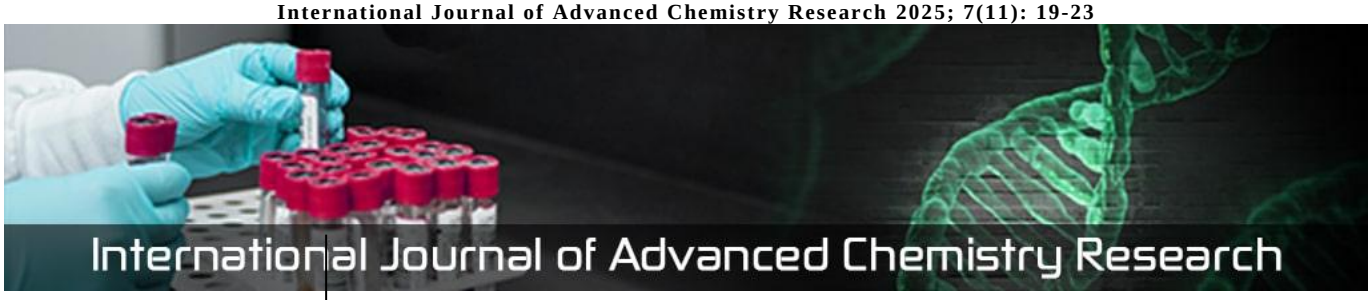

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Anuradha K Pawar
Department of Chemistry, Mungasaji Maharaj Mahavidyalaya, Darwha, Maharashtra, India

Nikhil L Khargade
Department of Chemistry, Rajiv vidnyan Va vanijya Mahavidyalaya, zari-jamani, Maharashtra, India

Dr. Nazia A Rashidi
Department of Chemistry, Mungasaji Maharaj Mahavidyalaya, Darwha, Maharashtra, India

Corresponding Author:
Anuradha K Pawar
Department of Chemistry, Mungasaji Maharaj Mahavidyalaya, Darwha, Maharashtra, India

Microwave-assisted synthesis and characterization of bioactive Benzimidazole-Oxadiazole Hybrids

Anuradha K Pawar, Nikhil L Khargade and Nazia A Rashidi

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Abstract
A series of new heterocyclic derivatives containing benzo[d]imidazole scaffolds was synthesized through a multi-step reaction procedure. Initially, ethyl 2-(1H-benzo[d]imidazol-1-yl) acetate was obtained from benzimidazole and ethyl 2-chloroacetate in ethanol. Subsequent treatment with hydrazine hydrate afforded 2-(hydrazinyloxy)-2-oxoethyl-1H-benzo[d]imidazole, which was converted to 2-(1H-benzo[d]imidazol-1-yl) acetohydrazide. The hydrazide was then condensed with benzaldehyde to give the corresponding Schiff base, (E)-2-(1H-benzo[d]imidazol-1-yl)-N-benzylideneacetohydrazide. Further cyclization under microwave irradiation in the presence of chloramine-T as a catalyst furnished 2-((1H-benzo[d]imidazol-1-yl) methyl)-5-phenyl-1, 3, 4-oxadiazole. This multistep microwave-assisted synthetic procedure providing an accelerated and sustainable approach with improved reaction efficiency. This synthetic route provides an efficient and convenient strategy for the preparation of bioactive benzimidazole-oxadiazole hybrids (T_1-T_5), which are of potential interest in medicinal chemistry due to their diverse pharmacological properties. Characterisation of synthesized compound (T_1-T_5) were confirmed by using IR (KBr), H-1 NMR spectral data, and reaction completion was monitor by using TLC.

