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Design and Synthesis of Novel Benzimidazole and Bisbenzimidazole Derivatives

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ABSTRACT

Benzimidazole and its derivatives represent an important class of heterocyclic compounds with significant therapeutic potential. The present study focuses on the synthesis and pharmacological evaluation of benzimidazole and bisbenzimidazole derivatives. The benzimidazole nucleus has been widely recognized for its structural similarity to purines, enabling interaction with various biological targets. In this work, a series of novel derivatives were synthesized using appropriate chemical methods and characterized by standard analytical techniques. The synthesized compounds were evaluated for their pharmacological activities, which may include antimicrobial, anti-inflammatory, or other relevant biological effects. The results demonstrated that several derivatives exhibited promising activity, indicating that structural modifications of the benzimidazole core can enhance biological efficacy. This study highlights the importance of benzimidazole scaffolds in drug discovery and provides a basis for further development of potent therapeutic agents.

Keywords: Benzimidazole, Bisbenzimidazole, Synthesis, Pharmacological evaluation, Heterocyclic compounds, Antimicrobial activity, Drug discovery, Structure–activity relationship.

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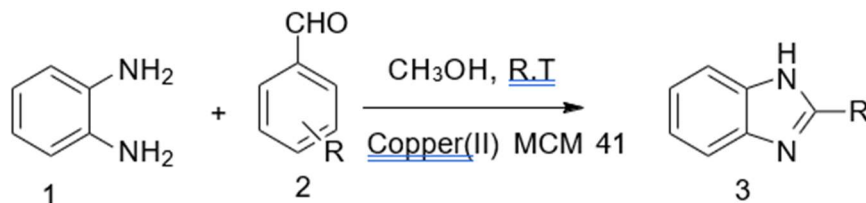
Conflict of interest: None.

INTRODUCTION

The significance of the benzimidazole nucleus dates back to 1944, when Woolley¹ suggested its similarity to purines. Later, Brink^{2,3} identified 5,6-dimethylbenzimidazole as a degradation product of vitamin B₁₂. These findings initiated extensive research on benzimidazole^{2,3}, which is now recognized as an important heterocyclic scaffold due to its structural versatility and ease of modification.

Scheme

The title compounds were synthesized following the synthetic route illustrated in the scheme below.



Synthesis of benzimidazoles and bisbenzimidazoles using Copper MCM 4

Over time, various substitutions on the benzimidazole core have enabled the development of numerous derivatives with diverse chemical properties⁴⁻¹². Recent studies have further highlighted its importance in synthetic chemistry, although comprehensive reports covering its full structural diversity remain limited. Additionally, benzimidazole derivatives serve as valuable intermediates in many organic synthesis reactions.^{5,8,10}

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MATERIALS AND METHODS

Chemicals

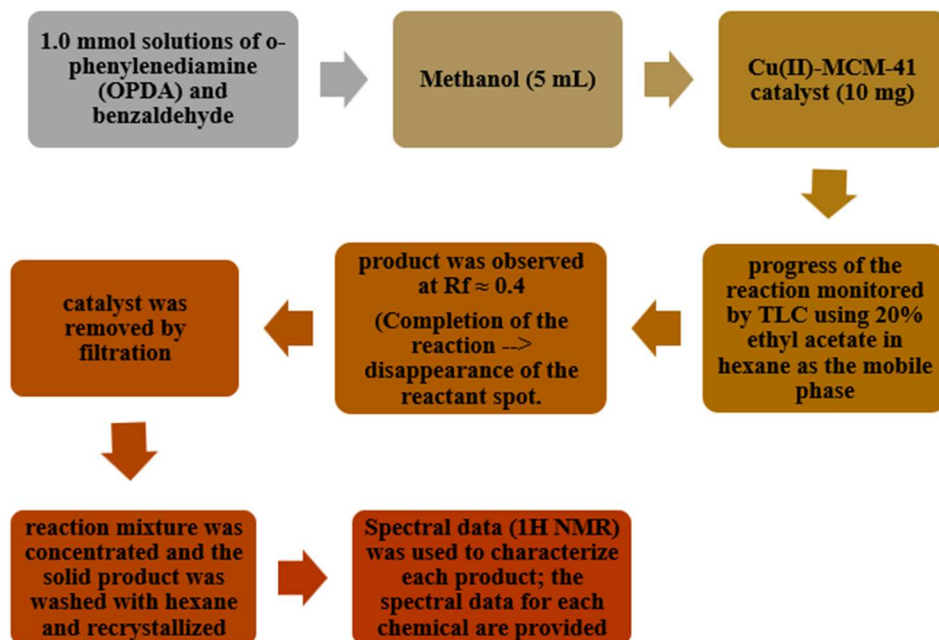
The chemicals and instruments used in the present study were of AR and LR grades, procured from SD Fine, Hychem, and Synthron Research Laboratory Chemicals. All experimental work was conducted at Dr. MACS Bio Pharma Ltd ^{13,14}.

Instruments:

1. Reaction monitoring: Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates (E-Merck Co.). Compounds were visualized either under UV light or by dipping in 10% aqueous potassium permanganate solution.
2. Infrared (IR) spectroscopy: Recorded as KBr disks on a Thermo Nicolet MX-1 FTIR spectrometer.
3. ¹H NMR spectroscopy: Recorded on an NMR spectrophotometer. Chemical shifts are reported in δ (ppm) units relative to TMS as the internal standard.
4. Mass spectrometry: Mass spectra of the compounds were also recorded.

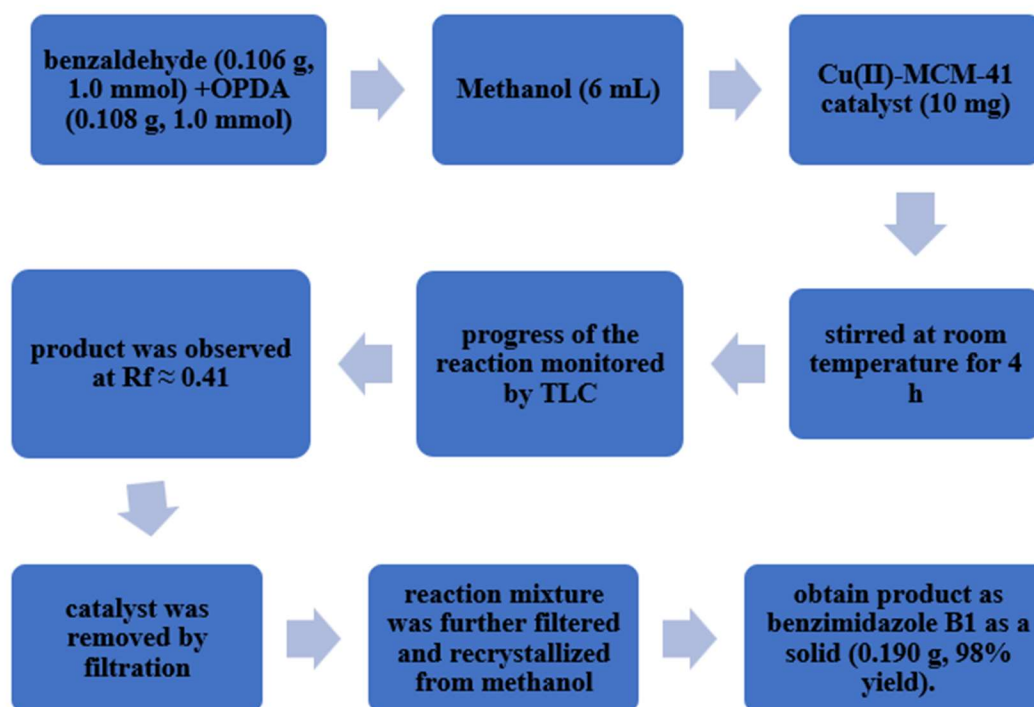
Experimental Procedure:

