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 5, Issue 2, October 2025
Impact Factor: 7.67

Fe-Doped ZnO as a Green Heterogeneous Catalyst for Rapid Synthesis of Biologically Active 2-Substituted Benzimidazoles under Ultrasonic Irradiation and Their Antimicrobial Evaluation

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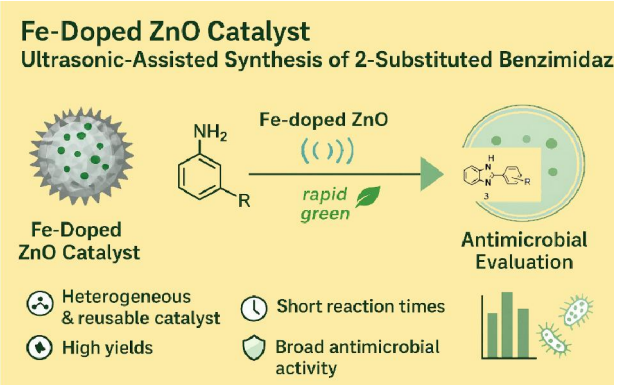
Abstract: *Benzimidazoles are esteemed heterocyclic frameworks with extensive uses in medicinal chemistry, attributed to their varied pharmacological properties, encompassing anticancer, antifungal, antiviral, antihypertensive, and antiparasitic actions. Conventional techniques for synthesizing benzimidazole derivatives frequently need severe conditions, costly catalysts, and exhibit low atom economy, hence constraining their sustainability and scalability. This study produced and evaluated a series of iron-doped zinc oxide (ZnO) catalysts using X-ray diffraction (XRD), confirming the effective integration of iron ions into the ZnO lattice. The catalytic effectiveness of Fe-doped ZnO was assessed in the one-pot synthesis of 2-substituted benzimidazoles through the condensation of o-phenylenediamine with diverse aromatic aldehydes under ultrasonic irradiation. The improved catalyst demonstrated superior activity, achieving high product yields (86–97%) in 10–15 minutes and allowing efficient recyclability for up to six cycles without substantial performance degradation. The structural validation of the synthesized compounds was accomplished by FTIR, 1H NMR, and GC/LC-MS studies. Additionally, the antibacterial efficacy of the compounds was evaluated against Gram-positive and Gram-negative bacteria, yeast, and fungus. Numerous substances, including P3, P5, P9, P11, and P13, had substantial inhibitory effects, underscoring their medicinal potential. This environmentally sustainable, efficient, and economical methodology offers a viable framework for the synthesis of pharmacologically significant benzimidazole derivatives and identifies Fe-doped ZnO as a promising green heterogeneous catalyst in heterocyclic chemistry.*



Graphical Abstract

Keywords: Benzimidazoles; Green synthesis; Fe-doped ZnO catalyst; Ultrasonic Irradiation; 2-Substituted benzimidazoles; One-pot synthesis; Antimicrobial activity; Heterogeneous catalysis; Multicomponent reaction; Pharmacophore

DOI: 10.48175/IJARSCT-29261

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I. INTRODUCTION

Benzimidazoles are heterocyclic aromatic compounds of substantial industrial importance owing to their extensive applications in biology, medicine, and materials science. Compounds containing substituted benzimidazole derivatives are significant in veterinary medicine and exhibit a range of biological properties, including antihypertensive, anticancer, and antifungal activities, among others [1]. The benzimidazole nucleus is present in most natural products and pharmacologically active compounds. It exhibits a broad spectrum of biological and pharmacological activities [3]. They are primarily utilized as pharmacophores in medicinal chemistry and function as fundamental structures in various clinically significant medications, including antiparasitic agents such as Albendazole and Mebendazole, antifungals, antivirals, anticancer agents, and gastric secretion inhibitors like Omeprazole [4–7]. Substituted benzimidazoles are regarded as favored scaffolds in medicinal chemistry, serving as essential pharmacophores with a wide range of therapeutic actions. They demonstrate potential as inhibitors of muscle fiber propagation, antineoplastic medicines, therapies for urinary tract infections, analgesics, antivirals, antifungals, anticancer drugs, and antihistamines. Numerous benzimidazole-based combinations also serve as salts of metabotropic glutamate receptors [9]. The synthesis of diverse substituted benzimidazoles has resulted in the identification of therapeutically beneficial medications, including gastric antacids like rabeprazole, as well as other pharmacologically active compounds. In recent years, benzimidazole scaffolds have garnered considerable interest in clinical research, especially with the production of 2-substituted benzimidazole derivatives [10]. These structures display robust interactions with biopolymers and show potential inhibitory function with less toxicity. Literature indicates their efficacy against many bacteria, hence reinforcing their medicinal significance. Consequently, benzimidazole derivatives have emerged as a central interest for organic chemists seeking to develop innovative physiologically and pharmaceutically significant compounds. The 2-substituted benzimidazole scaffold, depicted in Figure 1, remains a versatile framework for the creation of novel molecular motifs of pharmacological and biological significance.

