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A Sustainable Microwave Protocol for the Synthesis of Benzimidazole Scaffolds

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ABSTRACT: The green chemistry approach emphasizes reduced energy consumption, minimal solvent use, and safer reaction conditions, aligning with the principles of sustainability and environmental responsibility. Microwave irradiation, as a green synthetic tool, offers rapid, uniform heating, shorter reaction times, and enhanced efficiency, thus reducing the environmental footprint of chemical synthesis This work highlights the superiority of green microwave-assisted synthesis over traditional methods for the efficient and eco-friendly production of benzimidazole derivatives.In this study, four novel benzimidazole derivatives were synthesized using microwave reactor and one compound was synthesized by conventional method. In contrast, the green approach employed microwave-assisted synthesis, carried out under microwave irradiation for just 9–10 minutes, producing significantly higher yields than conventional synthesis.

KEYWORDS: Aryl aldehydes, Conventional synthesis, Microwave Reactor, TLC, FT-IR.

I. INTRODUCTION

Benzimidazole is a prominent heterocyclic aromatic compound composed of a fused benzene and imidazole ring. Its unique structure provides a versatile platform for the development of biologically active molecules. Benzimidazole and its derivatives have garnered considerable interest due to their wide range of pharmacological activities, including antimicrobial, antifungal, anticancer, antiviral, and anti-inflammatory properties. The presence of nitrogen atoms within the ring system contributes to strong interactions with various biological targets, enhancing its therapeutic potential.The structural similarity of benzimidazole to naturally occurring nucleotides enables it to interfere with biological processes, making it a valuable scaffold in drug design and medicinal chemistry. Furthermore, benzimidazole derivatives are also utilized in agricultural, industrial, and material science applications.Recent advancements in synthetic methods, particularly the use of environmentally friendly and time-efficient techniques such as microwave-assisted synthesis, have further increased the interest in benzimidazole chemistry. These approaches not only reduce reaction times and improve yields but also align with the principles of green chemistry, making them suitable for sustainable chemical development.

Green chemistry has emerged as a progressive and rapidly developing branch of chemistry focused on sustainability. It emphasizes designing chemical processes and products in ways that minimize or completely avoid the use and creation of harmful substances. Over the past few decades, there has been growing interest in the synthesis of heterocyclic compounds containing nitrogen, oxygen, and sulphur due to their broad spectrum of biological activities[1].In recent years, microwave-assisted synthesis has gained recognition as an efficient technique for the rapid construction of new chemical compounds. This method enhances the speed of various chemical reactions due to the selective absorption of microwave energy by reactants. The use of microwave irradiation, often in combination with catalysts or reagent-supported minerals, facilitates numerous organic transformations under mild conditions. This approach offers several advantages, including faster reaction rates, improved product yields, and reduced reaction times, making it a valuable tool in modern synthetic chemistry[2].

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Microwave-assisted methods significantly reduce the duration of chemical reactions, often by factors of 100 to 1000 compared to traditional techniques. In many cases, these modifications not only streamline the process but also result in higher product yields. Additionally, microwave technology enables access to novel synthetic pathways that are difficult or unattainable through conventional heating methods, offering new possibilities for innovation in organic synthesis[3].Despite progress, there remains a need to further advance eco-friendly synthetic strategies for producing bioactive compounds. Modern techniques such as microwave irradiation, ultrasound-assisted synthesis, flow chemistry, and other innovative approaches hold great potential for creating biologically active molecules through safer and more sustainable transformations. However, the full integration of these methodsespecially those using recyclable or biodegradable reagentsstill requires further development to maximize green chemistry's impact on improving environmental sustainability[4].

Benzimidazoles are among the most extensively studied classes of heterocyclic compounds, largely due to their diverse and significant pharmacological properties.Additionally, benzimidazole derivatives function as inhibitors of enzymes like aldose reductase, disruptors of photosynthetic pathways, and antagonists of certain neurotransmitter receptors[5].

II. METHODOLOGY

Materials

All chemicals used were of commercially available reagent grade. The aromatic aldehydes were purchased from Sigma Aldrich and the starting material 5-chloro-4-fluoro-2-nitrobenzamine was synthesized from 3-chloro-4-fluoro aniline in the laboratory and purified using standard methods, and their purity was confirmed through thin-layer chromatography (TLC).

