Int. J. Pharm. Investigation, 2025; 15(3):1006-1011.
https://www.jpionline.org

Original Article

Synthesis and Spectral Analysis of Novel Substituted Benzimidazole Derivatives

Bhagyashri D. Jadhav[1,*], Sushil Prabhakar Narkhede[2]

[1]School of Pharmaceutical Sciences, Sandip University, Nashik, Maharashtra, INDIA.
[2]Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Sandip University, Nashik, Maharashtra, INDIA.

ABSTRACT

Aim: The aim of the present study is to synthesize novel series of substituted benzimidazole derivatives and their spectral characterization. **Materials and Methods:** This study presents research on the synthesis of novel series of substituted benzimidazole derivatives using primary amine as the starting compound. **Results:** All synthesized compounds were analyzed using 1 hydrogen nuclear magnetic resonance, Fourier transform infrared and mass spectrometry to validate their structures. **Conclusion:** Overall, the exploration of substituted benzimidazole derivatives with varied functional groups as potential candidates for further advancement as therapeutic agents.

Keywords: 2-(2 Chloro Phenyl)-1H Benzimidazole, Amine, Primary, Substituted.

Correspondence:
Ms. Bhagyashri D. Jadhav
Research Scholar, School of Pharmaceutical Sciences, Sandip University, Nashik, Maharashtra, INDIA.
Email: jadhavvandana519@gmail.com

Received: 11-09-2024;
Revised: 25-11-2024;
Accepted: 05-03-2025.

INTRODUCTION

Benzimidazole is indeed an interesting aromatic heterocyclic compound. It features an imidazole ring fused to a benzene ring, giving it unique properties and reactivity. N-ribosyl-dimethyl-benzimidazole is a significant derivative, particularly because it plays a critical role in the structure of vitamin B_{12}. In vitamin B_{12}, this compound acts as an axial ligand for the cobalt ion, which is essential for the vitamin's biological function (Grimmett, 1997). Vitamin B_{12} is crucial for processes such as DNA synthesis and red blood cell formation, highlighting the importance of benzimidazole derivatives in biochemistry. Benzimidazole derivatives like mebendazole and thiabendazole play significant roles in medicine due to their anthelmintic (Abdelgawad *et al*., 2017) and antifungal properties. Some PPIs, which reduce stomach acid production, also contain the benzimidazole structure (Achar *et al*., 2010). They work by blocking the proton pump in the stomach lining, providing relief from conditions like acid reflux and ulcers. The structural features of benzimidazole allow for diverse modifications, leading to a wide range of pharmacological activities, making them valuable in drug development (Al-Hakimi *et al*., 2020; Khalil and Mohamed, 2022). Used as intermediates in the synthesis of various drugs, particularly those targeting parasitic infections and acid-related disorders. Benzimidazole derivatives are employed as fungicides and vermicides, helping to protect crops from pests and diseases. Used in formulations to prevent metal corrosion, extending the lifespan of materials. Acts as a hardener in epoxy resins, contributing to strong and durable materials. Enhances the performance characteristics of adhesives and plastics, improving their strength and flexibility. This wide-ranging utility highlights the importance of benzimidazole in synthetic organic chemistry and various industrial applications (Deshmukh *et al*., 2006; Jayachandran *et al*., 2003).

MATERIALS AND METHODS

All reagents used for the synthesis were of analytical grade and were employed without further purification. The melting points of the synthesized compounds were determined using an electric melting point apparatus via the open capillary method, reported in degrees Celsius and uncorrected. The progress of reactions and the purity of the synthesized compounds were monitored using silica gel-G aluminum TLC plates with various solvent combinations of differing polarities. Visualization of the spots was achieved with TLC cabinet. The FT-IR spectra of the synthesized compounds were recorded using a FT-IR spectrometer. Proton NMR (1H NMR) spectra were obtained using a Bruker AC-F 400 FT-NMR spectrometer at the Institute of Chemical Technology, Mumbai, Maharashtra, India and mass spectra at NMIMS Mumbai.

Synthetic Scheme

A: 2-(2 chloro phenyl)-1H benzimidazole.

B1-B10: Corresponding Substituted benzimidazoles.