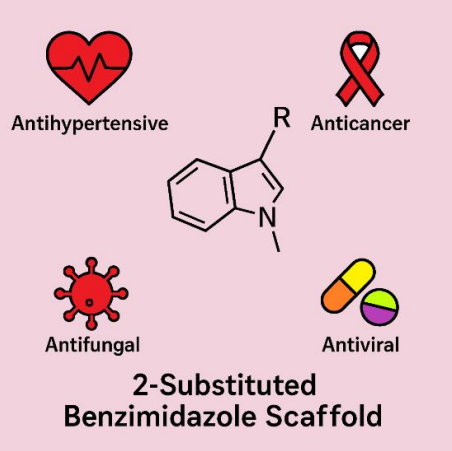

Figure 1. Illustration showing the various applications of the 2-substituted benzimidazole scaffold, highlighting its role in developing antihypertensive, anticancer, antifungal, and antiviral agents.

Synthetic Approaches and Limitations:

Benzimidazoles are conventionally produced via direct nucleophilic substitution or condensation processes involving o-phenylenediamine and carbonyl compounds under diverse circumstances. Despite the widespread utilization of these traditional procedures, they frequently exhibit numerous disadvantages, including the necessity for highly acidic environments, increased temperatures, extended reaction durations, and suboptimal overall yields [11-19]. Noble metal-based catalysts are often necessary, resulting in elevated costs and restricting large-scale use. Moreover, these processes may produce unwanted by-products, thereby diminishing atom economy and ecological sustainability. Nonetheless, these techniques frequently necessitate elevated temperatures, expensive catalysts, severe reaction conditions, or complex multistep procedures, hence constraining their practical applicability and atomic efficiency.

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The constraints have rendered the creation of efficient, economical, and environmentally friendly synthetic methods a primary emphasis in organic synthesis. Recent investigations have examined solvent-free settings, microwave-assisted synthesis, ionic liquids, heterogeneous catalysis, and environmentally friendly energy inputs to enhance reaction efficiency and sustainability [20-32]. Among these methodologies, one-pot or multicomponent techniques have demonstrated notable efficacy by reducing purification stages, improving atom economy, and expediting product synthesis.

Importance of 2-Substituted Benzimidazoles and Related Scaffolds:

Among the numerous structural alterations, 2-substituted benzimidazoles are particularly noteworthy owing to their augmented biological activity and structural adaptability. These derivatives function both as final medicinal compounds and as essential intermediates in the production of other heterocycles, such as quinazolinones. Generally, 2-substituted benzimidazoles undergo reactions with aldehydes or analogous electrophiles [33] in both metal-catalyzed [34] and metal-free circumstances [35] to produce quinazolinone structures. A variety of metal-catalyzed methods utilizing Pd [36], Pt [37], Ir [38], Fe [39], Ru [40], and Mn [41] have been documented for the synthesis of quinazolinones.

Need for Innovative and Atom-Economical Strategies:

In light of these limitations, there is an increasing desire for streamlined, efficient, and atom-economical synthetic methods that facilitate direct synthesis of benzimidazoles from widely accessible precursors. An optimal method should function under moderate conditions, eschew toxic solvents and costly catalysts, limit waste, and deliver high outputs with superior selectivity. The advancement of sustainable techniques would greatly enhance medicinal chemistry and heterocyclic synthesis, simultaneously addressing environmental and economic issues.