The general process for making benzimidazoles is as follows:



Synthesis of 2-phenyl-1H-benzimidazole (B1)

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Molecular formula : C₁₃ H₁₀ N₂

Melting Point : 292°C

Yield : 98%;

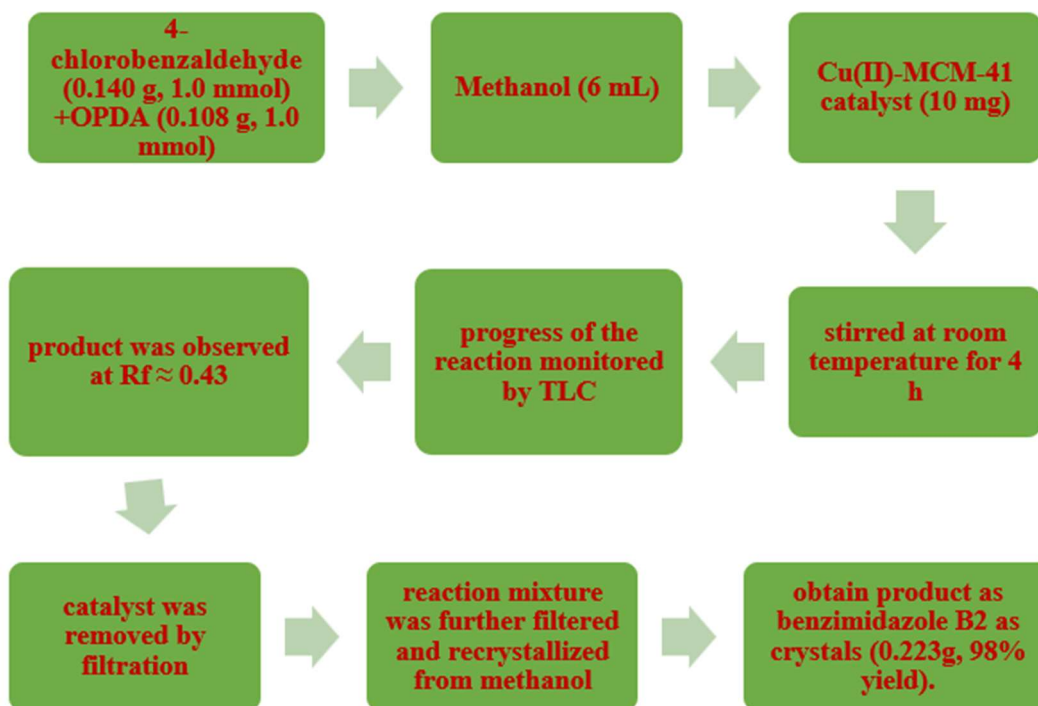
R_f: 0.41

IR (KBr) cm⁻¹ : 3039, 2964, 2638, 1460, 1409, 1309, 1108, 705 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) □ ppm: 7.22 (ddd, *J*=5.91, 3.11, 0.73 Hz, 2 H) 7.42 - 7.52 (m, 3 H) 7.58 - 7.65 (m, 2 H) 8.16 - 8.25 (m, 2 H).

Synthesis of 2-(4-chlorophenyl)-1H-benzimidazole (B2)

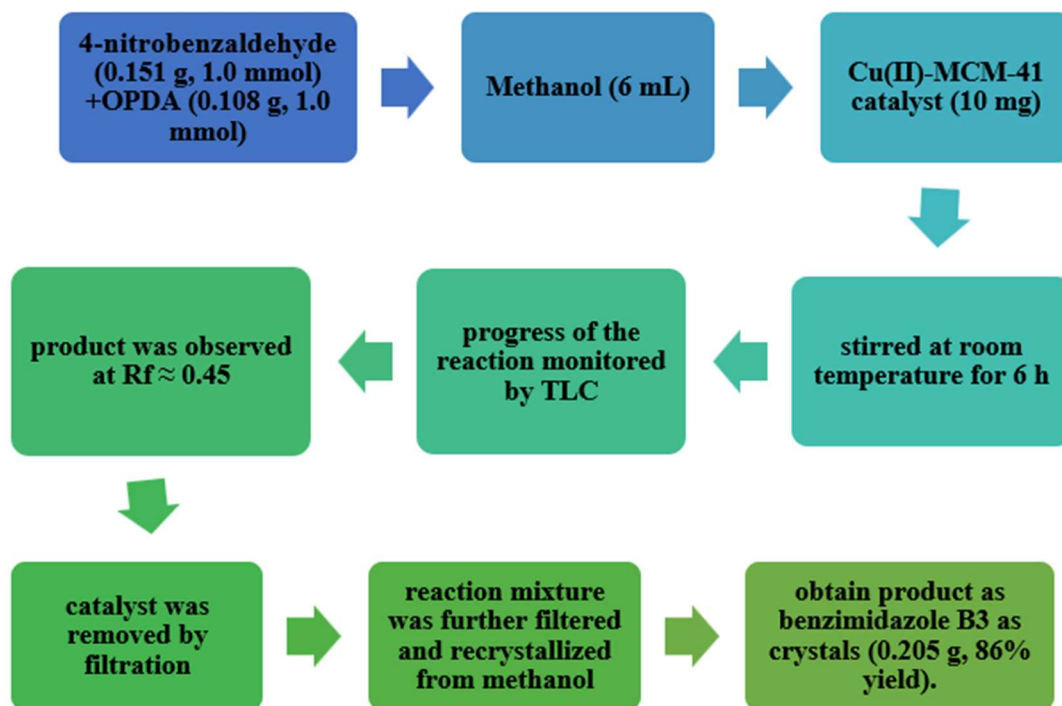
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Molecular Formula	: C ₁₃ H ₉ ClN ₂
Melting Point	: 289°C - 292°C
Yield	: 98%
R_f	: 0.43
IR (KBr) cm⁻¹	: 3049, 2944, 2736, 1429, 1273, 1090, 964, 831, 744 cm ⁻¹
¹H NMR (400 MHz, DMSO-<i>d</i>₆) □ ppm	: 7.212 (d, <i>J</i> =5.37 Hz, 2 H) 7.44 - 7.53 (m, 3 H) 7.82 (s, 1 H) 8.16 - 8.21 (m, 2 H) 12.55 - 12.85 (m, 1 H)

