

Efficient Microwave-Assisted Synthesis of Novel Benzimidazole-Linked Pyrazole Derivatives

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Abstract

A series of novel (2-aryl-1H-benzo[d]imidazol-1-yl)acetohydrazide (IIIa-g) and corresponding of 1-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)-2-(2-(aryl)-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVa-g) have been synthesized. The former compounds (IIIa-g) were obtained by the reaction of ethyl 2-(aryl-1H-benzo[d]imidazol-1-yl)acetate (IIIa-g) and ethyl acetoacetate. The 2-(aryl-1H-benzo[d]imidazol-1-yl)acetohydrazide (IIIa-g) undergoes cyclocondensation with ethyl acetoacetate in the microwave irradiation condition leads to the formation of a target five-membered pyrazole compound. That is 1-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)-2-(2-(aryl)-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVa-g). The microwave-assisted protocol afforded the target pyrazole derivatives in good yields within a short reaction time. The structures of the synthesized compounds were confirmed by elemental analyses, IR, ¹H-NMR and Mass spectra.

Keywords: pyrazole compound, Microwave-assisted, Novel, Elemental analyses.

Introduction

Pyrazole is a five-membered important class of heterocyclic compounds the ring possesses two adjacent nitrogen atoms shows remarkable biological activities (Salahuddin et al., 2017) . Compounds containing pyrazole ring system are known to exhibit antimicrobial (Luczynski & Kudelko, 2022; Panneerselvam & Geete Ganesh, n.d.) , antitubercular (de Andrade Danin Barbosa & de Aguiar, 2019) , antifungal (Panneerselvam & Geete Ganesh, n.d.), anticonvulsant, anti-inflammatory and anticancer properties. The naturally occurring nitrogen-containing pyrazole derivatives have pharmacological importance, making this heterocyclic system an indispensable structural motif in modern drug discovery (Maheshkumar et al., 2021) . In recent years, the combination of two biologically active heterocyclic systems within a single molecular framework has emerged as an effective strategy for developing compounds with biological potential (S et al., 2025; Sisodia et al., 2022) . The combination of benzimidazole and pyrazole nuclei in the same molecule may lead to compounds possessing improved physicochemical and pharmacological properties (Basu et al., 2013; Campodónico et al., 2010) . Therefore, the synthesis of benzimidazole-linked pyrazole derivatives has gained considerable importance (7.R. Kalirajan 03-IJPER-R.K, n.d.; Pal et al., 2008) .

A total of seven novel pyrazole derivatives (IVa–g) bearing different aryl substituents were synthesized. Microwave-assisted synthesis significantly reduced the reaction time while affording the desired products in good to excellent yields (Majumder et al., 2013a, 2013b) .Microwave-assisted organic synthesis has become a powerful technique in synthetic chemistry because of shorter reaction time, higher yield, cleaner reactions and reduced solvent consumption. microwave-assisted synthesis is considered an eco-friendly and efficient approach for the preparation of heterocyclic compounds(Sun et al., 2014; Tok & Koçyiğit-Kaymakçioğlu, 2023) .

In the present work, an attempt has been made to synthesize a series of novel 1-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)-2-(2-(aryl)-1H-benzo[d]imidazol-1-yl)ethan-1-one derivatives through a multi-step synthetic route under microwave irradiation conditions. The synthesized compounds were characterized on the basis of their physical properties, elemental analysis and spectral studies including IR, ¹H-NMR and Mass spectroscopy. The spectral data confirmed the formation of the desired heterocyclic systems and the successful synthesis of the target molecules.

Materials and Methods

Synthesis involved the use of various chemicals, including Benzaldehyde and its substituted derivatives, along with Sodium meta-bisulfate, o-phenylenediamine, ethyl chloroacetate, hydrazine hydrate, K₂CO₃, ethyl acetoacetate, KOH and NaOH. Common solvents such as ethanol, methanol, and glacial acetic acid 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.