Keywords: Benzimidazole, microwave irradiation, oxadiazole hybrids, heterocyclic compounds

Introduction
The heterocyclic compounds have become an essential part of the medicinal chemistry because of their prevalence in the bioactive molecules [1]. Benzimidazoles form a significant group of heterocycles that already has a proven pharmacological effects, such as antimicrobial, antiviral, anticancer, and anti-inflammatory effects [2]. Omeprazole, albendazole and mebendazole are examples of drugs containing benzimidazole as their pharmacophore [4, 3]. The 1, 3, 4-oxadiazoles are also versatile heterocyclic compounds used in pharmaceuticals, agrochemicals and materials science. They exhibit anti-inflammatory, antifungal, antibacterial, analgesic and anticancer activity, and frequently serve as bioisosteres to esters and amides where they enhance metabolic stability [2, 8].
The fact that these two moieties can be combined to produce a hybrid scaffold gives a useful approach to producing molecules containing synergetic activity. It has been shown that benzimidazole-oxadiazole derivatives have antimicrobial activity [7], anticancer activity [4] and enzyme-inhibitory activity [6]. In this paper, we describe the synthesis of a benzimidazole-oxadiazole conjugate, 2-((1H-benzo[d]imidazol-1-yl) methyl)-5-phenyl-1, 3, 4-oxadiazole (T_1-T_5), by a simple multistep process. Oxidative cyclization using microwave irradiation and chloramine-T allows the reaction to take place in a short period and with high yield [6], which is in line with the concept of green chemistry.

Materials and Methods
Chemicals and Reagents
The synthesis involved the use of various chemicals, including and its substituted Benzimidazole, Ethyl 2-chloroacetate, Hydrazine hydrate Derivatives along with ethyl chloroacetate, phenyl iso-thiocynate, NaOH Common solvents such as ethanol, methanol, glacial acetic acid, acetone, Benzaldehyde, Chloramine-T, Ethanol, methanol, and other standard solvents and dimethyl sulfoxide were also utilized.

All key chemicals were procured from Merck and Sigma-Aldrich, while the remaining solvents and reagents, all of analytical grade, were obtained from other commercial sources.

Instrumentation

A microwave, a vacuum desiccator, an electrical heating mantle, a magnetic stirrer with a hot plate, a water bath, and a melting point apparatus were used for the experimental setup. Additionally, a Value vacuum pump was used. Throughout the investigation, borosilicate glassware was utilized, which was cleaned with a chromic acid solution, rinsed with distilled water, and dried in a Biotechnics India hot air oven before use.

IR spectra were recorded at Accu Analytical lab Instrument ID No: AA-ID-002 IR (KBr), 1H NMR spectra were obtained on a 400 MHz spectrometer using $CdCl_3$ solvent, Mass spectra were obtained using Synthesis.