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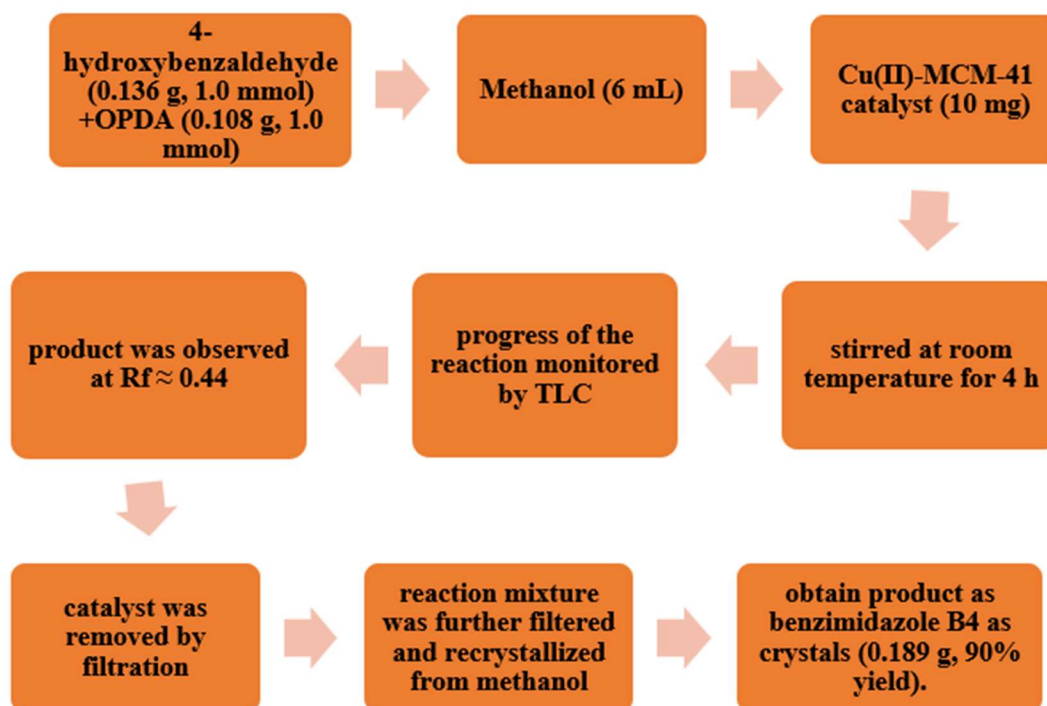
Synthesis of 2-(4-nitrophenyl)-1H-benzimidazole (B3)



Molecular Formula	: $C_{13}H_9N_3O_2$
Melting Point	: 310°C -314°C
Yield	: 86%
R_f	: 0.45
IR (KBr) cm^{-1}	: 3567, 3064, 1628, 1527, 1342, 783 cm^{-1}
1H NMR (400 MHz, DMSO- d_6) δ ppm	: 7.20 - 7.31 (m, 2 H) 7.56 (d, $J=7.81$ Hz, 1 H) 7.67 (d, $J=7.80$ Hz, 1 H) 7.74 - 7.76 (m, 1 H) 7.87 (t, $J=7.57$ Hz, 1 H) 7.97 (d, $J=7.06$ Hz, 1 H) 8.02 (d, $J=8.04$ Hz, 1 H) 13.05 (br. s., 1 H)

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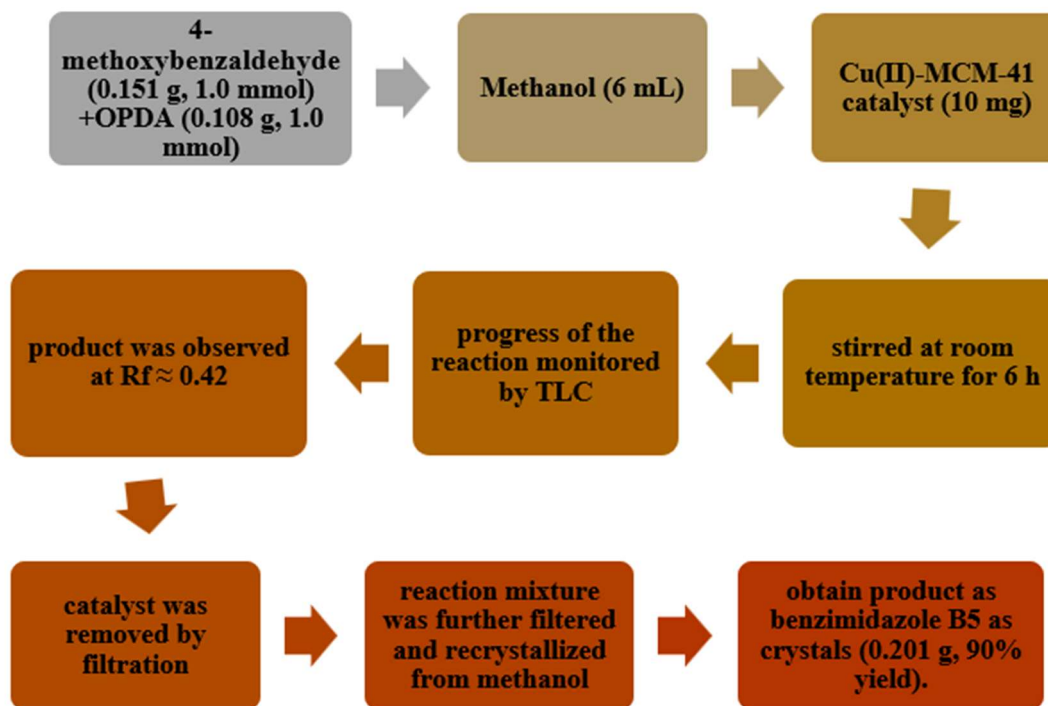
Synthesis of 4-(1H-benzimidazole-2-yl) phenol (B4)



Molecular Formula	: C ₁₃ H ₁₀ N ₂ O
Melting Point	: 290°C-294°C
Yield	: 90%
R_f	: 0.44
IR (KBr) cm⁻¹	: 3286, 3061, 1581, 1456, 1230, 729 cm ⁻¹
¹H NMR (400 MHz, DMSO-d₆) □ ppm	: 6.91 (d, <i>J</i> =7.80 Hz, 1 H) 7.20 (t, <i>J</i> =6.95 Hz, 2 H) 7.35 (t, <i>J</i> =7.44 Hz, 1 H) 7.52 (d, <i>J</i> =7.32 Hz, 1 H) 7.57 - 7.68 (m, 3 H) 9.75 (s, 1 H) 12.83 (br. s., 1 H)

