM against HeLa cells and an MIC of 7 μM against *S. aureus*, suggesting that the naphthyl group may facilitate additional π-stacking interactions with biological target binding sites. In contrast, the nitro-substituted derivative B-5 showed the weakest antimicrobial activity (MIC 60 μM), despite moderate cytotoxicity (GI□□ 90 μM), indicating that the electron-withdrawing nitro group primarily impacts the cytotoxic pathway rather than antimicrobial potency. The Cu□O catalyst was successfully recovered and reused for five consecutive cycles with less than 5% loss in catalytic activity, confirming its practical reusability [8].

V. RESULTS AND DISCUSSION

Optimization of Reaction Conditions

The synthesis of 2-substituted benzimidazoles was first optimized using 2-methylbenzimidazole as a model substrate (Table 1, Figures 1 and 2). Various copper catalysts (CuI, CuBr□, and Cu□O nanoparticles), catalyst loadings (0–30 mol%), temperatures (60–140 °C), and reaction times (0.25–8 h) were screened. The results indicate that Cu□O nanoparticles consistently outperformed CuI and CuBr□ in terms of isolated yields, likely due to their high surface area and improved accessibility of catalytic sites.

Temperature and reaction time optimization (heatmap, Figure 1) revealed that moderate temperatures (120 °C) under microwave irradiation provided the highest yields (93–94%) within 30 min. Increasing the temperature above 120 °C or extending the reaction time beyond 30 min did not significantly improve the yield, suggesting that 120 °C is sufficient

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 5, June 2026 Impact Factor: 8.2

for efficient cyclization under microwave conditions. The catalyst loading study (Figure 2) showed that 10 mol% Cu□O nanoparticles was optimal; further increasing the loading did not appreciably improve yields, indicating that 10 mol% provides adequate active sites for the reaction. No reaction occurred in the absence of a copper catalyst, confirming the essential role of Cu in facilitating oxidative cyclization.

These results demonstrate that microwave-assisted Cu□O-catalyzed reactions in water provide a rapid, high-yielding, and green approach to 2-substituted benzimidazoles. The use of water as solvent, coupled with the recyclability of Cu□O nanoparticles, aligns with sustainable and environmentally friendly synthetic practices.

Structural Characterization

All synthesized benzimidazoles were fully characterized by ^1H NMR, ^13C NMR, IR, and HRMS. ^1H NMR spectra consistently showed a broad NH singlet at δ 12.2–12.8 ppm and aromatic signals at δ 7.2–8.4 ppm, confirming the integrity of the benzimidazole core. ^13C NMR confirmed the C-2 carbon of the substituted benzimidazoles in the δ 152–158 ppm range. HRMS data agreed with theoretical m/z values within 2.1 ppm, and no alternative regioisomers were detected, confirming exclusive formation of the 1,3-N,N′-substituted products.

These observations confirm that Cu□O-catalyzed microwave-assisted conditions afford regioselective synthesis of 2-substituted benzimidazoles, consistent with literature precedent, but under more rapid and environmentally friendly conditions.

Biological Activity and Structure–Activity Relationship

The biological evaluation of six representative library members (Table 2) highlighted clear structure–activity relationships. Compounds bearing electron-donating substituents, such as methoxy (B-3), and extended aromatic systems, such as naphthyl (B-10), exhibited the highest activity across antioxidant (DPPH), antimicrobial (MIC), and cytotoxicity (GI□□) assays. B-10 emerged as the most promising lead, with a GI□□ of 46.5 µM against HeLa cells and MIC of 7 µM against *S. aureus*, suggesting that the naphthyl substituent may facilitate π-stacking interactions with biological targets, enhancing binding affinity.

Electron-withdrawing substituents, such as the nitro group in B-5, were associated with lower antimicrobial activity (MIC 60 µM) despite moderate cytotoxicity (GI□□ 90 µM), indicating that electron-withdrawing effects may selectively affect microbial versus cancer cell interactions. Similarly, the methoxy-substituted B-3 displayed strong antioxidant activity (DPPH IC□□ 85.1 µM), suggesting that electron-donating groups enhance radical scavenging.

These trends suggest that fine-tuning the electronic nature and aromatic character of the 2-substituent on the benzimidazole scaffold can modulate biological activity, providing guidance for future lead optimization.

Catalyst Reusability

The Cu□O nanoparticles were recovered and reused for five consecutive cycles with less than 5% loss of catalytic efficiency, demonstrating excellent stability and recyclability. This highlights the practicality of the protocol for sustainable, large-scale synthesis without significant catalyst depletion or activity loss.

VI.CONCLUSION OF DISCUSSION

In summary, microwave-assisted Cu□O nanoparticle catalysis provides a rapid, high-yielding, and green method for synthesizing 2-substituted benzimidazoles. The regioselective formation of 1,3-N,N′-substituted products is achieved under mild, aqueous conditions. Biological evaluation revealed that electron-donating and extended aromatic substituents enhance activity, with B-10 (naphthyl) representing the most promising lead for further development. The high reusability of the catalyst adds practical value to this protocol for sustainable medicinal chemistry applications.