Apparatus

Infrared (IR) spectra were recorded using KBr pellets on aShimadzu 8700 instrument equipped with IR Solution software. Microwave-assisted reactions were performed using a microwave reactor (top load), specifically designed for organic synthesis. Melting points were measured on a Yanagimoto micro melting point apparatus and are reported without correction. The purity of starting materials and the progress of reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (Polygram SILG/UV 254) supplied by Merck.

General experimental procedure for synthesis of benzimidazole derivatives

Conventional synthesis (Scheme 1a): An equimolar quantity of 5-chloro-4-fluoro-2-nitrobenzamine and corresponding aromatic aldehydes were treated in the presence of sodium dithionite and refluxed for about 12 hrs. Then, the mixture was cooled to room temperature and filtered, obtained filtrate was further extracted with ethyl acetate. The purity was determined by TLC using suitable solvents[6]. A moderate yield of about 65% was found.

Microwave assisted synthesis (Scheme 1b):A mixture of 5-chloro-4-fluoro-2-nitrobenzamine (1.0 mmol) and an aryl aldehyde (1.0 mmol) was dissolved in ethanol (4 mL) and placed in an open Erlenmeyer flask. To this solution, 1 M aqueous sodium dithionite ($Na_2S_2O_4$,3.0 mmol) was added. The reaction mixture was then subjected to microwave irradiation for 9-10 min. Progress of the reaction was monitored using thin-layer chromatography (TLC). Upon completion, the reaction mixture was poured into an ice-water mixture. The resulting solid was filtered, washed with cold water, and collected as the crude product. This crude material was further purified by recrystallization from methanol, yielding the pure 2-substituted benzimidazole compound.[7].

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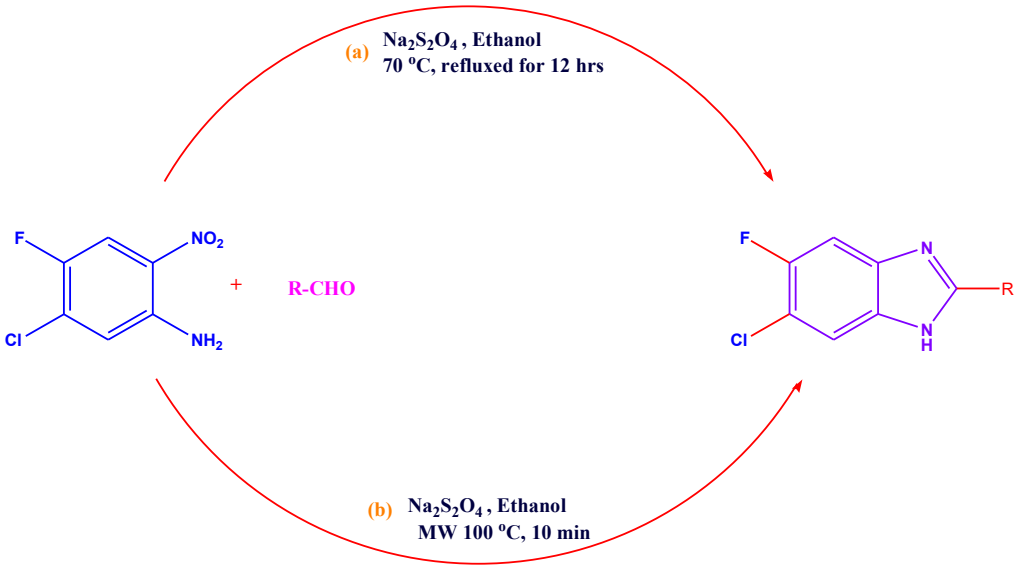


Scheme 1: (a) Conventional synthesis (b) Microwave synthesis

Characterisation techniques

Thin Layer Chromatography (TLC): To assess the completion of the reaction and the purity of the synthesized products, thin-layer chromatography was performed. Silica gel GF 254 was used as the stationary phase, and various combinations of solvents were employed as the mobile phase depending on the compound. Visualization of the spots was done under a UV chamber, and R_f values were calculated and documented accordingly[8].