Scheme 1

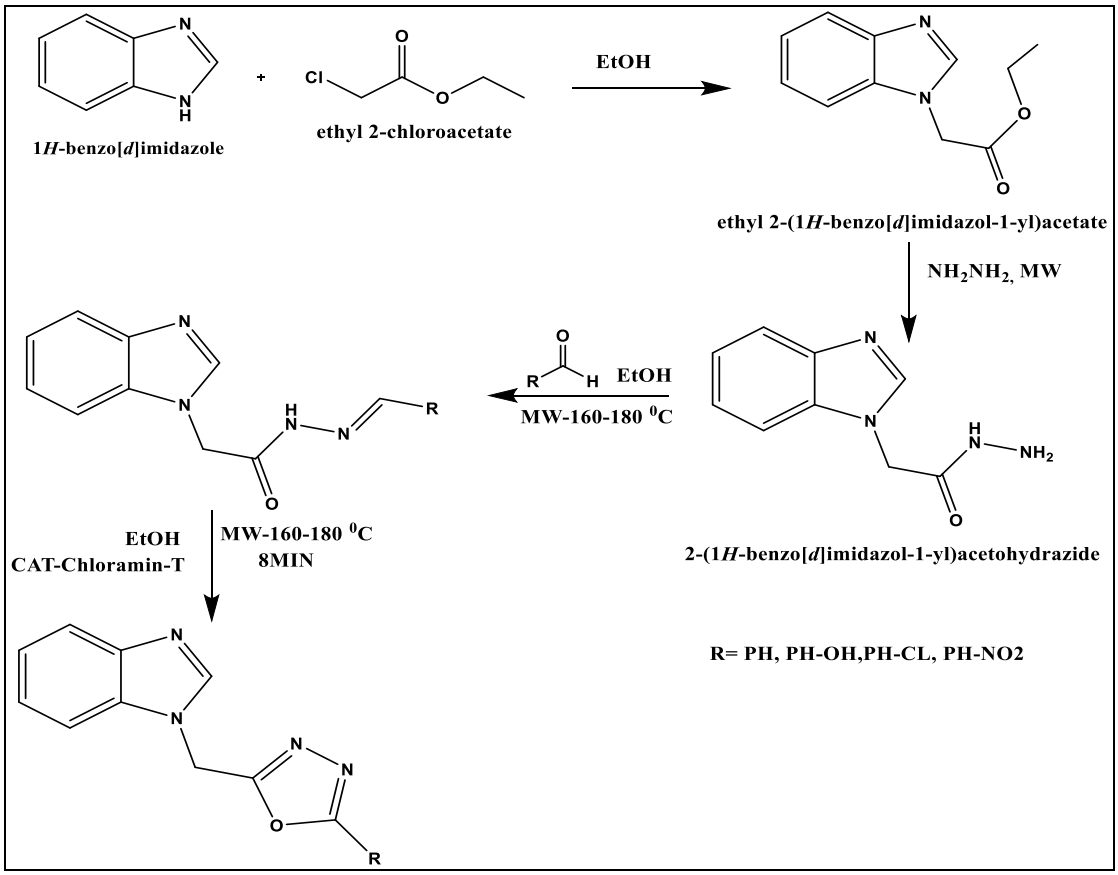


Fig 1: Synthetic route to Benzimidazole-Oxadiazole Hybrid

General Synthesis of Ethyl 2-(1H-benzo[d]imidazol-1-yl) acetate

Benzimidazole (6.0 g, 0.05 mol), ethyl chloroacetate (4.2 mL, 0.04 mol), and potassium carbonate (4.0 g, 0.029 mol) were suspended in 30 mL of ethanol. The reaction mixture was subjected to microwave irradiation at medium power for 6-8 min. Progress of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate: hexane (3:1) as the mobile phase. Upon completion, the mixture was poured onto crushed ice, and the precipitate obtained was collected by vacuum filtration. The crude product was washed with cold water, dried under oven, and recrystallized from hot ethanol to give the pure White crystalline solid compound. Yield: 4.3 g (70%), Melting point: 180 °C.

Preparation of 2-(1H-[d]imidazol-1-yl)acetohydrazide

The ester (Ethyl 2-(1H-benzo[d]imidazol-1-yl) acetate (4.2gm, 0.01mol) was reacted with hydrazine hydrate (80%, 5 mL) in ethanol. This reaction proceeded through microwave irradiation for 6-9 to minutes. The mixture was poured onto crushed ice cold water, and the precipitate obtained was collected by vacuum filtration. The crude product was washed with cold water, dried in an oven, and recrystallized from hot ethanol to give the pure corresponding hydrazide Yield: 3.3 g (78%), Melting point: 160-185 °C.

Formation of Schiff Base (E)-2-(1H-benzo[d]imidazol-1-yl)-N-benzylideneacetohydrazide

Hydrazide (1.09gm, 1 mmol) was condensed with benzaldehyde (1.06 gm, 1 mmol) in ethanol with a few drops of acetic acid, then subjected to microwave irradiation for 8-10 minutes at medium power. Afterward, the mixture was poured into a beaker with ice-cold water and refrigerated overnight. The resulting product was filtered using a vacuum pump, washed several times with ice-cold water, and recrystallized from ethanol to obtain the final compound. Yield: 64%, melting point: 185°C.