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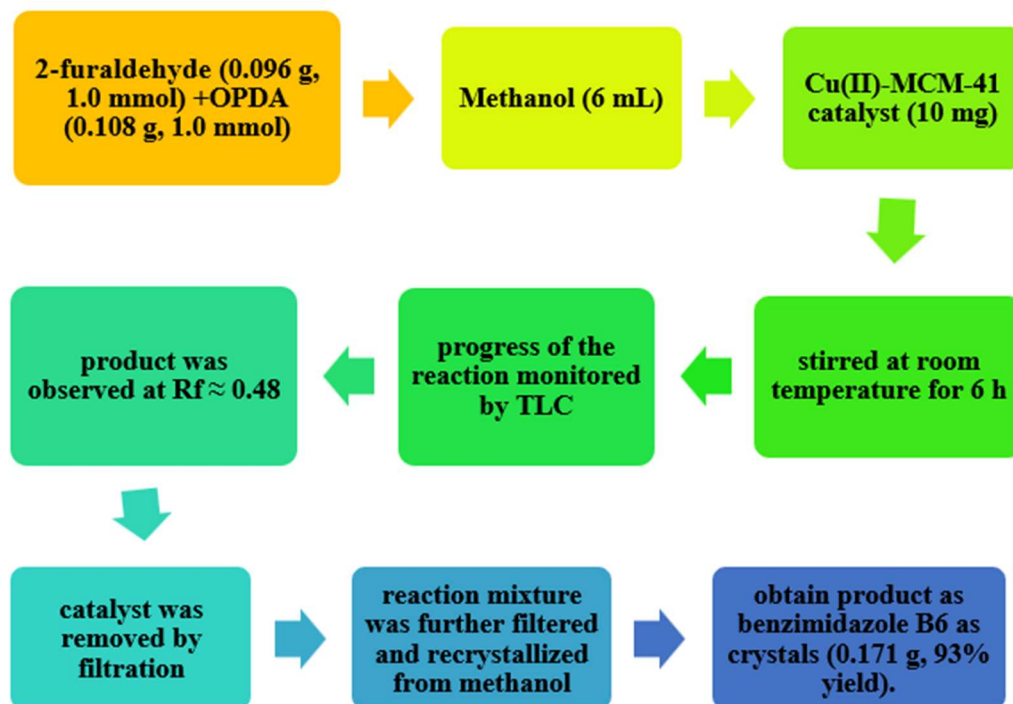
Synthesis of 2-(4-methoxyphenyl)-1H-benzimidazole (B5)



Molecular Formula	: C ₁₄ H ₁₂ N ₂ O
Melting Point	: 226°C
R_f	: 0.42
Yield	: 90%
IR (KBr) cm⁻¹	: 3566, 3039, 1610, 1435, 1259, 1184, 1034, 833, 733 cm ⁻¹
¹H NMR (400 MHz, DMSO-<i>d</i>₆) □ ppm	: 2.43 (d, <i>J</i> =7.56 Hz, 3 H) 7.05 (dd, =14.27, 8.17 Hz, 1 H) 7.33 (s, 1 H) 7.39 - 7.50 (m, 1 H) 7.55 (d, <i>J</i> =8.29 Hz, 1 H) 7.62 (m, <i>J</i> =8.54 Hz, 2 H) 8.18 (m, <i>J</i> =8.54 Hz, 2 H) 12.85 (d, <i>J</i> =16.10 Hz, 1 H)

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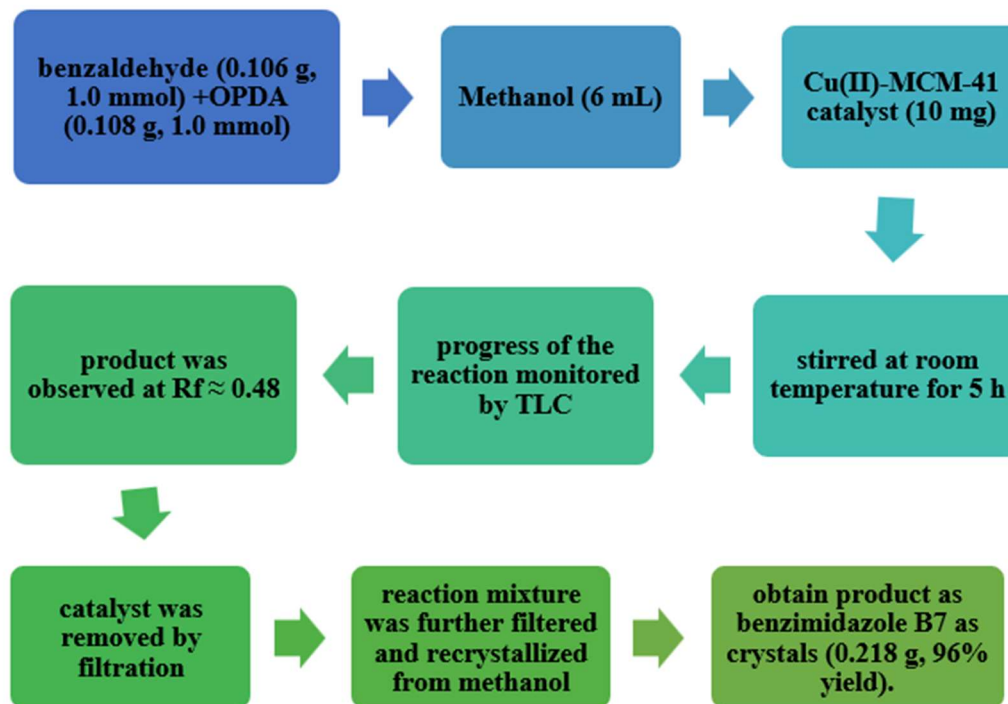
Synthesis of 2-(furan-2-yl)-1H-benzimidazole (B6)



Molecular Formula	: $C_{11}H_8N_2O$
Melting Point	: 287 °C
Yield	: 93%
R_f	: 0.48
IR (KBr) cm^{-1}	: 3049, 2355, 1635, 1417, 1234, 980, 739 cm^{-1}
1H NMR (400 MHz, DMSO- d_6) δ ppm	: 6.71 - 6.76 (m, 1 H) 7.21 (d, $J=3.18$ Hz, 3 H) 7.51 (d, $J=7.08$ Hz, 1 H) 7.62 (d, $J=6.43$ Hz, 1 H) 7.95 (s, 1 H) 12.92 (br. s., 1 H)

