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Synthesis and Characterization of Novel Benzimidazole Derivatives using CdO NPs and their Application as Antibacterial and Antifungal Agents

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ABSTRACT: ***Background:*** *Benzimidazoles are a class of compounds characterized by a fusion of benzene and imidazole rings. This unique structure endows them with a broad spectrum of biological activities, making them invaluable in medicinal and pharmaceutical research. The benzene ring provides aromatic stability, while the imidazole ring offers a site for various chemical modifications, enhancing their versatility and functionality. Benzimidazoles are known for their diverse pharmacological properties, including antimicrobial, antiviral, anticancer, anti-inflammatory, and antiparasitic.* ***Objective:*** *Synthesis of new benzimidazole derivatives and their application as antibacterial and antifungal agents.* ***Methods:*** *The benzimidazole derivatives (A1-A5) were synthesized in high yields by condensing 2-(4-hydroxyphenyl) benzimidazole with different aldehydes (p- nitro benzaldehyde and p- bromo benzaldehyde) and amides (benzamide and acetamide) utilizing cadmium oxide nanoparticle (CdO NPs) as a catalyst.* ***Results:*** *The synthesized benzimidazole derivatives (A1-A5) were characterized using FTIR and 1HNMR spectra, and showed good antibacterial activity (inhibition zone: 5-23 mm) with various concentrations (250, 500, and 1000 mg/L) while the compounds (A1, A3, A4, and A5) also exhibited moderate antifungal activities (inhibition zone: 5-10 mm) except the A2 compound.* ***Conclusions:*** *The antimicrobial and antifungal effectiveness of these synthesized derivatives was evaluated, showing satisfactory antimicrobial activity and suitable antifungal activity for all except the A2 compound. It is recommended that further research and structural modifications of these derivatives be conducted to develop more potent benzimidazole derivatives.*

KEYWORDS: *Benzimidazole; CdO NPs; Antibacterial; Antifungal; NMR spectroscopy*

INTRODUCTION

Benzimidazoles represent fused privileged heterocyclic structures with a broad spectrum of biological and pharmaceutical properties. Synthetic chemists have extensively explored benzimidazole scaffolds, making them one of the most thoroughly investigated compound classes [1]–[7]. The benzimidazole ring system shares a structural resemblance with certain naturally occurring components like purines and vitamin B12. As a result, benzimidazole derivatives tend to engage with biomolecules within living organisms readily. Moreover, benzimidazole comprises two aromatic N-heterocycles that can form hydrogen bonds with enzymes or receptors, either through coordination with metal ions or hydrophobic interactions. Numerous potential antitumor agents have been discovered to incorporate the benzimidazole ring structure [8]–[13]. Magnetic nanoparticles (MNPs), characterized by their tiny size and large surface area, have been introduced as a novel type of catalyst. They show improved catalytic behavior compared to traditional heterogeneous catalysts. Typically, there are synthetic methods used to create benzimidazole derivatives. Creating these benzimidazole compounds usually involves a condensation reaction between o-phenylenediamine and various carbonyl compounds using different catalysts [14]–[17]. The primary shortcomings of the mentioned benzimidazoles synthesis

reactions, which take place in homogeneous environments, include low yields of product, complex and time-consuming work-up procedures, severe reaction conditions, lengthy reaction times, the simultaneous occurrence of various side reactions, and in certain instances, a multi-step synthesis procedure [18]–[22]. The present work aims to synthesize benzimidazole derivatives using cadmium oxide nanoparticles as a catalyst, characterize them, and use them as antibacterial and antifungal agents (see Figure 1).

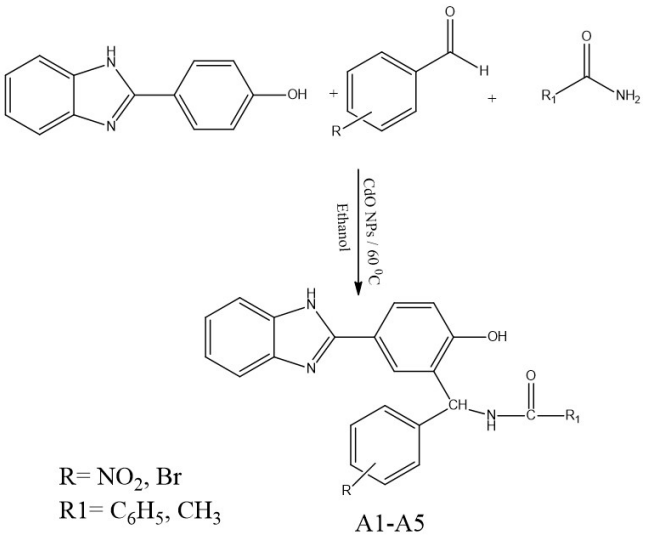

Figure 1. Synthesis of novel benzimidazole derivatives

MATERIALS AND METHODS

Every necessary material was procured from BDH or Sigma-Aldrich and utilized without further purification. The benzimidazole derivatives that were produced were then analyzed using FTIR spectra, with the aid of a Bruker, alpha 2 from Germany. These products were further characterized using ^{1}HNMR spectra through a Bruker Bio Spin GmbH Spectrometer operating at 400 MHz, also from Germany, and this was executed in a deuterated DMSO solvent.