IR (KBr) 1650-1690 cm^{-1}(C=O acyl hydrazide), 1590-1640 cm^{-1}(C=N imine), 3310-3350 cm^{-1} (N-H) 3050 cm^{-1} (aromatic C-H) 2850-2890 cm^{-1} (aliphatic CH_2), 1200-1330 cm^{-1} (C-N). H-1 NMR (Solvent=CDCl3 400 MHz): N-H 11.07 (sec. amide) 1-C from sec. amide, C-H 8.16 (benzimidazole) C-H 7.64 (benzimidazole), C-H 7.93

(benzylidenimin,) CH 7.20 benzimidazole C-H 7.27 (benzimidazole), C-H 7.93(benzylidenimin), C-H 7.58 (benzylidenimin), CH_2 4.62 1.37 methylene, 1 alpha-N* C-H 8.47 8.11 benzylidenimin.

Cyclization to 2-((1H-benzo[d]imidazol-1-yl) methyl)-5-phenyl-1,3,4-oxadiazole

The Schiff base (2.29 gm, 1 mmol) was cyclized in ethanol using chloramine-T (2.27gm, 1.2 mmol) under microwave irradiation for 10-15 min. Reaction completion was monitored by TLC, The solid product was filtered by a vacuum pump and recrystallized using ethanol to obtain the final product Yield: 73%, melting point: 210℃.

IR (KBr) 3050 cm^{-1} (aromatic C-H), 1590-1630 cm^{-1} (C=N), 1500-1600 cm^{-1} (aromatic C=C), 3300 cm^{-1} (N-H),1250-1350 cm^{-1} (C-O or C-N),700-900 cm^{-1} (aromatic C-H) H-1 NMR (Solvent=$CDCl_3$ 400 MHz): C-H 8.1 (benzimidazole), CH 7.64 (benzimidazole), C-H 7.64 benzimidazole, C-H 8.02 1-benzene 1-C*R, C-H 7.20 (benzimidazole), C-H 7.27 (benzimidazole) C-H 8.02 (1-benzene) 0.34 1-C*R, C-H 7.62 (1-benzene) 0.19 1-C*R, C-H 7.62 (1-benzene) 1-C*R, C-H 7.62 (1-benzene) 1-C*R, CH2 4.99 (methylene) 1 alpha-N*R.

Results and Discussion

The synthetic route was accomplished in four steps. The ester and hydrazide intermediates were obtained in moderate to good yields. Schiff base formation proceeded smoothly, as evidenced by the disappearance of the hydrazide NH2 signal and the appearance of the imine (-CH=N-) stretch at ~1620 cm^{-1} in the IR spectrum. Cyclization to the oxadiazole was confirmed by the absence of the imine band and the appearance of characteristic oxadiazole ring absorptions in IR (~1540-1560 cm^{-1}). ^1H NMR spectra showed the disappearance of the imine proton and the presence of signals consistent with the oxadiazole framework. Mass spectrometry further confirmed the molecular ion peak corresponding to the target compound. The use of microwave irradiation significantly reduced reaction time compared to conventional heating [6] (minutes vs. hours), while chloramine-T served as an efficient, mild oxidizing agent for ring closure.

The final product, bearing both benzimidazole and oxadiazole pharmacophores, represents a promising scaffold for further biological evaluation. Literature supports its potential as an antimicrobial, anticancer, or anti-inflammatory activitie [12, 14].