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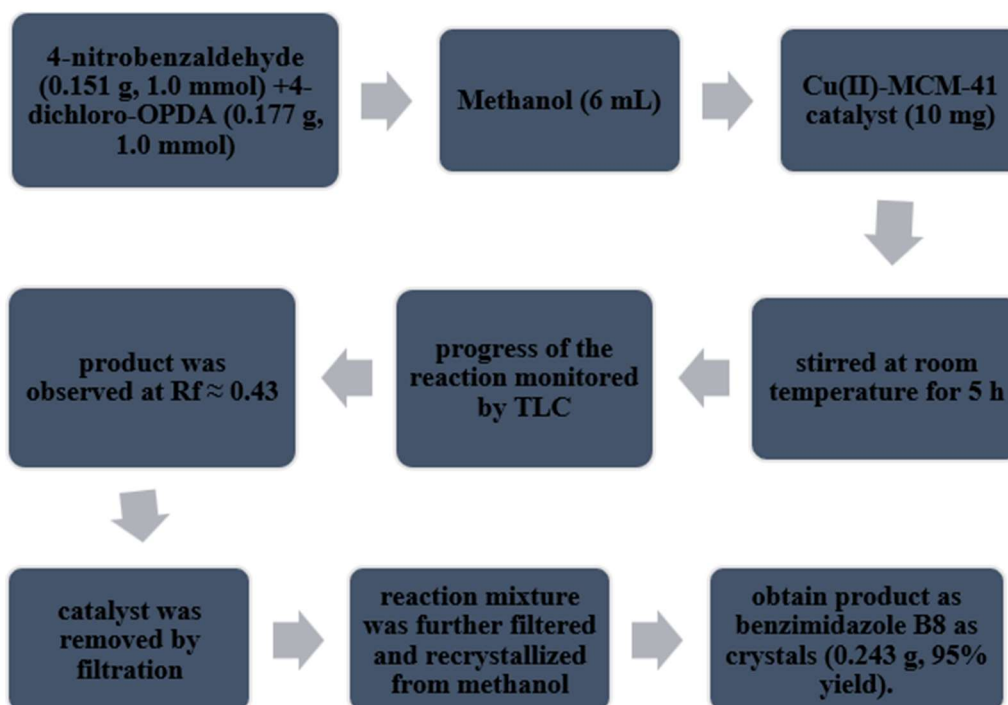
Synthesis of 5-chloro-2-phenyl-1H-benzimidazole (B7)



Molecular Formula	: C ₁₃ H ₉ ClN ₂
Melting Point	: 287°C
Yield	: 96%
R_f	: 0.46
IR (KBr) cm⁻¹	: 3246, 2920, 1417, 1086, 833, 731 cm ⁻¹
¹H NMR (400 MHz, DMSO-<i>d</i>₆) □ ppm	: 7.24 (d, <i>J</i> =8.54 Hz, 1 H) 7.46 - 7.76 (m, 5 H) 8.18 (d, <i>J</i> =7.56 Hz, 2 H) 13.11 (br. s., 1 H)

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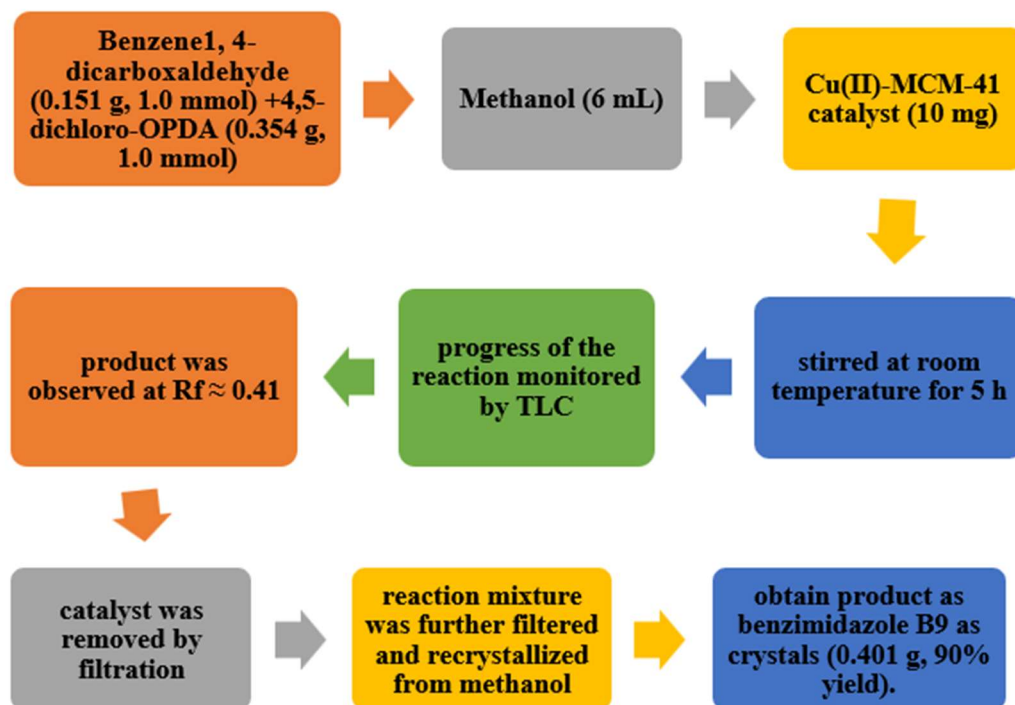
Synthesis of 5, 6-dichloro-2-phenyl-1H-benzimidazole (B8)



Molecular Formula	: C ₁₃ H ₈ Cl ₂ N ₂
Melting Point	: 350°C
Yield	: 95%
R_f	: 0.43
IR (KBr) cm⁻¹	: 3032, 2945, 1684, 1450, 1385, 1288, 966, 858, 696 cm ⁻¹
¹H NMR (400 MHz, DMSO-<i>d</i>₆) □ ppm	: 7.49 - 7.62 (m, 3 H) 7.76 (s, 1 H) 7.95 (br. s., 1 H) 8.18 (d, <i>J</i> =6.83 Hz, 2 H) 13.25 (br. s., 1 H)

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Synthesis of 2,2'-bis(4-chlorophenyl)-1H,1'H-5,5'-bi-benzimidazole (B9)