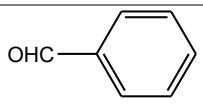
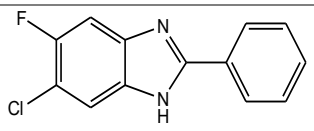
Melting point: In this study, the melting point of the synthesized compounds was determined using the open capillary method, also known as Thiele's tube method. A Thiele tube was filled with paraffin oil, and a capillary tube containing the sample was placed inside it. The capillary was secured alongside a thermometer, and heat was applied to the side arm of the Thiele tube to ensure uniform heating of the oil. The temperature at which the sample visibly melted was recorded as the uncorrected melting point[9].

FT-IR Spectroscopy: The functional groups present in the synthesized molecules were identified using Fourier Transform Infrared (FT-IR) spectroscopy. The analysis was conducted using a Shimadzu 8700 instrument equipped with IR Solution software. Spectra were recorded in the range of 400 to 4000 cm^{-1}, and the KBr pellet method was employed for sample preparation[10].

III. RESULTS

Four novel benzimidazole derivatives (MW1-MW4) were synthesized by employing two methods such as conventional and green chemistry approach.

Table 1: Reaction of aryl aldehydes with 5-chloro-4-fluoro-2-nitrobenzamine

Code	Substrate	Product	Time (min)
MW1			10

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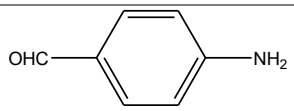
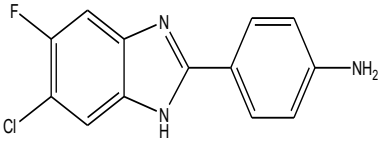
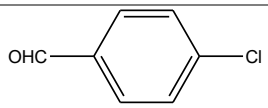
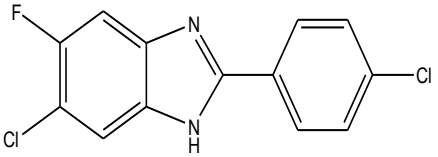
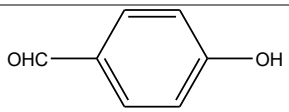
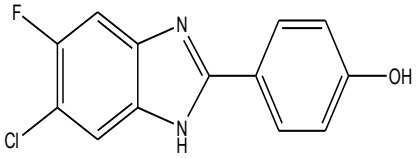
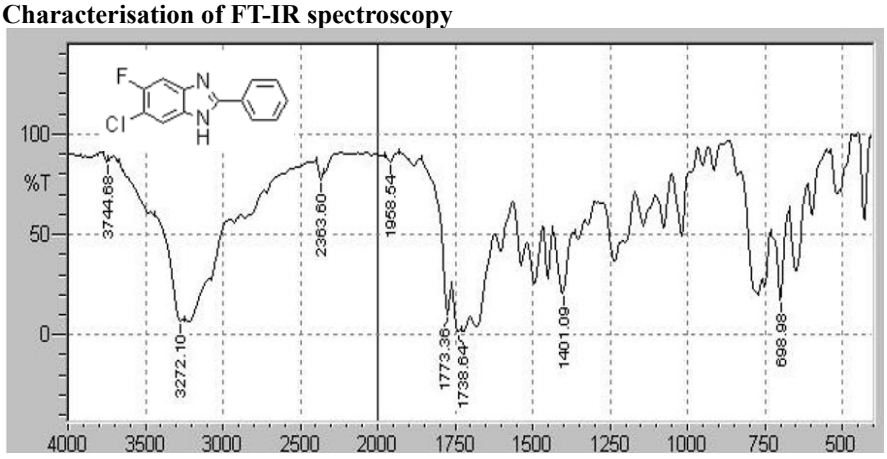
MW2			10
MW3			9
MW4			10

Table 2: Determination of TLC, M.P., Percentage yield

Code	TLC (R_f value)	Melting point (ºC)	% yield
MW1	0.76	200-205	91%
MW2	0.78	190-195	89%
MW3	0.73	195-200	95%
MW4	0.79	185-190	84%

Characterisation of FT-IR spectroscopy



Functional group	*IR(KBr) cm^{-1}*
NH stretch	*3272.10*
CH aromatic	*2900.00*
C=C	*1730.64*
C=N	*1401.09*
C-F	*750.00*
C-Cl	*898.98*