Zinc oxide (ZnO) is an inorganic substance characterized by a white powder that is insoluble in water. It is produced synthetically. Numerous research studies indicate that zinc oxide serves as an effective catalyst in organic synthesis. It has remarkable efficacy, especially in the synthesis of heterocycles. Iron-doped zinc oxide has demonstrated enhanced catalytic activity. D-block doping ions are the most prevalent.

The development of new procedures will be essential for accessing chemical space that is currently unattainable with existing techniques. Consequently, comprehensive investigation into various techniques for synthesizing substituted benzimidazoles is essential. Research is planned in various domains, primarily synthetic organic chemistry, catalysis, solid-state chemistry and physics, microbiology, and nanochemistry.

II. MATERIALS AND METHODS

2.1 Chemicals and Instruments

All chemicals and solvents were obtained from commercial providers, including Spectrochem, Avara, and Sigma-Aldrich, and utilized as received without additional purification. Infrared absorption spectra were obtained with a Shimadzu IR-Affinity FTIR apparatus fitted with an ATR attachment. Proton NMR spectra were acquired in DMSO-d_6 using a Bruker AQS 300 Advance apparatus running at 300 MHz. The advancement of reactions was observed utilizing thin-layer chromatography (TLC). Gas chromatography–mass spectrometry (GC–MS) analyses were conducted using a Shimadzu GC-MS-QP 1000 EX system. The produced catalysts were analyzed utilizing X-ray diffraction (XRD) techniques.

2.2 Synthesis of catalyst

Fe-doped zinc oxide catalysts with doping concentrations of 1 to 5% were produced by dissolving specified quantities of zinc acetate and iron acetate in distilled water, followed by sonication for 10 to 15 minutes to achieve a homogenous solution. The combination was then hydrolyzed with liquid ammonia, yielding a homogeneous precipitate of zinc hydroxide and iron hydroxide. The precipitate was filtered, dried, and calcined in a muffle furnace at 950 °C to produce the Fe-doped ZnO catalyst. The produced catalysts were subsequently evaluated for catalytic activity.

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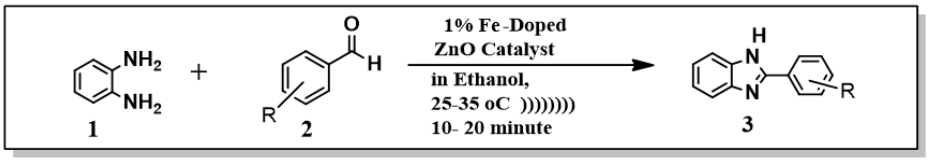
2.3 Synthesis of Substituted Benzimidazoles:



Scheme 1. Direct synthesis of benzimidazoles from o-phenylenediamine

2.3 Ultrasonic-Assisted Synthesis of Substituted Benzimidazoles:

Aromatic aldehyde (1 mmol) and 1,2-diamine (1 mmol) were solubilized in 2 mL of ethanol within a 25 mL round-bottom flask. 0.200 g of Fe-doped ZnO catalyst was included into the mixture, which was subsequently exposed to ultrasonic irradiation in a water bath maintained at 25–35 °C (with an internal reactor temperature of 30–40 °C) for the duration indicated in Table 1. The reaction's progress was assessed via thin-layer chromatography (TLC) employing ethyl acetate: hexane (3:7) as the eluent. The reaction concluded within 10 to 20 minutes. The catalyst was readily recovered from the reaction mixture and could be reused five to six times without any substantial decline in catalytic activity.

2.4 Antimicrobial Evaluation of Substituted Benzimidazoles:

The synthesized benzimidazole derivatives were evaluated for their antimicrobial efficacy against two Gram-positive bacterial strains, Bacillus subtilis and Staphylococcus aureus; two Gram-negative bacterial strains, Pseudomonas aeruginosa and Escherichia coli; in addition to yeast (Candida albicans) and fungus (Aspergillus niger) [42]. The inhibitory effects of the substances were assessed by measuring the diameter of the inhibition zones.