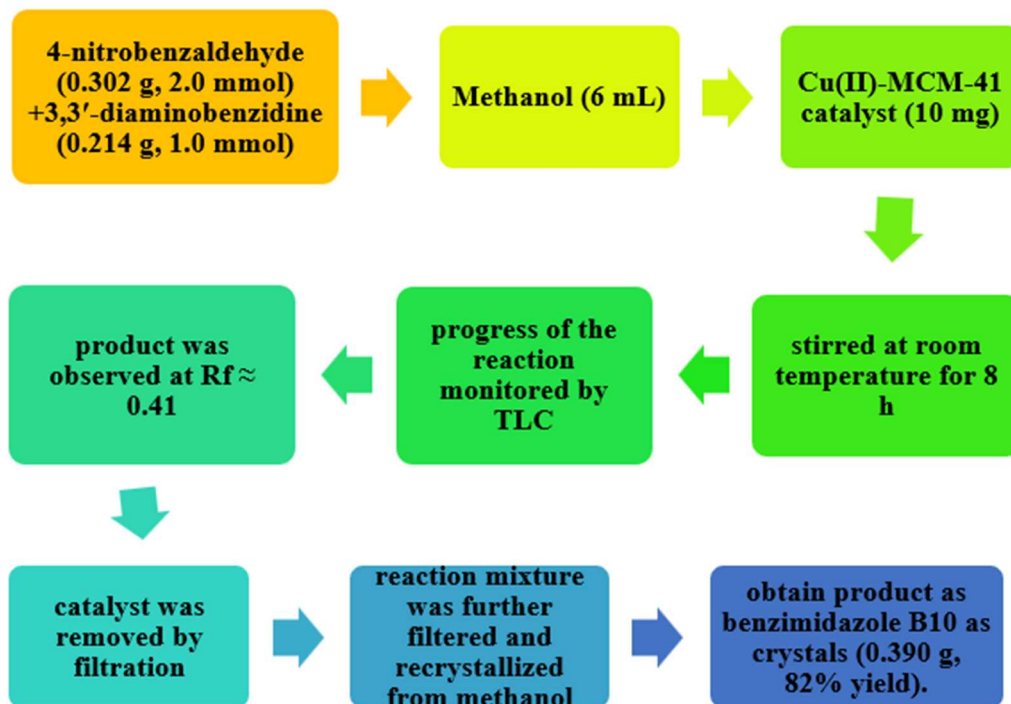


Molecular Formula	: C ₂₀ H ₁₀ Cl ₄ N ₄
Melting Point	: 450°C
Yield	: 90%
R_f	: 0.41
IR (KBr) cm⁻¹	: 3109, 2810, 1626, 1471, 1306, 1061, 930, 802, 698 cm ⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) □ ppm: 7.33 (d, *J*=1.95 Hz, 1 H) 7.35 (d, *J*=1.71 Hz, 1 H) 7.69 (s, 1 H) 7.71 (s, 1 H) 7.73 - 7.76 (m, 2 H) 8.41 (s, 4 H)
Mass spectra : 448.18 (*M*⁺), 449.12 (*M*⁺²)

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Synthesis of 2,2'-bis(4-nitrophenyl)-1*H*,1'*H*-5,5'-bibenzimidazole (B10)

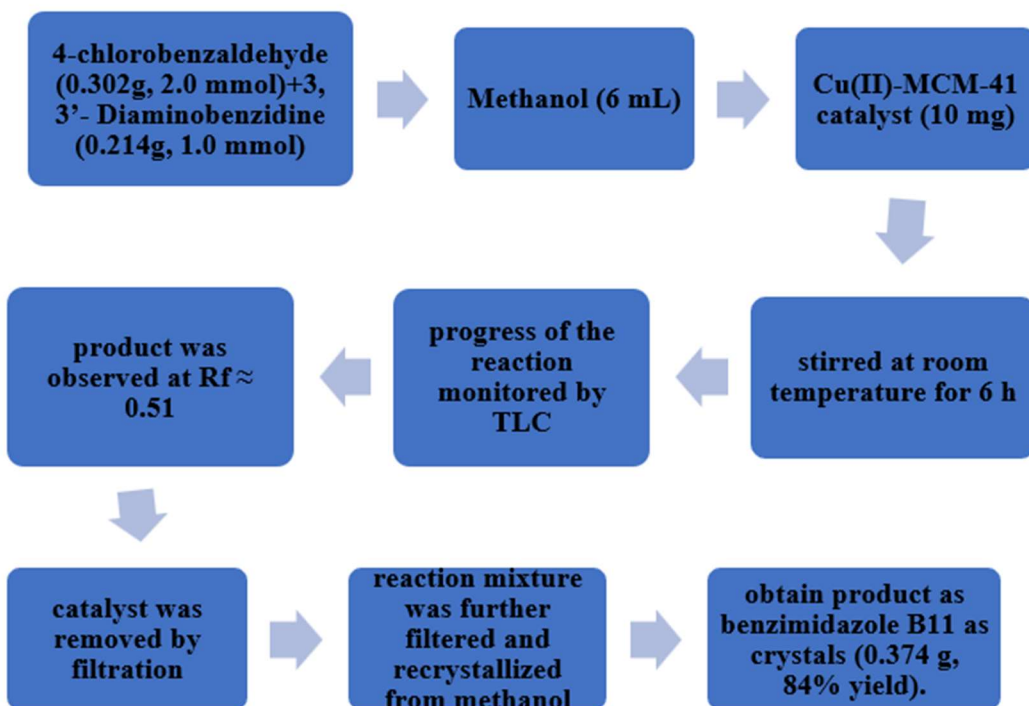


Molecular Formula	: C ₂₆ H ₁₆ N ₆ O ₄
Melting Point	: 550°C
Yield	: 82%
R_f	: 0.41
IR (KBr) cm⁻¹	: 3062, 2862, 2684, 1525, 1446, 1340, 964, 764 cm ⁻¹
¹H NMR (400 MHz, DMSO-<i>d</i>₆) □ ppm	: 7.58 - 7.62 (m, 2 H) 7.66 (d, <i>J</i> =8.54 Hz, 4 H) 7.71 (d, <i>J</i> =8.29 Hz, 2 H) 7.88 (br. s., 2 H) 8.24 (d, <i>J</i> =8.54 Hz, 4 H)

Mass spectra: 475.18 (*M*⁺)

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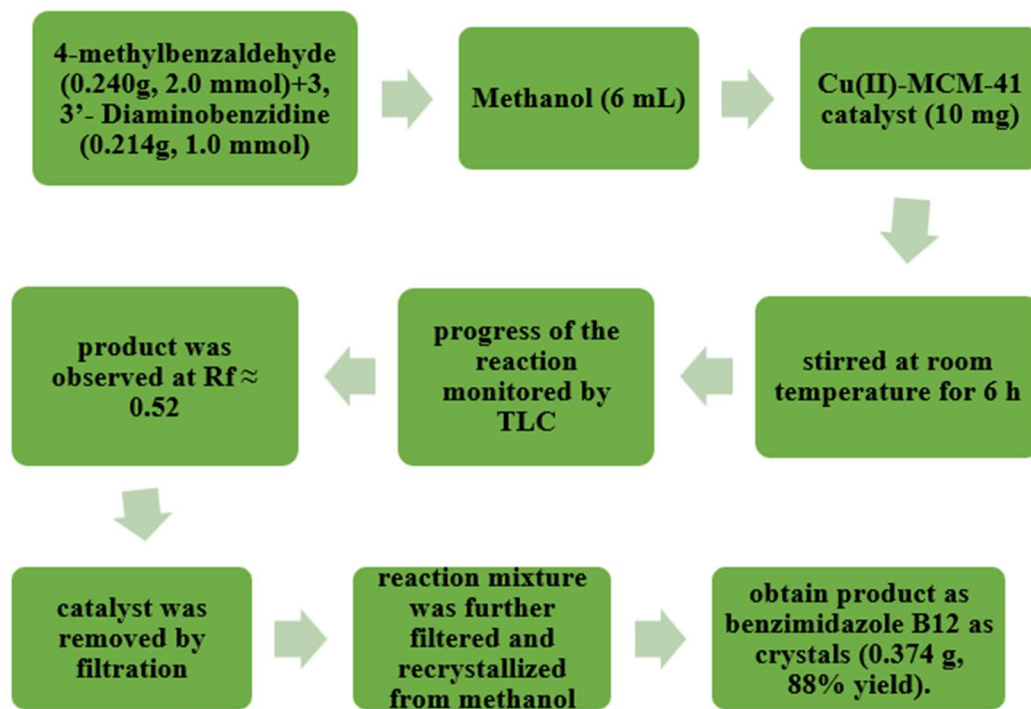
Synthesis of 2,2'-bis(4-chlorophenyl)-1*H*,1'*H*-5,5'-bibenzimidazole (B11)