DOI: 10.5530/ijpi.20250160

General Method for Synthesis of Corresponding substituted benzimidazoles

Procedure for Synthesis of 2-(2 chloro phenyl)-1H benzimidazole (A) (Step I)

A solution of 2-chloro benzoic acid (0.01 mol) and 1,2-phenylenediamine (ortho-phenylenediamine) (0.01 mol) in 20 mL of glacial acetic acid was irradiated for 7 min in a synthetic microwave oven at 350 watts as shown in Scheme 1. After irradiation, a precipitate was formed upon the addition of 10% NaOH while in an ice bath (Conrad *et al.*, 2000). The resulting product was then filtered, dried in a hot air oven and recrystallized from ethanol. The compounds were identified using TLC (n-Hexane: Ethanol, 3:2) and by determining their melting point described in Table 2.

Procedure for Synthesis of 2-(2 chloro phenyl)-1H benzimidazole Derivatives (Corresponding substituted benzimidazoles) (B1-B10) (Step II)

To the ethanolic solution of 2-(2 chloro phenyl)-1H benzimidazole (0.005 mol), primary substituted amine 0.005 mol were added. Subsequently (Goudgaon *et al.*, 2004), the reaction mixture was irradiated for 3 to 4 min in a synthetic microwave oven at 400 watts as shown in Scheme 1. After, the resulting product hot mixture was poured in crushed ice with constant stirring. Separated solid was filtered, dried and recrystallized from ethanol, methanol. The compounds were further purified using TLC ($CHCl_3$: Ethanol, 4:1) and characterized by determining their melting points described in Table 2.

RESULTS AND DISCUSSION

Spectral Data of Synthesized Compounds

Compound A

^{1}H NMR spectra (δ ppm): 7.13-7.17 doublet 2H, 7.12 singlet 1H, 7.42-7.56 doublet 2H, 7.51 singlet 1H, 7.53 singlet 1H, 7.57-7.58 quartet 4H, 7.85 singlet 1H, 7.87 singlet 1H, 7.89 singlet 1H.

IR Spectra (cm^{-1}): C=C AR Stretching 1606, C-N Stretching 1328, N-H Stretching 3234, C-Cl Stretching 624.

MS: m/z: 229 $[M+H]^+$ Mol. Wt.: 228.

Compound B1

^{1}H NMR spectra (δ ppm): 1.46 quartet 4H, 1.63 quartet 4H, 2.57-2.64 multiple 8H, 2.73 singlet 1H, 3.52 singlet 1H, 7.21-7.34 multiple 5H, 7.02 singlet 1H, 7.11 singlet 1H, 7.12 singlet 1H, 7.24 singlet 1H, 7.32 singlet 1H, 7.63-7.65 doublet 2H, 7.76 singlet 1H, 7.79 singlet 1H, 7.83 singlet 1H.

IR Spectra (cm^{-1}): C=C AR Stretching 1584, C-N Stretching 1394, C-C stretching 1462, N-H Stretching 3123.

MS: m/z: 362 $[M+H]^+$ Mol. Wt.: 361.

Compound B2

^{1}H NMR spectra (δ ppm): 1.54 doublet 2H, 1.86 quartet 4H, 2.96 quartet 4H, 7.02-7.05 multiple 5H, 7.14 singlet 1H, 7.16 singlet 1H, 7.22 singlet 1H, 7.28 singlet 1H, 7.53 singlet 1H, 7.65-7.86 doublet 2H, 7.75 singlet 1H, 7.84 singlet 1H.

IR Spectra (cm^{-1}): C=C Ar Stretching 1487, C-N Stretching 1397, C-C stretching 1401.

MS: m/z: 293 $[M+H]^+$ Mol. Wt.: 292.

Compound B3

^{1}H NMR spectra (δ ppm): 2.43 triplet 3H, 2.55 quartet 4H, 2.79 quartet 4H, 7.03-7.52 multiple 5H, 7.08 singlet 1H, 7.14 singlet 1H, 7.22 singlet 1H, 7.28 singlet 1H, 7.33 singlet 1H, 7.64-7.86 doublet 2H, 7.73 singlet 1H, 7.75 singlet 1H, 7.82 singlet 1H.

IR Spectra (cm^{-1}): C=C AR Stretching 1592, C-N Stretching 1321, N-H stretching 1291, C-C stretching 1351.

MS: m/z: 308 $[M+H]^+$ Mol. Wt.: 307.

Compound B4

^{1}H NMR spectra (δ ppm): 7.05-7.32 triplet 3H, 7.11 singlet 1H, 7.18 singlet 1H, 7.26 singlet 1H, 7.53 singlet 1H, 7.62-8.08 multiple 6H, 7.74 singlet 1H, 7.72 singlet 1H, 7.75 singlet 1H, 7.83 singlet 1H, 7.92 singlet 1H, 8.05 doublet 2H.