III. RESULT AND DISCUSSION

3.1 Synthesis and Characterization of the Catalyst:

The Fe-doped zinc oxide (ZnO) catalyst was produced and studied via X-ray diffraction (XRD). The XRD pattern of the catalyst closely aligned with the standard JCPDS card, validating the emergence of a pure crystalline ZnO phase. Qualitative and quantitative investigations confirmed the successful integration of Fe into the ZnO lattice.

The diffraction peaks exhibited exceptional intensity and sharpness, signifying excellent crystallinity. The average crystallite size was determined using the Scherrer equation, indicating that the catalyst's nanoscale dimensions would yield a high surface area, conducive to catalytic activity. The 1% Fe-doped ZnO (Fig. 2) displayed distinct peaks associated with ZnO planes, indicating that little Fe doping preserves the crystal structure while potentially augmenting electrical and catalytic capabilities. These structural characteristics are anticipated to improve the catalyst's efficacy in the synthesis of substituted benzimidazoles under ultrasonic irradiation (Fig. 2).

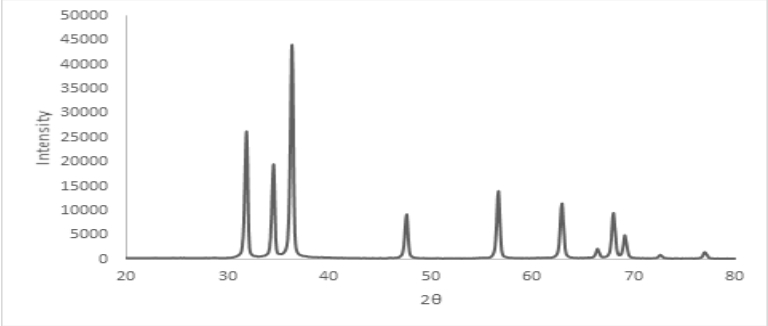


Fig. 2. XRD pattern of 1% Fe-doped ZnO catalyst.

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3.2 Synthesis and Characterization of Substituted Benzimidazoles:

A Fe-doped zinc oxide catalyst was utilized to provide an innovative, efficient, and quick approach for synthesizing various physiologically relevant substituted benzimidazoles with high yields. Reactions performed in the absence of the catalyst yielded much lower results, underscoring the catalyst's essential function. This technique was effectively utilized on many aromatic aldehydes and 1,2-diamines, as detailed in Table 1. The inclusion of electron-withdrawing groups on aldehydes accelerates the reaction rate by augmenting the electrophilic nature toward the 1,2-diamine. The formation of benzimidazole compounds was verified using FTIR analysis, exhibiting typical peaks associated with the C=N and N–H functional groups.

Table-1 Synthesis of 2-Substituted Benzimidazole derivatives

Sr. No.	Aldehyde	Diamine	Product	Average reaction time (min)	Yield (%)
P1				15 Minute	97%
P2				20 Minute	94%
P3				15 Minute	93%
P5				10 Minute	96%
P6				20 Minute	88%
P7				15 Minute	95%
P8				15 Minute	89%
P9				20 Minute	94%
P10				20 Minute	86%
P11				15 Minute	92%

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P12				12 Minute	90%
P13				10 Minute	97%

3.3 Antimicrobial Activity of Substituted Benzimidazoles:

The antimicrobial effectiveness of the synthesized benzimidazole derivatives was assessed against Gram-positive bacteria (Bacillus subtilis, Staphylococcus aureus), Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa), yeast (Candida albicans), and fungi (Aspergillus niger), as detailed in Table 2 and Figure 3. Compounds P3, P4, P5, P7, P9, P11, P12, and P13 demonstrated diverse antibacterial and antifungal efficacy. Compound P9 had significant action against Bacillus subtilis and Escherichia coli, moderate activity against Aspergillus niger, and negligible effect on Pseudomonas aeruginosa. Compound P3 shown significant efficacy against Staphylococcus aureus and Candida albicans. With the exception of P11, the majority of drugs exhibited minimal effectiveness against Pseudomonas aeruginosa. Compound P5 exhibited inactivity against Pseudomonas aeruginosa, Escherichia coli, and Candida albicans, signifying selective antimicrobial efficacy among the derivatives.