Molecular Formula	: C ₂₆ H ₁₆ Cl ₂ O ₄
Melting Point	: 645°C
Yield	: 84%
R_f	: 0.51
IR (KBr) cm⁻¹	: 3040, 2877, 1599, 1421, 1292, 1095, 1012, 808,806, 735 cm ⁻¹
¹H NMR (400 MHz, DMSO-<i>d</i>₆) □ ppm	: 7.59 (d, <i>J</i> =1.22 Hz, 1 H) 7.61 (s, 1 H) 7.67 (d, <i>J</i> =8.54 Hz, 4 H) 7.70 (br. s., 1 H) 7.72 (br. s., 1 H) 7.88 (br. s., 2 H) 8.23 (s, 2 H) 8.25 (s, 2 H) 12.79 - 13.38 (m, 1 H)
Mass spectra:	454.18 (M ⁺)

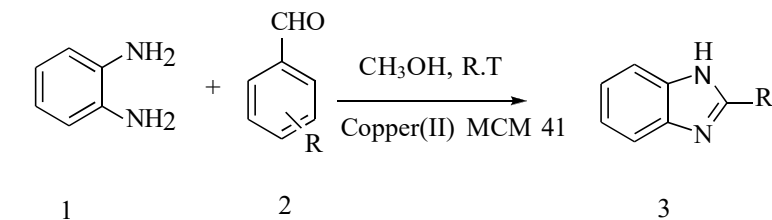
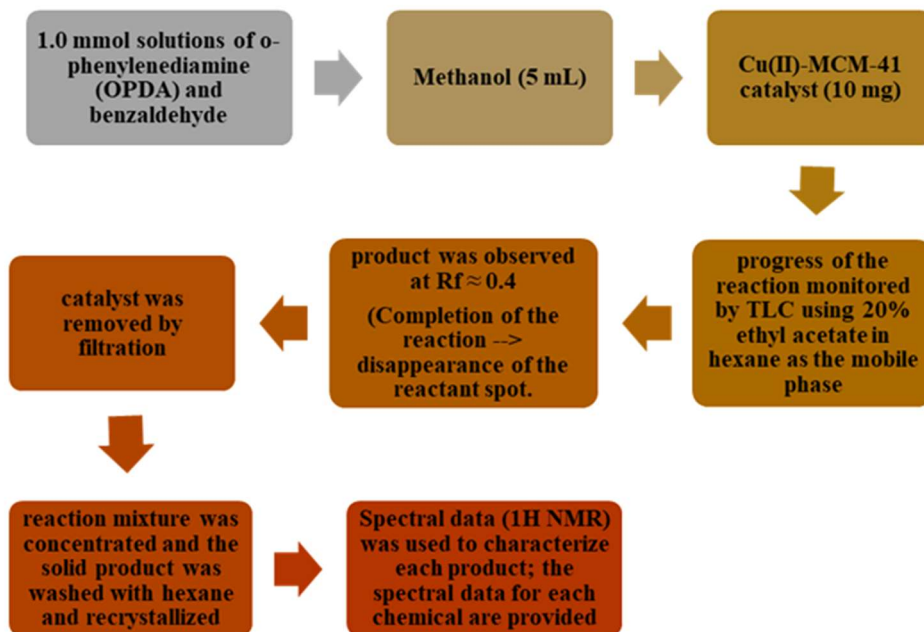
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Synthesis of 2-p-tolyl-5-(2-p-tolyl-1H-benzimidazol-5-yl)-1H-benzimidazole (B12)

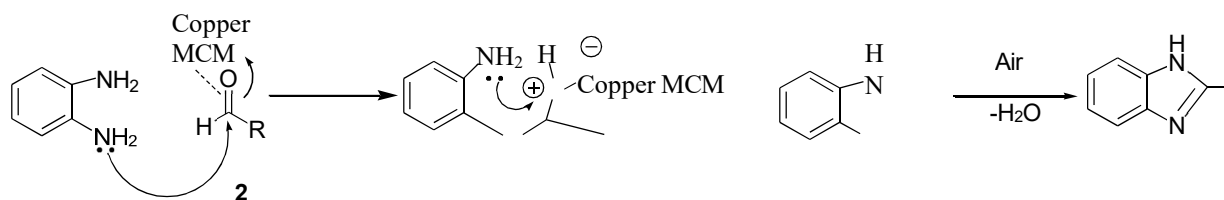


Molecular Formula	: C ₂₈ H ₂₂ N ₄
Melting Point	: 695°C
Yield	: 84%
R _f	: 0.52
IR (KBr) cm ⁻¹	: 3018, 2914, 1624, 1444, 1286, 823, 727, cm ⁻¹
¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) □ ppm	: 2.36 - 2.49 (m, 6 H) 7.39 (d, <i>J</i> =8.05 Hz, 4 H) 7.56 (d, <i>J</i> =8.05 Hz, 2 H) 7.67 (d, <i>J</i> =7.80 Hz, 2 H) 7.74 - 7.98 (m, 2 H) 8.11 (d, <i>J</i> =8.05 Hz, 4 H)
Mass spectra:	414.18 (M ⁺)

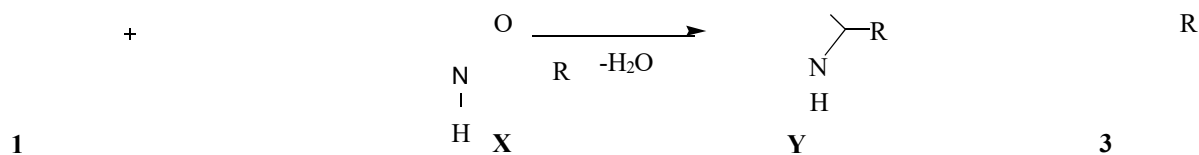
RESULTS AND DISCUSSION

A.Chemistry:
SynthesisGeneral procedure for the synthesis of benzimidazoles¹:

Synthesis of benzimidazoles using Copper MCM 41.



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Plausible mechanism of the above reaction.

Explanation :

Condensation of 1,2-phenylenediamine (1.0 mmol) with benzaldehyde (1.2 mmol, R = Ph) in ethanol at room temperature under open-air conditions in the absence of a catalyst for 6 h resulted in 27.6% of 2-phenylbenzimidazole (3) and 0.1% of 1-benzyl-2-phenyl-1H-benzimidazole (4). Prolonging the reaction to 12 h led to a mixture of 2-phenylbenzimidazole (3, 29.1%) and the side product 1-benzyl-2-phenyl-1H-benzimidazole (4, 2%).¹

Optimization of the catalyst:

In the optimization of the Cu MCM 41 catalyst we observed that there is good % yield at 15 mole % but choose to go with 10 mole percent as per references.