IR Spectra (cm^{-1}): C=C AR Stretching 1478, C-N Stretching 1273, N-H stretching 1691, S=O stretching 1151.

MS: m/z: 365 $[M+H]^+$ Mol. Wt.: 364.

Compound B5

^{1}H NMR spectra (δ ppm): 6.93 singlet 1H, 7.03-7.66 multiple 9H, 7.18 singlet 1H, 7.16 singlet 1H, 7.24 singlet 1H, 7.22 singlet 1H, 7.33 singlet 1H, 7.45 singlet 1H, 7.62 singlet 1H, 7.64-7.69 doublet 2H, 7.56 singlet 1H, 7.82 singlet 1H, 7.82 singlet 1H.

IR Spectra (cm^{-1}): C=C AR Stretching 1621, C-N Stretching 1196, N-H stretching 3332.

MS: m/z: 286 $[M+H]^+$ Mol. Wt.: 285.

Compound B6

^{1}H NMR spectra (δ ppm): 7.03-7.54 multiple 7H, 7.14 singlet 1H, 7.23 singlet 1H, 7.24 singlet 1H, 7.53 singlet 1H, 7.56 singlet 1H, 7.52 singlet 1H, 7.61-7.67 triplet 3H, 7.82 singlet 1H, 7.72 singlet 1H, 7.76 singlet 1H, 7.83-8.04 triplet 3H, 7.98 singlet 1H, 8.21 singlet 1H.

IR Spectra (cm^{-1}): C=C AR Stretching 1498, C-N Stretching 1230, N-H stretching 3351, C=O stretching 1651.

MS: m/z: 314 $[M+H]^+$ Mol. Wt.: 313.

Compound B7

^{1}H NMR spectra (δ ppm): 1.24 triplet 3H, 4.25 doublet 2H, 7.02-7.32 triplet 3H, 7.08 singlet 1H, 7.14 singlet 1H, 7.26 singlet 1H, 7.46-7.52 triplet 3H, 7.46 singlet 1H, 7.42 singlet 1H, 7.64-7.85 multiple 6H, 7.72 singlet 1H, 7.53 singlet 1H, 7.89 singlet 1H, 7.78 singlet 1H, 7.82 singlet 1H.

IR Spectra (cm^{-1}): C=C AR Stretching 1537, C-N Stretching 1283, N-H stretching 3340, C=O stretching 1561.

MS: m/z: 358 [M+H] $^+$ Mol. Wt.: 357.

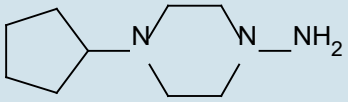
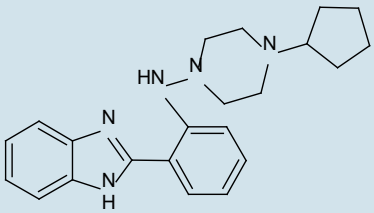
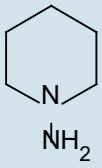
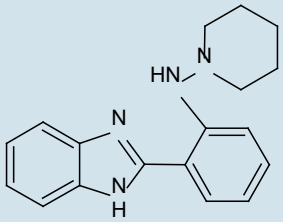
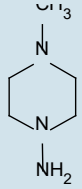
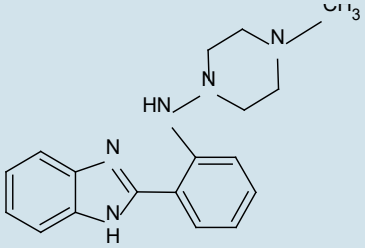
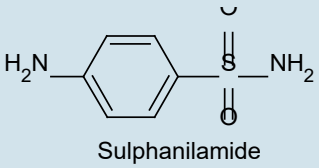
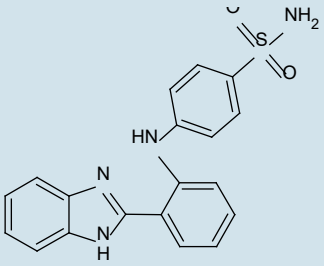
Compound B8