Co-precipitation Method for the Reparation of CdO NPs

Cadmium oxide nanoparticles were formed using a co-precipitation procedure [23]. The cadmium source was $Cd(NO_3)_2.4H_2O$; sodium hydroxide was utilized as the precipitating agent. In a round bottom flask with a magnetic stirrer, 0.015 mole (4.22 g) of $Cd(NO_3)_2.4H_2O$ was dissolved in a (60 mL) mixture of water and ethanol in a 1:1 ratio. The mixture's pH was adjusted to 10 using a 2 M NaOH aqueous solution. This mixture was then stirred at room temperature for the entire night. Following that, the solution was centrifuged at 5000 rpm for 25 minutes. The obtained precipitate pellets were re-dispersed and rinsed with a 1:1 mixture of deionized water and ethanol before being centrifuged and washed again. Finally, the precipitate was dried in an oven at 80 °C for 20 hours to yield the desired product, CdO nanoparticles.

Synthesis of Benzimidazole Derivatives

A mixture consisting of aromatic aldehyde (1 mmol), 2(4-hydroxyphenyl) benzimidazole (1 mmol, 0.21 g), a variety of amide (1 mmol), and CdO NPs catalyst (0.04 g) was prepared using ethanol as a solvent. This mixture was subsequently stirred and kept at a temperature of 60 °C for 6 hrs. After this, the CdO NPs catalyst was separated using a filtration method [24]. Finally, column chromatography was used to purify the crude products using ethyl acetoacetate: hexane (2:1).

Antimicrobial Activity Assay

The antimicrobial activities of compounds (A1-A5) were evaluated using the good diffusion method [25]. The testing was conducted *in vitro* against strains of both Gram-positive bacteria (*Staphylo-*

coccus aureus, *Staphylococcus epidermidis*) and Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*), as well as fungi (*Candida albicans*). The outcomes were then juxtaposed with the influences of conventional antibiotics, specifically Chloramphenicol and Fluconazole.

RESULTS AND DISCUSSION

The synthesis of compounds (A1-A5) has been illustrated in Figure 1. 2-(4-hydroxyphenyl) benzimidazole reacted with different aldehydes and amides to yield (A1-A5) having yields of 90, 83, 87, 92 and 85% respectively. The structures of the compounds were elucidated by analysis of their FTIR and ^{1}HNMR spectral data. The suggested mechanism is shown in Figure 2.