Quantity of Cu (II)MCM 41 catalyst	time (h)	Yield (%)
5	2	90
10		98
15		98.5

Table 5.1: Optimization of catalyst

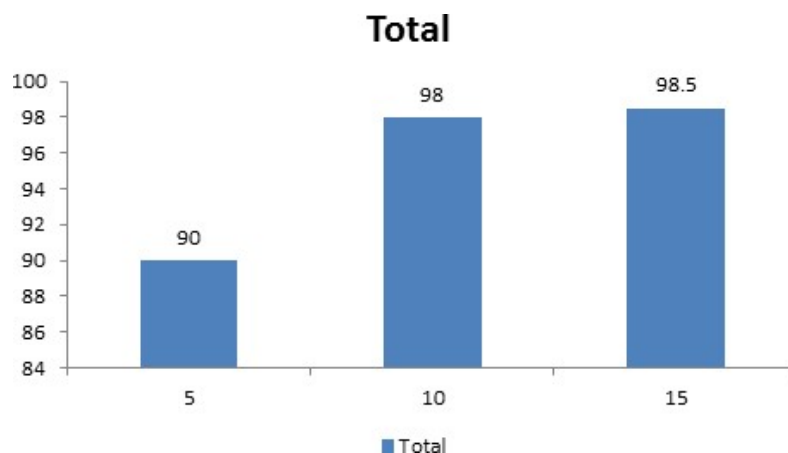


Fig. 5.1: Optimization catalyst

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15 mole percent found to give more percent yield, but 10mole percent more appropriate so we have used for our synthesis.

Recyclability of catalyst:

In recyclability of catalyst it proves that reuse of catalyst can be done properly as shown in the figure.

No. of cycle	Yield (%)
1	98
2	97
3	96

Table 5.2: Recyclability of catalyst.

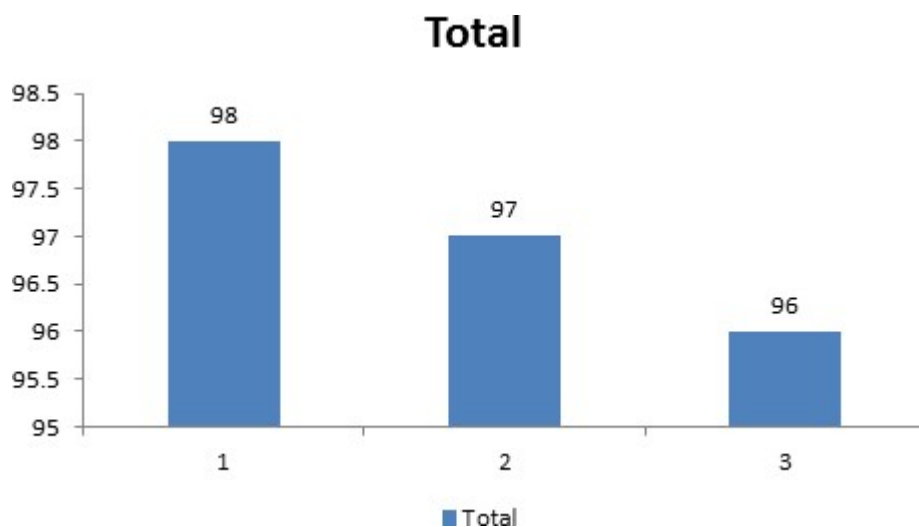


Fig. 5.2 Recyclability of catalyst.

Entry	Diamine	Aldehyde	Product (B) LH	Time (h)	Yield (%)
1				4	96
				2	H ₂

IJDDT, Volume 16 Issue 56s, 2026

RESEARCH PAPER

3			4	98
4			6	86
4			5	90
5			6	90
6			6	93
7			5	96
8			5	95
8			7	80
9			8	82
9			6	84
10			6	88
10			6	88

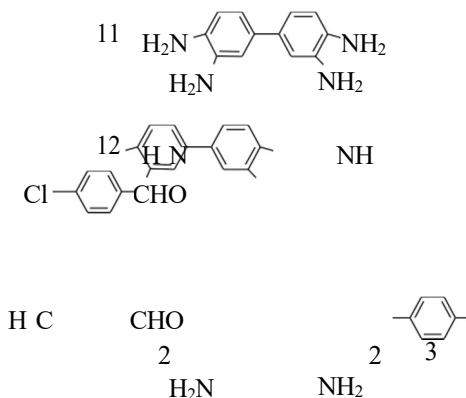
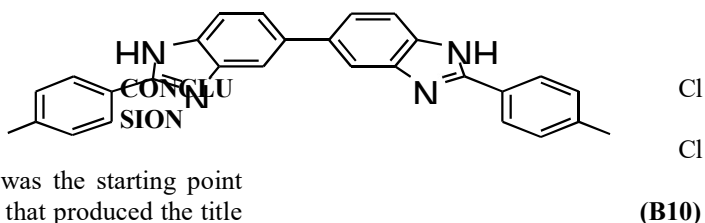


Fig. 9.3. Chart showing total scheme of synthesized compounds - benzimidazoles and bisbenzimidazoles.

The formation of the title compounds was established by IR and ^1H NMR spectroscopy. In the IR spectra of compounds B12 and B10, the loss of peaks corresponding to the initial materials and the appearance of a C–N stretching signal at 1664 cm^{-1} indicated successful formation of the benzimidazole core. Additional peaks were observed around 1650 and 1728 cm^{-1} . The ^1H NMR spectra displayed a singlet at δ 8.42–8.7 ppm corresponding to the NH proton, while a multiplet at δ 6.89–7.68 ppm was observed for the aromatic protons.



Ortho-phenylenediamine was the starting point for the multistep synthesis that produced the title compounds in fair to good yields. These compounds were then identified by their spectral data, including their mass, NMR, and infrared spectra.

Carrageenan-induced inflammation in Wistar rats was used to test the anti-inflammatory properties of all the title compounds. The test substances shielded the animals against inflammation-induced edema to varying degrees (between 55 and 61%), according to the inflammation activity data. The identical substituents over the second position of the imidazoline ring exerted varying biological activity, according to the Structural Activity Relationship (SAR). The compound 2,2'-bis(4-chlorophenyl)-1H,1'H-5,5'-bibenzimidazole (B10) was shown to be the most active among the substituents, with the chlorophenyl moiety exhibiting the most potent activity. This compound will be used as a lead molecule for further development.

Nowadays, a wide range of disorders are treated in clinics using a variety of chemicals developed from benzimidazoles. With over 198 references, the current work attempts to give a thorough and focused analysis of compounds generated from benzimidazoles, providing important information for the creation of molecules that are therapeutically viable. ^{6,8,10,12}

Acknowledgement

The authors express their sincere gratitude to the management and principal of **Bharat Institute of Pharmacy, Ibrahimpatnam**, for providing the necessary facilities, infrastructure, and continuous support to carry out this research work.

The authors also acknowledge the faculty members and laboratory staff of the respective departments for their valuable assistance and cooperation during the experimental work.

Authors contribution:

Aastha Sumit Yadav contributed to the conceptualization of the study, design of the synthetic pathway for benzimidazole and bisbenzimidazole derivatives, and manuscript drafting.

Dr. Duguta Tirumala supervised the research work, guided the pharmacological evaluation, validated the results, and critically revised the manuscript for intellectual content.

Ankita Rameshwar Yadav performed literature review, assisted in synthesis planning, and contributed to interpretation of pharmacological data.

Mudiga Anuradha carried out experimental work related to synthesis and contributed to data collection.

Gangadevi Shirisha contributed to formulation aspects (if applicable), manuscript editing, and final preparation of the document

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