Figure 1: FT-IR spectrum of compound MW1

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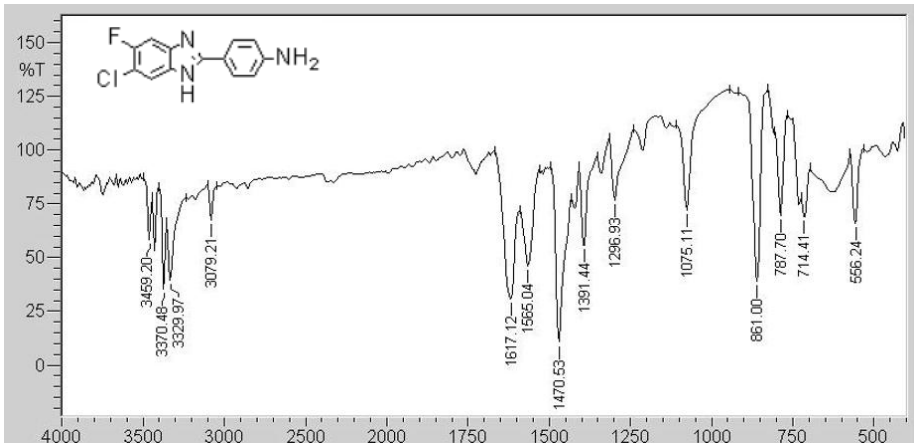
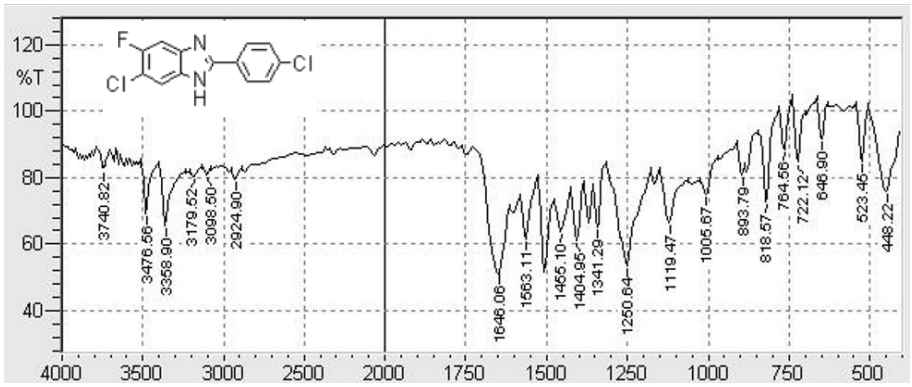


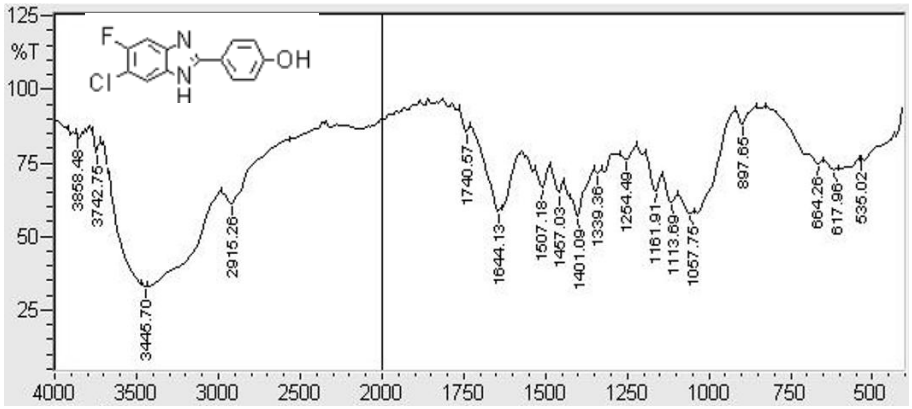
Functional group	*IR(KBr) cm^{-1}*
NH_2 stretch	*3459.20*
NH stretch	*3370.48*
CH aromatic	*3079.21*
C=C	*1617.12*
C=N	*1470.53*
C-F	*556.24*
C-Cl	*861.00*