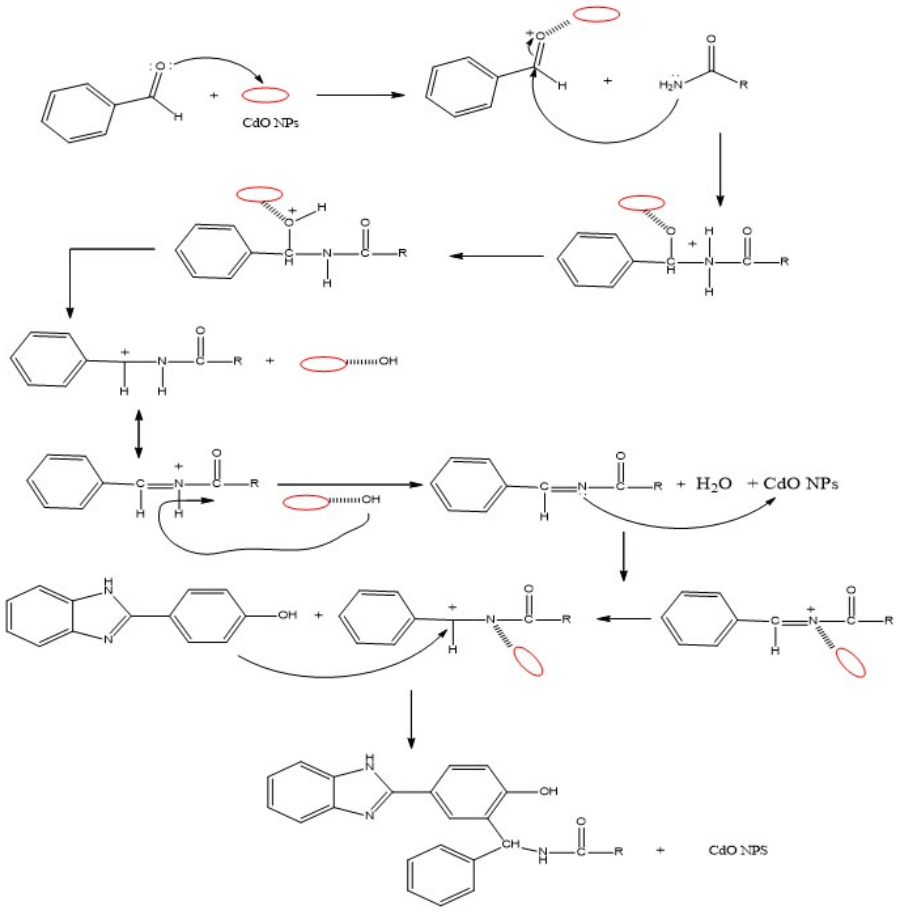

Figure 2. Suggested mechanism of synthesized compounds

N-((5-(1H-benzo[d] imidazol-2-yl)-2-hydroxyphenyl)(4-nitrophenyl)methyl)acetamide (A1). Colour: Brwon, 85% , Rf = 0.72, Oily compound; FTIR (cm^{-1}): 3470 (OH), 3341(NH of imidazole ring), 3193(NH of amide group), 2931&2855(CH aliphatic), 1697(C=O group), 1657(C=N group),1558(C=C group), 1341&1514(NO_2 group); ^{1}HNMR (DMSO-d_6, 400 MHz): δ 12.78(s, 1H, NH of imidazole ring), 9.93(s, 1H, phenolic), 8.43(s, 1H, NH of amide group), 5.31(s, 1H, CH proton between two aromatic rings), 1.23 (s, 3H, CH_3 group), 6.55-8.28 (m, 11H, proton of aromatic ring). Figures 3 and 4 show the FTIR and ^{1}HNMR spectra of A1 compound.