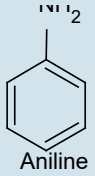
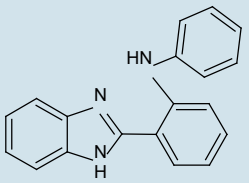
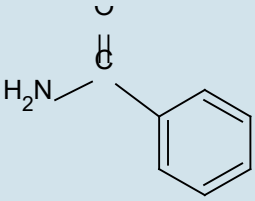
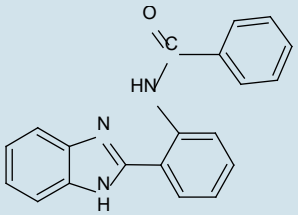
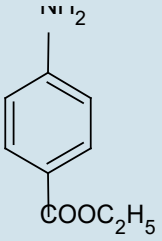
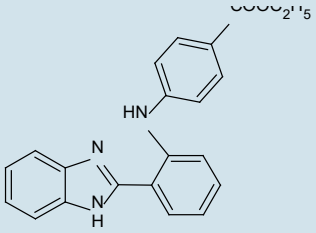
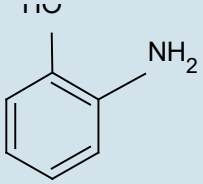
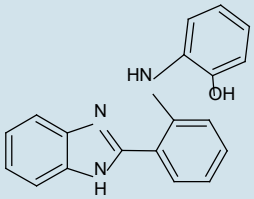
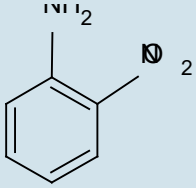
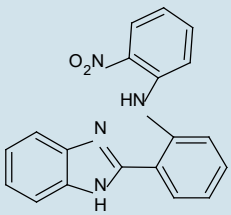
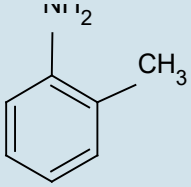
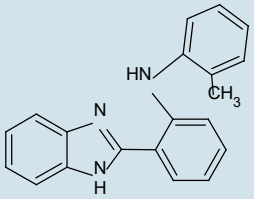
^{1}H NMR spectra (δ ppm): 6.82 singlet 1H, 6.81-7.32 quartet 5H, 6.87 singlet 1H, 7.32 singlet 1H, 7.12 singlet 1H, 7.22 singlet 1H, 7.24 singlet 1H, 7.33-7.87 multiple 5H, 7.52 singlet 1H, 7.66 singlet 1H, 7.84 singlet 1H, 7.73 singlet 1H, 7.72 singlet 1H, 7.82 singlet 1H.

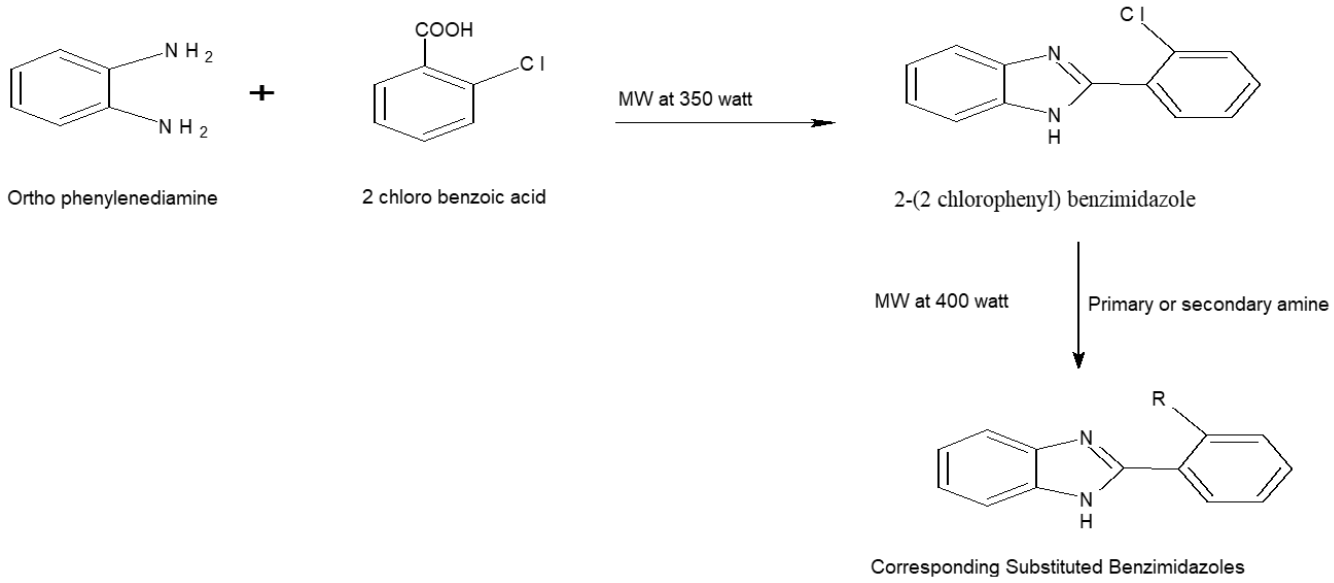
IR Spectra (cm^{-1}): C=C AR Stretching 1523, C-N Stretching 1236, N-H stretching 3301, O-H stretching 3340.