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 all used in the experimental setup (analytical grade). Additionally, a vacuum pump was used. Throughout the investigation, borosilicate glassware was used, cleaned with a chromic acid solution, rinsed with distilled water, and dried before use. IR spectra were recorded at the Accu Analytical Lab (Instrument ID No: AA-ID-002 IR(KBr), ¹H NMR spectra were obtained on a 400 MHz spectrometer using CDCl₃ as a solvent

Experimental Part

The reagents substituted benzimidazole used in synthesis of synthesis of 1-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)-2-(2-(aryl)-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVa-g) have been prepared by the already known methods. Step wise synthetic procedure for preparation of pyrazole derivative was given below.

1.Synthesis of the substituted Benzimidazole

O-phenyldiamine (2mmol), benzaldehyde (2mmol) and sodium meta bisulfite (4 mmol) were added 20 ml of ethanol and water (9:1v/v) and mixture was stirred constantly at a room temperature for two hours. The reaction progress was monitor by using TLC, after reaction completion reaction mixture was subjected to the vacuum filtration, dried and recrystallized from ethanol to obtain pure substituted benzimidazole (Ia-g)

1.Synthesis of Compound II (N-alkylation of Benzimidazole) A mixture of substituted benzimidazole (1.0 equiv) was dissolved in ethanol (20–30 mL). To this solution, ethyl chloroacetate (1.1–1.2 equiv) was added slowly with stirring. The reaction mixture was subjected to microwave irradiation (MW) for 11–13 minutes. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and poured into ice-cold water. The precipitated solid was filtered, washed with water, and recrystallized from ethanol to afford ethyl 2-(2-(aryl)-1H-benzo[d]imidazol-1-yl)acetate(**IIa-g**).

2.Synthesis of Compound IIIa–g (Hydrazide formation)

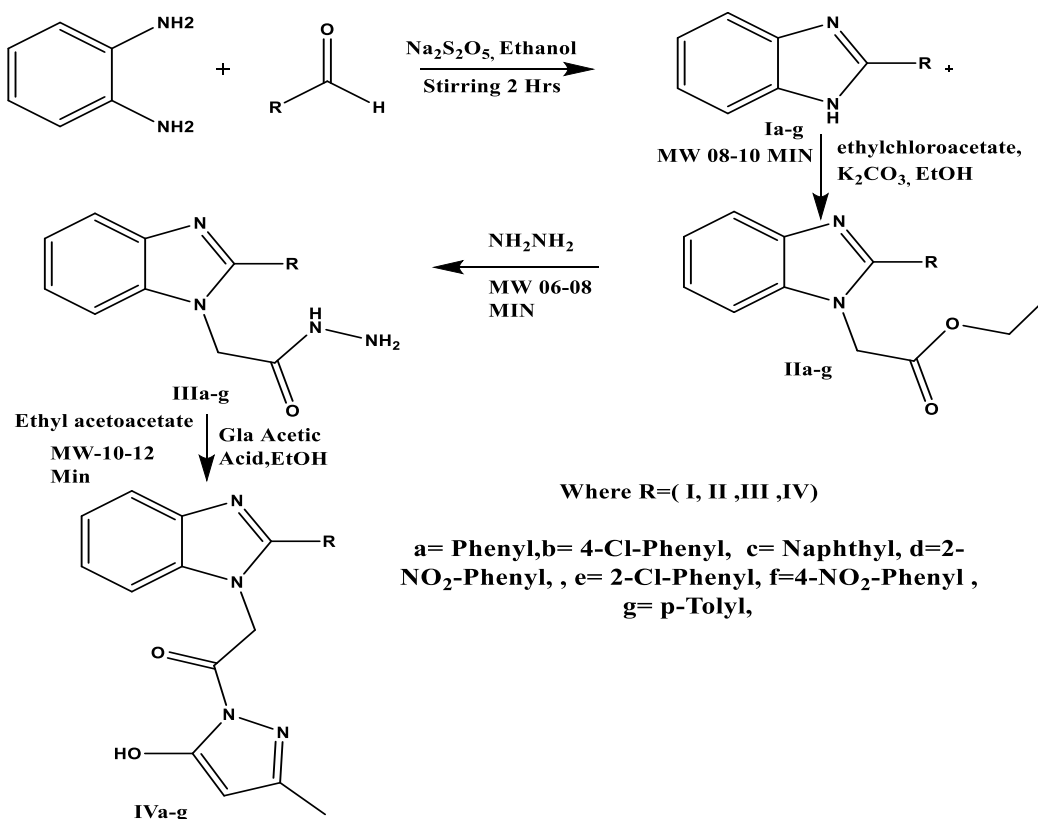
To the solution of ethyl 2-(2-(aryl)-1H-benzo[d]imidazol-1-yl)acetate(**IIa-g**) in ethanol (20 mL), hydrazine hydrate (2.0–3.0 equiv) was added dropwise. The reaction mixture was subjected to microwave irradiation After completion; the mixture was cooled and poured into ice water. The solid obtained was filtered, washed with cold ethanol, and dried to yield acid hydrazide derivatives **IIIa–g** (2-(2-aryl-1H-benzo[d]imidazol-1-yl)aceto hydrazide)