Similarly, as shown in Figure 1, we synthesized another substituted Benzimidazole-Oxadiazole (T_1-T_5) hybrid using the synthetic route scheme 1. And table no. 1 shows Physical data of synthesized compounds

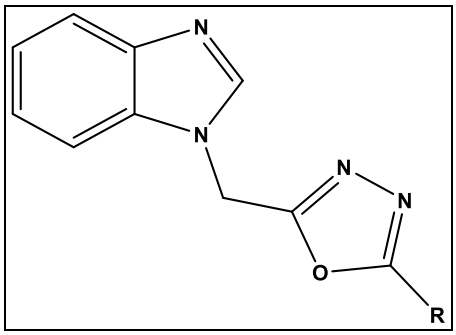
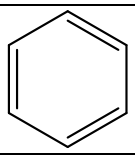
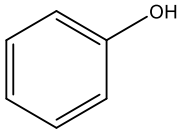
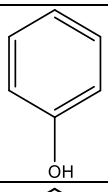
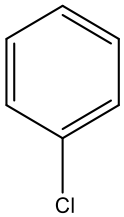
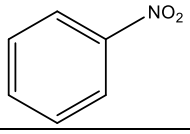


Fig 2: Substituted Benzimidazole-Oxadiazole (T_1-T_5) hybrid

Table 1: Physical data of synthesized compounds

Compound	R (Substitute)	Molecular Formula	Molecular weight	Melting point °C	Yield (%)	Colour	Reaction Time Min (MW)
T_1		$C_{16}H_{12}N_4O$	276.30	198	75	Off-White	8-10
T_2		$C_{16}H_{12}N_4O_2$	292.30	148	85	Yellow	7-8
T_3		$C_{16}H_{12}N_4O_2$	292.30	178	82	Gray	9-10
T_4		$C_{16}H_{11}ClN_4O$	310.74	98	74	White	8-10
T_5		$C_{16}H_{11}N_5O_3$	321.30	168	65	Yellow	8-10

2-((1H-benzo[d]imidazol-1-yl) methyl)-5-phenyl-1,3,4-oxadiazole-T_1

Protocol of the H-1 NMR (VARIAN 400MHz NMR): Solvent: $CDCl_3$

C-H 8.16 (benzimidazole), C-H 7.64 (benzimidazole), C-H 7.64 (benzimidazole), C-H 8.02 (1-benzene) 1-C*R, C-H 7.20 (benzimidazole), C-H 7.27 (benzimidazole), C-H 8.02 (1-benzene)1-C*R, C-H 7.62 (1-benzene)1-C*R, C-H 7.62 (1-benzene) 1-C*R, C-H 7.62 (1-benzene), CH2 4.99 (methylene) alpha-N*R IR(KBr) 3050 cm^{-1} (aromatic C-H),1590-1630 cm^{-1} (C=N), 1500-1600 cm^{-1} (aromatic C=C), 3300 cm^{-1} (N-H),1250-1350 cm^{-1} (C-O or C-N),700-900 cm^{-1} (aromatic C-H)

2-(5-((1H-benzo[d]imidazol-1-yl) methyl)-1,3,4-oxadiazol-2-yl)phenol-T_2

H-1 NMR (VARIAN 400MHz NMR): Solvent: $CDCl_3$ (ppm rel. to TMS) O-H 9.61 (alcohol)1-C*R, C-H 8.16 (benzimidazole), C-H 7.64 (benzimidazole), C-H 7.64 (benzimidazole)1-C*R, C-H7.60 (1-benzene) 1-O1-C*R,C-H 7.20 (benzimidazole), C-H 7.27 (benzimidazole) CH 7.32 (1-benzene)1-C*R, C-H 7.06 (1-benzene), CH2 4.99 (methylene) 1 alpha-N*R IR(-KBr) 3420 cm^{-1} (O-H stretch), 3260 cm^{-1} (N-H stretch),1700 cm^{-1}C=O stretch (triazolone) 1610 cm^{-1} C=N stretch,1240 cm^{-1} C-O stretch, 760-800 cm^{-1}(aromatic C-H bending).