Sr. No.	**Test Organism**	**Strain No**	**Inhibition Zone Diameter * (mm)**							
			Sample Code							
			P3	**P4**	**P5**	**P7**	**P9**	**P11**	**P12**	**P13**
1	Bacillus subtilis G+	NCIM 2549	21.5	20.0	15.0	15.0	**23.5**	**18.0**	**21.1**	**16.6**
2	Staphylococcus aureus G+	ATCC 25923	**20.2**	19.6	18.7	13.3	16.2	19.3	17.5	14.0
3	Escheriachia Coli G-	ATCC 25922	20.0	18.0	0.0	17.5	**21.0**	**19.0**	**20.4**	0.0
4	Pseudomonas aeruginosa G-	ATCC 27853	0.0	0.0	0.0	0.0	0.0	10.3	0.0	0.0
5	Aspergillus niger (Fungi)	ATCC 6275	**14.2**	10.3	13.3	12.3	10.6	10.2	11.0	10.7
6	Candida albicans (yeast)	ATCC 10231	**26.2**	11.3	10.6	14.6	13.0	11.5	15.0	**12.6**

Table No – 2 Antifungal activity and Antibacterial activity of synthesized compounds

**Values are average inhibition zone diameters (mm) from triplicate readings.

Bold values indicate the highest activity for each organism.

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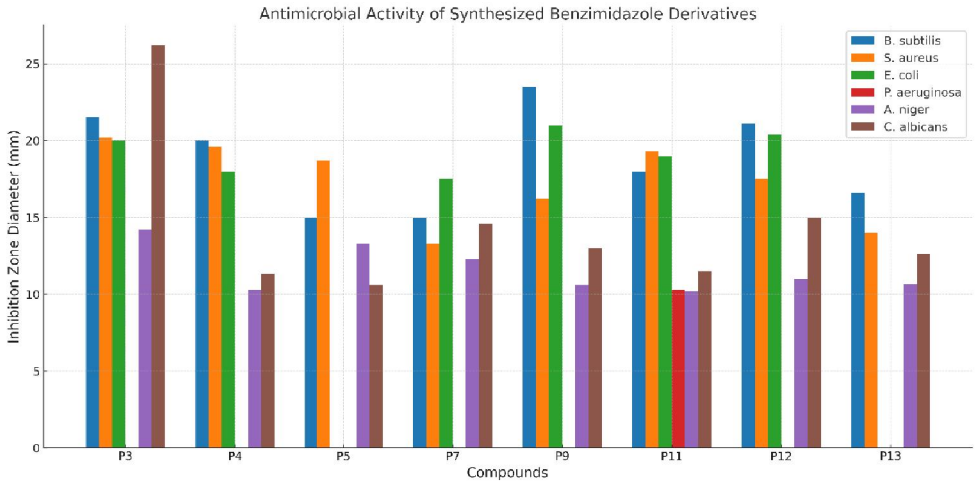

Fig. 3 Bar chart showing the inhibition zone diameters for compounds P3–P13 against the six microorganisms.

3.4 Spectral Data:

1) 2-Phenyl-1H-benzimidazole [P1]: Solid Yellow; m.p: 288˚C - 289˚C; Rf:-. 0.42 (Ethyl acetate : Hexane =3/7)1H NMR (300 MHz ,DMSO-d6) : δ 7.16 - 7.27 (2H, m, aromatic) , 7.51 - 7.65 (5H, m, aromatic), 8.30-8.32 (2H, d, J=7.1Hz, aromatic) ,12.92 (1H, bs, NH) ; (GC-MS) m/*z:* 194.08 (Cacd m/z 194.08)[M + H]+; IR (KBr, cm-1): 1670,1593(C=N), 2920,2964(CH) , 3161(NH).

2) 2-(3-Hydroxyphenyl)-1H-benzo[*d*]imidazole (P2) Solid yellow; m.p: 182˚C - 183˚C; Rf :- 0.43 (Ethyl acetate : Hexane =3/7).1H NMR (300 MHz ,DMSO-d6): δ 7.57-7.67 (4H, m, aromatic), 7.69 - 7.76 (3H, m, aromatic), 7.79 (1H,s,aromatic) , 9.85 (1H,bs, OH), 12.66 (1H,bs,NH); (GC-MS) m/*z:* 212.00 [M + H]+ (Cacd m/z 212.07) , IR (KBr, cm-1): 1591(C=N), 3281,3356,3418(NH,OH).