3. Synthesis of Compound (IVa–g) Aryl-1H-benzo[d]imidazol-1-yl)-1-(3-methyl-1H-pyrazol-1-yl)ethan-1-one

The mixture of acid hydrazide ((2-(2-aryl-1H-benzo[d]imidazol-1-yl)aceto hydrazide **IIIa-g**) and acetylacetone was irradiated under microwave for 8–10 min. The reaction involves condensation between the hydrazide and acetylacetone, resulting in the formation of the corresponding hydrazone intermediate. The hydrazone intermediate undergoes intramolecular nucleophilic attack followed by dehydration leads to the formation of a five-membered pyrazole derivative (IV a-g), that was Aryl-1H-benzo[d]imidazol-1-yl)-1-(3-methyl-1H-pyrazol-1-yl)ethan-1-one (**IVa-g**).

Result and Discussion

The synthetic strategies for obtaining of the target compounds is showed in **Scheme 1**. The reaction of substituted benzimidazole (Ia-g) with ethyl chloroacetate in the presence of K₂CO₃ yielded molecule (**IIa-g**), which upon reaction with hydrazine hydrate in alcoholic solution to afford desired hydrazide derivative (**IIIa-g**). The compounds (**IVa-g**) were obtained by reaction of compounds (**IIIa-g**) with ethyl acetoacetate. **Table 1** summarizes the main physicochemical properties of compounds **IVa–g**. The yield, reaction time, colour, and melting point varied depending on the aryl substituent present in the molecule. The structures of synthesized compounds were confirmed by ¹H-NMR, IR spectroscopy techniques, Spectral Characterization of the developed substituted hybrid is given below.



Scheme: 1 Synthetic route to synthesize 1-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)-2-(2-(aryl)-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVa-g)

Preparation of 1-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)-2-(2-phenyl-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVa)

IR (KBr, $\nu_{\max}$, cm^{-1}): 3055 (Ar-C-H), 2924 (aliphatic C-H), 1683 (C=O), 1608 (C=N), 1520 (Ar-C=C), 1342 (C-N), 1245 (N-N/C-N). ¹H NMR (400 MHz, CDCl₃, δ ppm): 8.08 (s, 1H, pyrazole-H), 7.69–7.26 (m, 4H, Ar-H, benzimidazole), 8.28–7.50 (m, 5H, Ar-H), 6.03 (s, 1H, pyrazole-H), 4.84 (s, 2H, CH₂), 2.30 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 168.3, 153.3, 148.9, 142.7, 134.2, 132.5, 131.1, 130.6, 129.2, 127.5, 123.0, 123.0, 119.5, 110.0, 108.6, 51.6, 12.9.

Preparation of 2-(2-(4-chlorophenyl)-1H-benzo[d]imidazol-1-yl)-1-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)ethan-1-one (IVb).