4-(5-((1H-benzo[d]imidazol-1-yl) methyl)-1,3,4-oxadiazol-2-yl)phenol-T_3

H-1 NMR (Lib=SU Solvent=$CdCl_3$400 MHz): $CDCl_3$ (ppm rel. to TMS)O-H 9.67 (alcohol)1-C*R, CH 8.16 (benzimidazole) C-H 7.64 (benzimidazole), C-H 7.64 (benzimidazole), C-H 6.91 (1-benzene)1-O, C-H 7.85 1-benzene 1-C*R, C-H 6.91 (1-benzene)1-C*R, C-H 7.20 (benzimidazole) C-H 7.27(benzimidazole), C-H 7.85 (1-benzene)1-O CH2 4.99 (methylene)1 alpha-N*R IR(-KBr) 3400-3200 cm^{-1} Phenolic OH, 3300-3150 cm^{-1} (N-H stretch of benzimidazole) 2935-2850 (aliphatic C-H), 1700-1680 C=O, 1650-1600 C=N/conjugated C=O/(aromatic C=C), 1250-1200 C-O (phenolic/ether). 1100-1000 C-N/C-O. 900-700 aromatic C-H.

2-((1H-benzo[d]imidazol-1-yl) methyl)-5-(2-chlorophenyl)-1, 3, 4-oxadiazole-T_4

H-1 NMR (VARIAN 400MHz NMR): Solvent: $CDCl_3$ (ppm rel. to TMS)C-H 8.16 (benzimidazole), C-H 7.64 (benzimidazole), C-H 7.64 (benzimidazole), C-H 7.61 (1-benzene)1-Cl, C-H 7.71 (1-benzene)1-Cl 1-C*R, C-H 7.20 (benzimidazole), C-H7.27(benzimidazole), C-H 7.38 (1-benzene) 1-Cl, C-H 7.38 (1-benzene) 1-C*R, C-H2 4.99 (methylene) 1 alpha-C*R IR(-KBr) ~3300 cm^{-1} (NH), 2930-2850 cm^{-1} (CH_2), 1700-1680 cm^{-1} (s, C=O), 1650-1600 cm^{-1} (C=N/aromatic C=C), 1500-1450 cm^{-1} (aromatic), 1250-1200 cm^{-1} (C-O/C-N), 900-700 cm^{-1} (aromatic C-H), 750-710 cm^{-1} (C-Cl).

2-((1H-benzo[d]imidazol-1-yl) methyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole-T_5

H-1 NMR (VARIAN 400MHz NMR): Solvent: $CDCl_3$CH 8.16 benzimidazole, C-H 7.64 benzimidazole, C-H 7.64 (benzimidazole), C-H 8.41 (1-benzene) 1-N(=O)=O 1-C*R, C-H 0 8.23 (1-benzene) 1-N(=O)=O 1-C*RCH 8.41 (1-benzene)1-N(=O)=O, C-H 7.20 (benzimidazole), C-H 7.27 (benzimidazole), C-H 8.23 (1-benzene)1-N(=O)=O, CH2 4.99 (methylene)1 alpha-N*R IR(-KBr) 3420 (NH),3120-3000 (aromatic C-H), 2950-2850 (aliphatic CH_2); 1650-1580 (C=N/aromatic C=C); 1525 (s, NO_2 asymmetric); 1345 (NO_2 symmetric) 1260-1100 (C-O/C-N); 900-700 (aromatic C-H

Conclusion

In short, we have built a compact, microwave-accelerated, and sustainable synthetic method of the efficient reagent preparation of a sequence of benzimidazole-oxadiazole hybrids (T_1-T_5). The multistep process-starting with readily accessible benzimidazole, through the steps of esterification, formation of hydrazide, Schiff base condensation and finally cyclization-gives the target heterocycles in high overall yield and good purity as evidenced by IR, 1H NMR and TLC. The chloramine-T catalyzed rapid microwave-assisted cyclization has a significant impact on the reaction time and yields that are significantly shorter in time in comparison with the traditional heating conditions. The resultant library of benzimidazole-oxadiazole hybrids are expected to show diverse pharmacological activities and thereby have scope for further research and potential discovery of new drugs.

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