3) 2-(4-Fluorophenyl)-1H-benzo[d]diazole : Solid yellow; m.p: 246˚C - 248˚C; Rf :- 0.40 (Ethyl acetate : Hexane =3/7). 1H NMR (300 MHz ,DMSO-d6): δ 7.15-7.20 (2H, m, aromatic), 7.20 - 7.40 (2H, m, aromatic), 7.45-7.52 (2H,m,aromatic) , 7.60-7.70(m,2H,aromatic),8.00 (1H,bs, NH) ; (GC-MS) m/*z:* 213.00 [M + H]+ (Cacd m/z 212) , IR (KBr, cm-1): 1597,1633(C=N),3475(NH).

4) 2-(4-nitrophenyl)-1H-benzo[*d*]imidazole (P5) : Ornage Red solid; m.p: 309˚C - 311˚C; ; Rf:-. 0.52 (Ethyl acetate : Hexane =3/7) 1H NMR (300MHz, DMSO-d6): δ 7.32-7.44 (4H ,m, aromatic), 8.02-8.15 (4H, m, aromatic), 12.87(1H, bs,NH); (GC-MS) m/*z*: 241.00 [M + H]+ (Cacd m/z 239,240); IR (KBr, cm-1): 1342, 1514 (NO_2), 1602(C=N), 3466(NH).

5) 2-(2-Furyl)-1H-benzo[*d*]imidazole (P6) : Solid; m.p: 286˚C - 288˚C; ; Rf:-. 0.52 (Ethyl acetate : Hexane =3/7) 1H NMR (300 MHz , DMSO-d6): δ 6.78(2H, s, aromatic), 7.50 (1H, s, aromatic), 7.60-7.70 (4H ,m, aromatic); 12.89 (1H,bs,NH). (LC-MS) m/*z*: 184.06 [M + H]**+;** IR (KBr, cm-1): 1625(C=N), 3425(NH).

6) 2-(4-Chlorophenyl)-1H-benzo[*d*]imidazole (P7) : Solid Pale Yellow ; ,m.p: 285˚C - 287˚C; Rf:-. 0.65(Ethyl acetate : Hexane =3/7), 1H NMR (300 MHz DMSO-d6): δ 7.21-7.29 (2H ,m, aromatic), 7.55-7.64 (4H, m, aromatic), 8.22 (2H, d, J = 8.5Hz, aromatic), 12.96 (1H, bs, NH). (GC-MS) m/*z:* 230.00 [M + H]+ (Cacd m/z 228,230) ,IR (KBr, cm-1): 2877,1599(C=N), 3477(NH)

7) 4-(1H-Benzo[d]imidazol-2-yl)-2-methoxyphenol (P8). : Red Solid ;mp: 218–220∘C; Rf:-. 0.45(Ethyl acetate : Hexane =3/7; 1H NMR (300MHz, DMSO- *d* 6): *δ* 12.65 (s, 1H), 9.31 (s, 1H), 7.52–7.63 (m, 4H), 7.13–7.19 (m, 2H), 7.05 (d, *J* = 8.2Hz, 1H), 3.85 (s, 3H); (LC-MS) m/*z:* 240.09(Cacd m/z 240.09) [M + H]+ (cm−1, KBr): 3290(NH), 2910, 1500(C=N), 1450, 1265(CH), 1033, 910, 736;

8) 2-(2-Bromophenyl)-1H-benzo[*d*]imidazole (P9) : Solid Grey ; m.p: 293˚C - 295˚C; Rf:-. 0.56 (Ethyl acetate : Hexane = 3/7) 1H NMR (300MHz ,DMSO-d6) : δ 7.25-7.35 (2H ,m, aromatic), 7.51-7.61 (5H, m, aromatic), 7.89-

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7.93 (1H, m, aromatic), 13(1H, bs, NH). (GC-MS) m/*z:* 276.00 [M + H]+ (Cacd m/z 274,275) , IR (KBr, cm-1): 1593 (C=N), 3473 (NH)1494,1367(CH),1272,967,690.