MS: m/z: 302 [M+H] $^+$ Mol. Wt.: 301.

Table 1: Different Primary amine substitution (R).

Sl. No.	Compound Code	R Substitution	Corresponding Substituted Benzimidazoles
1.	B1	 1-Amino-4-cyclopentylPiperidine	 2- [(4-Cyclopentyl piperazin-1-yl) imino] -(2-phenyl)1H-Benzimidazole.
2.	B2	 1-Amino Piperidine	 2-[(piperidine)-imino)] -(2-phenyl)1H-Benzimidazole.
3.	B3	 1 amino 4 methyl piperazine	 2- [(4-methyl piperidin-1-yl) imino]-2-phenyl)1H-Benzimidazole.
4.	B4	 Sulphanilamide	 2- [(sulphanilamido benzene) imino]-2-phenyl)1H-Benzimidazole.

Sl. No.	Compound Code	R Substitution	Corresponding Substituted Benzimidazoles
5.	B5	 Aniline	 2-[(phenyl imino)]-2-phenyl)1H-Benzimidazole.
6.	B6	 Benzamide	 2- [(Benzene carboxamide) imino]-2-phenyl)1H-Benzimidazole.
7.	B7	 Ethyl 4 amino benzoate	 2- [(ethyl benzoate) imino]-2-phenyl)1H-Benzimidazole.
8.	B8	 Ortho amino phenol	 2-[(phenol)imino]-2-phenyl)1H-Benzimidazole.
9.	B9	 Ortho nitroaniline	 2- [(nitro benzene) imino]-2-phenyl)1H-Benzimidazole.
10.	B10	 Ortho Toluidine	 2- [(methyl benzene) imino]-2-phenyl)1H-Benzimidazole.



Scheme 1: Synthetic Scheme for Corresponding substituted benzimidazoles (B1-B10) from Table 1.

Table 2: Physical Characterization data of synthesis of Corresponding substituted benzimidazoles (B1-B10).

Sl. No.	Compound Code	Molecular Formula	Molecular Weight gm/mol	Melting Point (°C)	% Yield	R_f Values	Reaction Time
1.	A	$C_{13}H_9ClN_2$	228	234-236	75	0.56	7
2.	B1	$C_{22}H_{27}N_5$	361	190-192	57	0.79	4
3.	B2	$C_{18}H_{20}N_4$	292	298-300	65	0.82	4
4.	B3	$C_{18}H_{21}N_5$	307	213-215	58	0.65	3
5.	B4	$C_{19}H_{16}N_4O_2S$	364	302-304	72	0.84	3
6.	B5	$C_{19}H_{15}N_3$	285	185-187	64	0.52	4
7.	B6	$C_{20}H_{15}N_3O$	313	265-267	67	0.48	4
8.	B7	$C_{22}H_{19}N_3O_2$	357	153-155	79	0.42	4
9.	B8	$C_{19}H_{15}N_3O$	301	320-322	72	0.58	4
10.	B9	$C_{19}H_{14}N_4O_2$	330	290-292	79	0.63	4
11.	B10	$C_{20}H_{17}N_3$	299	340-342	63	0.86	4

Compound B9

^{1}H NMR spectra (δ ppm): 7.03-7.42 quartet 5H, 7.11 singlet 1H, 7.18 singlet 1H, 7.23 singlet 1H, 7.23 singlet 1H, 7.42 singlet 1H, 7.45-7.82 quartet 5H, 7.52 singlet 1H, 7.73 singlet 1H, 7.85 singlet 1H, 7.83 singlet 1H, 7.83 singlet 1H, 8.02-8.18 doublet 2H, 8.01 singlet 1H, 8.03 singlet 1H.