Yield: 58.36% **Melting Point**-240 -2420C, **Colour** -milky-white. (Found: C,62.18; H, 4.16; N, 15.27; Cl 9.64 O, 8.70%, C₁₉H₁₅N₄ClO₂, requires: C, 62.22; H, 4.12; Cl, 9.66; N, 15.27; O, 8.72)

IR (KBr, $\nu_{\max}$, cm^{-1}): ~3300–3450 (O-H), 3050 (Ar-C-H), 2920 (aliphatic C-H), 1650–1680 (C=O), 1590–1620 (C=N), 1450–1510 (aromatic C=C), 1200–1300 (C-O). ¹H NMR (400 MHz, CdCl₃, δ): 10.5–12.0 (br s, 1H, OH), 7.55–8.15 (m, 2H, benzimidazole), 7.15–7.50 (m, 4H, Ar-H), 6.95–7.10 (m, 2H, Ar-H), 5.55–5.90 (s, 1H, pyrazole-H), 5.05–5.40 (s, 2H, N-CH₂-CO), 2.25–2.35 (s, 3H, Ar-CH₃), 2.05–2.25 (s, 3H, pyrazole-CH₃).

Preparation of 1-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)-2-(2-(naphthalen-1-yl)-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVc).

Yield: 45.22%, **Melting Point**-250-2510C, **Colour**-white. (Found: C,72.23.; H, 4.71; N, 14.60; O, 8.31%, C₂₃H₁₈N₄O₂, requires C, 72.24; H, 4.74; N, 14.65; O, 8.3). IR (KBr, $\nu_{\max}$, cm^{-1}):~3300–3450 (O-H), 3060 (Ar-C-H), 2920–2850 (aliphatic C-H), 1650–1680 (C=O), 1590–1620 (C=N/C=C), 1450–1500 (Ar-C=C), 1200–1300 (C-O).

¹H NMR (400 MHz, CdCl₃, δ): 10.5–12.0 (br s, 1H, OH), 7.80–8.40 (m, aromatic H of naphthyl/benzimidazole), 7.20–7.75 (m, aromatic H), 5.5–5.9 (s, 1H, pyrazole-H), 5.0–5.4 (s, 2H, N-CH₂-CO), 2.05–2.30 (s, 3H, CH₃).

Preparation of 1-(3-methyl-1H-pyrazol-1-yl)-2-(2-(2-nitrophenyl)-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVd)

Yield: 68. % Melting Point-254-255°C. Colour -light yellow. (Found: C, 60.45; H, 4.2; N, 18.52; O, 16.93%, C₁₉H₁₅N₅O₄, requires C, 60.48; H, 4.01; N, 18.56; O, 16.96).

IR (KBr, $\nu_{\max}$, cm⁻¹): ~3300–3450 (O–H), 3060 (Ar–C–H), 2920 (C–H), 1650–1680 (C=O), 1590–1620 (C=N), 1510–1550 and 1330–1370 (NO₂ asymmetric and symmetric stretching), 1450–1500 (Ar–C=C), 1200–1300 (C–O). ¹H NMR (400 MHz, CdCl₃): δ 10.5–12.0 (br s, 1H, OH), 8.15–8.35 (d, $J \approx 8.5$ –9 Hz, 2H, Ar-H), 7.80–8.10 (m, 2H, benzimidazole-H), 7.55–7.75 (d, $J \approx 8.5$ –9 Hz, 2H, Ar-H), 7.20–7.45 (m, 2H), 5.55–5.90 (s, 1H, pyrazole-H), 5.05–5.40 (s, 2H, N–CH₂–CO), 2.05–2.25 (s, 3H, CH₃).

Preparation of 2-(2-(2-chlorophenyl)-1H-benzo[d]imidazol-1-yl)-1-(3-methyl-1H-pyrazol-1-yl)ethan-1-one (IVe)

Yield: 52.15 % Melting Point-255–257°C. Colour -cream. (Found: C, 62.18; H, 4.13; N, 15.27; Cl 9.63 O, 8.72%, C₁₉H₁₅N₄ClO₂, requires: C, 62.22; H, 4.12; Cl, 9.66; N, 15.27; O, 8.72 ¹H NMR (400 MHz, CdCl₃): δ 10.5–12.0 (br s, 1H, OH), 7.75–8.20 (m, 2H), 7.35–7.70 (m, 3H), 7.15–7.40 (m, 3H), 5.50–5.90 (s, 1H, pyrazole-H), 5.05–5.40 (s, 2H, N–CH₂–CO), 2.05–2.25 (s, 3H, CH₃). ¹³C NMR: δ 160–165 (C=O), 153–160 (C–OH), 145–152 (C=N), 130–140 (C–Cl/quaternary aromatic C), 125–135 (aromatic C), 115–125 (aromatic C), 100–105 (pyrazole C–H), 50–55 (N–CH₂–CO), 10–15 (CH₃).