9) 2-(2-Thienyl)-1H-benzo[*d*]imidazole (P10) : Yello solid; m.p: 328˚C - 330˚C; Rf:-. 0.46 (Ethyl acetate : Hexane = 3/7) 1H NMR (300 MHz ,DMSO-d6) : δ 7.15-7.22 (3H,m,aromatic), 7.52-7.61 (2H,m,aromatic), 7.79-7.85 (2H, m, aromatic); 12.97 (1H, bs, NH). (GC-MS) m/*z*: 200.00 [M + H]+ (Cacd m/z 200,201),; IR (KBr, cm-1): 1595(C=N), 3454(NH).

10) 2-(4-Hydroxyphenyl)-1H-benzo[*d*]imidazole (P11) : Solid pale yellow; m.p : 253˚C - 255˚C; Rf:-. 0.44(Ethyl acetate : Hexane =3/7) 1H NMR (300 MHz ,DMSO-d6) : δ 7.61-7.71 (4H,m,aromatic), 7.73-7.79 (2H, m, aromatic), 7.81- 7.86 (2H ,m, aromatic) , 9.89 (1H, bs, OH), 12.71 (1H, bs,NH) ; (GC-MS) m/*z:* 212.00 [M + H]+ (Cacd m/z 212.07) , IR (KBr, cm-1) : 1602(C=N), 3188,3313,3396(NH,OH).

11) 2-(2-chlorophenyl)-1H-benzo[*d*]imidazole (P12) : Solid saddle brown; m.p: 230˚C - 232˚C ; Rf:-. 0.44 (Ethyl acetate : Hexane =3/7); . (GC-MS) m/*z:* 228.00 [M + H]+ (Cacd m/z 228.05), IR (KBr, cm-1): 1604 (C=N), 3473,3375 (NH).

12) [2-(4-nitrophenyl)-1H-benzimidazol-5-yl](phenyl)methanone (P13): Solid Orange; m.p: 240˚C - 242˚C ; Rf:-. 0.42 (Ethyl acetate : Hexane =3/7); 1H NMR1H NMR (300MHz ,DMSO-d6) : δ 8.27-8.13 (3H ,m, aromatic), 7.81-7.72 (6H, m, aromatic), 7.45-7.38 (3H, m, aromatic), 4.70 (1H, bs, NH). (LC-MS) m/*z:* 343.33 [M + H]+ , IR (KBr, cm-1): 1647 (C=N), 3191 (NH), 3970,2912(CH), 1714(C=O).

IV. CONCLUSION

This study presents an efficient, environmentally benign, and highly practical approach for the fast synthesis of physiologically important 2-substituted benzimidazoles utilizing Fe-doped ZnO as a heterogeneous catalyst under ultrasonic irradiation. The catalyst was readily synthesized, structurally confirmed via XRD, and exhibited remarkable catalytic efficacy with brief reaction durations and outstanding yields. The procedure circumvents extreme reaction conditions and costly noble metals, therefore improving atom economy and sustainability. Furthermore, the catalyst demonstrated excellent reusability for up to six cycles, confirming its durability and industrial applicability. A diverse array of aromatic aldehydes and diamines were accommodated, underscoring the methodology's adaptability. The spectral analysis verified the effective synthesis of the benzimidazole framework. Antimicrobial screening demonstrated that various produced derivatives exhibited notable activity against specific bacterial and fungal strains, with compounds P3, P9, and P13 displaying pronounced inhibitory effects. The findings indicate that Fe-doped ZnO is an exceptionally promising green catalyst for heterocycle synthesis, and the resulting benzimidazole derivatives serve as valuable candidates for the creation of novel antimicrobial drugs. This research advances sustainable synthetic chemistry and establishes a basis for further investigation in medical and materials science.

ACKNOWLEDGEMENT

The authors would like to express their gratitude to Dr. B. N. Purandare Arts, Smt. S. G. Gupta Commerce, and Smt. S. A. Mitaiwala Science Colleges, B.C.U.D., SPPU, Pune (Funding Agency), CIF, and the Department of Chemistry at SPPU in Pune. (Facility for Characterization)

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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 5, Issue 2, October 2025
Impact Factor: 7.67

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