IR Spectra (cm^{-1}): C=C Ar Stretching 1623, C-N Stretching 1470, N-H stretching 3520.

MS: m/z: 331 $[M+H]^+$ Mol. Wt.: 330.

Compound B10

^{1}H NMR spectra (δ ppm): 2.13 triplet 3H, 6.54 singlet 1H, 6.87-7.89 multiple 10H, 6.58 singlet 1H, 7.05 singlet 1H, 7.10 singlet 1H, 7.17 singlet 1H, 7.24 singlet 1H, 7.24 singlet 1H, 7.53 singlet 1H, 7.58 singlet 1H, 7.56 singlet 1H, 7.87 singlet 1H, 7.89 singlet 1H.

IR Spectra (cm^{-1}): C=C AR Stretching 1447, C-N Stretching 1332, N-H stretching 3447, CH_3 1294.

MS: m/z: 300 $[M+H]^+$ Mol. Wt.: 299.

CONCLUSION

Corresponding Substituted benzimidazoles Derivatives was successfully synthesized. Using microwave irradiation for small-scale reactions is an effective approach to optimize the synthesis of novel benzimidazole derivatives. This method often enhances reaction rates, improves yields and can lead to more efficient processes. Synthesizing Schiff Bases of 2-(2 chloro phenyl)-1H benzimidazole derivatives using microwave irradiation is an excellent approach. The use of microwave

irradiation can significantly reduce the reaction time and improve yields compared to conventional heating methods. The exploration of Schiff Bases of 2-(2 chloro phenyl)-1H benzimidazole derivatives with varied functional groups holds great potential for discovering novel pharmacological agents. This area is indeed worth pursuing, as it may lead to the development of compounds with enhanced efficacy.

ACKNOWLEDGEMENT

The authors are thankful to the Sandip University, School of Pharmaceutical Sciences, Nashik, Maharashtra, India.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Abdelgawad, M. A., Bakr, R. B., & Omar, H. A. (2017). Design, synthesis and biological evaluation of some novel benzothiazole/benzoxazole and/or benzimidazole derivatives incorporating a pyrazole scaffold as antiproliferative agents. Bioorganic Chemistry, 74, 82-90. https://doi.org/10.1016/j.bioorg.2017.07.007

Achar, K. C. S., Hosamani, K. M., & Seetharamareddy, H. R. (2010). *In vivo* analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives. European Journal of Medicinal Chemistry, 45(5), 2048-2054. https://doi.org/10.1016/j.ejmech.2010.01.029

Al-Hakimi, A. N., Alminderej, F., Aroua, L., Alhag, S. K., Alfaifi, M. Y., M, S. O., Mahyoub, J. A., Eldin I. Elbehairi, S., & Alnafisah, A. S. (2020). Design, synthesis, characterization of zirconium (IV), cadmium (II) and iron (III) complexes derived from Schiff base 2-aminomethylbenzimidazole, 2-hydroxynaphtadehyde and evaluation of their biological activity. Arabian Journal of Chemistry, 13(10), 7378-7389. https://doi.org/10.1016/j.arabjc.2020.08.014

Conrad, M., Assmann, L., Wroblowsky, H. J., Casser, C., & Bielefeldt, D. Process for preparing 2-chloro-benzimidazole derivatives, U.S. Patent 6054589. (2000).

Deshmukh, M. B., Jagtap, S. S., & Deshmukh, S. A. (2006). Journal of the Indian Chemical Society, 83, 1055.

Goudgaon, N. M., Dhondiba, V., & Vijayalaxmi, A. (2004). Indian Journal of Heterocyclic Chemistry, 13, 271.

Grimmett, M. R. (1997). Imidazole and benzimidazole synthesis (pp. 23-96). Academic Press.

Jayachandran, E., Naragund, L. V. G., Shivakumar, B., & Bhatias, K. (2003). Oriental Journal of Chemistry, 19, 139.

Khalil, E. A. M., & Mohamed, G. G. (2022). Preparation, spectroscopic characterization and antitumor-antimicrobial studies of some Schiff base transition and inner transition mixed ligand complexes. Journal of Molecular Structure, 1249. https://doi.org/10.1016/j.molstruc.2021.131612

Cite this article: Jadhav BD, Narkhede SP. Synthesis and Spectral Analysis of Novel Substituted Benzimidazole Derivatives. Int. J. Pharm. Investigation. 2025;15(3):1006-11.