Figure 2: FT-IR spectrum of compound MW2



Functional group	*IR(KBr) cm^{-1}*
NH stretch	*3476.56*
CH aromatic	*3358.90*
C=C	*1646.06*
C=N	*1563.11*
C-F	*523.45*
C-Cl	*818.57*

Figure 3: FT-IR spectrum of compound MW3



Functional group	*IR(KBr) cm^{-1}*
OH stretch	*3445.70*
NH stretch	*3742.75*
CH aromatic	*2915.26*
C=C	*1644.13*
C=N	*1401.09*
C-F	*535.02*
C-Cl	*897.65*

Figure 4: FT-IR spectrum of compound MW4

IV. CONCLUSION

The comparative analysis between conventional and green (microwave-assisted) synthesis methods for the preparation of benzimidazole derivatives demonstrates a clear advantage in favour of the green approach. The conventional method, involving prolonged reflux for approximately 12 hours with moderate yields (~65%), is both time-consuming and energy-intensive. In contrast, the microwave-assisted green synthesis significantly reduced reaction time to just 9–10 minutes and yielded high product efficiency, with yields ranging from 84% to 95%.

Thin Layer Chromatography (TLC) using ethyl acetate: n-hexane (3:1) confirmed product formation in all microwave-assisted reactions, and the purity of the compounds was further validated by melting point analysis and the functional group

was determined by the characterisation of FT-IR spectroscopic technique. Thus, green synthesis not only enhances reaction efficiency but also aligns with the principles of sustainable chemistry by reducing solvent use, minimizing energy consumption, and avoiding harsh reaction conditions.Thus, microwave-assisted green synthesis offers a faster, cleaner, and more efficient alternative to conventional methods for the synthesis of benzimidazole derivatives.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

REFERENCES

[1]. Prashant NK, Ravi Kumar K. Green synthesis of benzimidazole derivatives: an overview of bulk drug synthesis. *Int J PharmTech Res*. 2015;8(9):60–8.

[2]. Sharma P, Reddy TS, Kumar NP, Senwar KR, Bhargava SK, Shankaraiah N. Conventional and microwave-assisted synthesis of new 1H-benzimidazole-thiazolidinedione derivatives: a potential anticancer scaffold. *Eur J Med Chem*. 2017 Sep 29; 138:234–45.

[3]. Chawla A, Kaur G, Sharma AK. Green chemistry as a versatile technique for the synthesis of benzimidazole derivatives: review. *Int J Pharm Phytopharmacol Res*. 2012;2(3):148–59.

[4]. Frecentese F, Sodano F, Corvino A, Schiano ME, Magli E, Albrizio S, et al. The application of microwaves, ultrasounds, and their combination in the synthesis of nitrogen-containing bicyclic heterocycles. *Int J Mol Sci*. 2023 Jun 27;24(13):10722.

[5]. Tripathi JP. Microwave-assisted synthesis of benzimidazoles catalysed by oxalic acid. *Int J Res Appl Sci Eng Technol*. 2018 Mar 31;6(3):94–9.

[6]. Dasgupta HR, Mukherjee S, Ghosh P. One pot reductive synthesis of benzimidazole derivatives from 2-nitro aniline and aromatic aldehydes using Zn/$NaHSO_3$ in water medium. *Prog Chem Biochem Res*. 2021 Jan 1;4(1):57–67.

[7]. Naeimi H, Alishahi N. An efficient and one-pot reductive cyclization for synthesis of 2-substituted benzimidazoles from o-nitroaniline under microwave conditions. *J Ind Eng Chem*. 2014 Jul;20(4):2543–7.

[8]. Thin Layer Chromatography - Chemistry Libre Texts [Internet]. Available from: https://chem.libretexts.org/Bookshelves/Analytical_Chemistry/Supplemental_Modules_(Analytical_Chemistry)/Instrumental_Analysis/Chromatography/Thin_Layer_Chromatography.

[9]. Melting Point Apparatus Working Principle » Flair Pharma The Knowledge Kit [Internet]. Available from: https://flairpharma.com/melting-point-apparatus-working-principle/

[10]. FTIR: Principle, Instrumentation, Applications, Advantages [Internet]. Available from: https://www.pharmaguideline.com/2021/09/ftir-principle-instrumentation-applications.html