Preparation of 1-(3-methyl-1H-pyrazol-1-yl)-2-(2-(4-nitrophenyl)-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVf)

Yield: 63.21% Melting Point- 256-257°C. Colour -off-white. (Found: C, 60.44; H, 4.01; , 18.59; O, 16.91%, C₁₉H₁₅N₅O₄, requires C, 60.48; H, 4.01; N, 18.56; O, 16.96).

¹H NMR (400 MHz, CdCl₃): δ 10.5–12.0 (br s, 1H, OH), 7.85–8.25 (m, 3H), 7.50–7.80 (m, 3H), 7.20–7.50 (m, 2H), 5.50–5.90 (s, 1H, pyrazole-H), 5.05–5.40 (s, 2H, N–CH₂–CO), 2.05–2.25 (s, 3H, CH₃). ¹³C NMR: δ 160–165 (C=O), 153–160 (C–OH), 148–155 (C–NO₂/C=N), 135–145 (quaternary aromatic C), 125–140 (aromatic C), 115–125 (aromatic C), 100–105 (pyrazole C–H), 50–55 (N–CH₂–CO), 10–15 (CH₃).

Preparation of 1-(3-methyl-1H-pyrazol-1-yl)-2-(2-(p-tolyl)-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVg).

Yield: 64.81 % Melting Point-235°C. Colour-light yellow

IR (KBr, $\nu_{\max}$, cm⁻¹, ~3300–3450 (O–H), 3060 (Ar–C–H), 2920–2850 (aliphatic C–H), 1650–1680 (C=O), 1590–1620 (C=N/C=C), 1450–1500 (Ar–C=C), 1200–1300 (C–O). ¹H NMR δ 10.5–12.0 (br s, 1H, OH), 7.80–8.40 (m, aromatic H of naphthyl/benzimidazole), 7.20–7.75 (m, aromatic H), 5.5–5.9 (s, 1H, pyrazole-H), 5.0–5.4 (s, 2H, N–CH₂–CO), 2.05–2.30 (s, 3H, CH₃)

Table 1. physicochemical properties of 1-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)-2-(2-(aryl)-1H-benzo[d]imidazol-1-yl)ethan-1-one (IVa–g)

Compound	R Group	Molecular formula	Yield (%)	Reaction time (last Step) min	Colour	MP (°C)
IVa	Phenyl	C ₁₉ H ₁₆ N ₄ O ₂	58	7-8	white	223-224
IVb	4-Cl-Phenyl	C ₁₉ H ₁₅ N ₄ ClO ₂	44	8-9	Milky-White	242
IVc	Naphthyl	C ₂₃ H ₁₈ N ₄ O ₂	45.22	7	white	250
IVd	2-NO ₂ -Phenyl	C ₁₉ H ₁₅ N ₅ O ₄	68	6-7	light yellow	254-255
IVe	2-Cl-Phenyl	C ₁₉ H ₁₅ N ₄ ClO ₂	52.12	8-10	cream	227-228
IVf	4-NO ₂ -Phenyl	C ₁₉ H ₁₅ N ₅ O ₄	63.21	11	Off-white	256-257
IVg	p-Tolyl	C ₂₀ H ₁₈ N ₄ O ₂	64.2	7	Light- yellow	235

Conclusion

In the present investigation, a series of new benzimidazole-based pyrazole derivatives (IVa–g) were synthesized by microwave aided cyclocondensation reaction of 2-(aryl-1H-benzo[d]imidazol-1-yl)acetohydrazides (IIIa–g) with ethyl acetoacetate. The intended compounds were obtained in good yields in a short reaction time by microwave irradiation, which demonstrated the efficiency of the synthetic methodology. The produced compounds

were characterized by elemental analysis, IR, ¹H NMR and mass spectral investigations. The presented approach provides a facile and fast pathway for the synthesis of novel benzimidazole-pyrazole hybrid molecules which can serve as helpful scaffolds for further chemical and biological investigations.

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