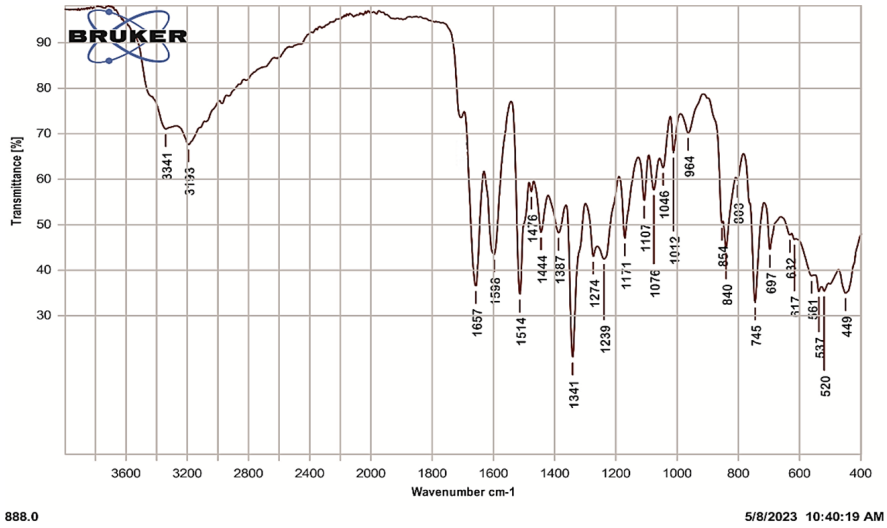

Figure 3. FTIR spectrum of A1 compound

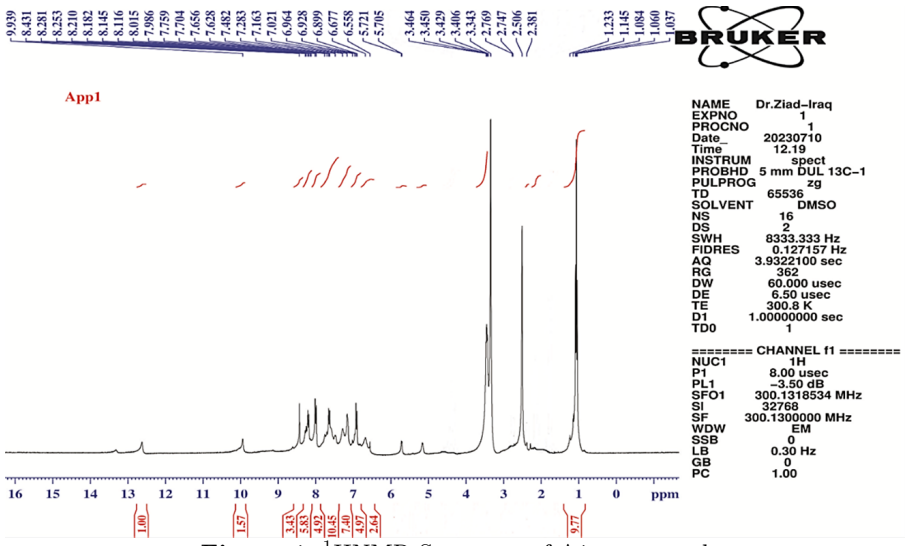

Figure 4. ^{1}HNMR Spectrum of A1 compound

N-((5-(1H-benzo [d]imidazol-2-yl)-2-hydroxyphenyl) (4-hydroxyphenyl) methyl) acetamide (A2). Colour: Brwon, 73%, Rf = 0.77, Oily compound; FTIR (cm^{-1}): 3475 (OH), 3310(NH of imidazole ring), 3163(NH of amide group), 2956&2816(CH aliphatic), 1663(C=O group), 1600(C=N group),1578 &1509 (C=C group), 1213(C-O group); ^{1}HNMR (DMSO-d$_6$, 400 MHz): δ 12.61(s, 1H, NH of imidazole ring), 9.79 (s, 1H, phenolic),10.59(s, 1H, OH of benzimidazole), 8.21 (s, 1H, NH of amide group), 4.35 (s, 1H, CH proton between two aromatic rings), 1.22 (s, 3H, CH3 group), 6.56-8.14 (m, 11H, proton of aromatic ring). Figures 5 and 6 represent the FTIR and ^{1}HNMR spectra of A2 compound.

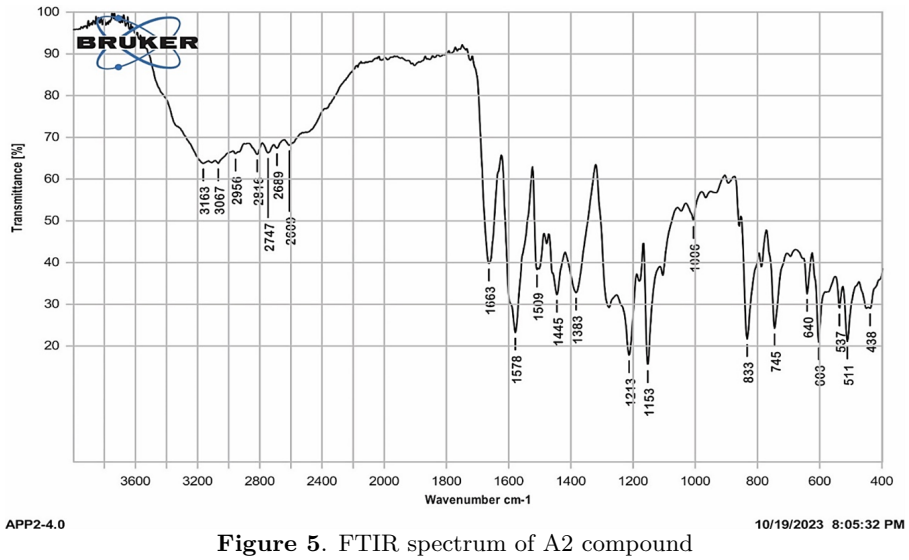

Figure 5. FTIR spectrum of A2 compound

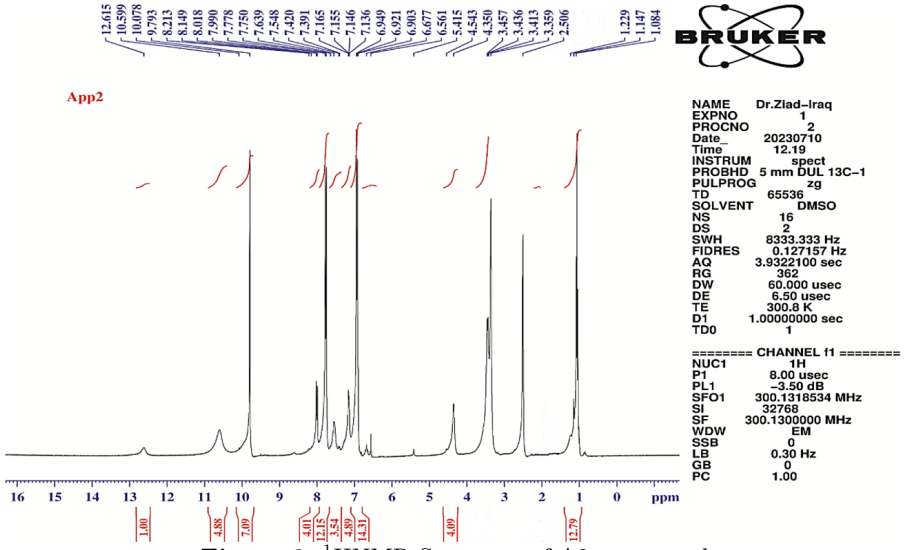

Figure 6. ^{1}HNMR Spectrum of A2 compound

N-((5-(1H-benzo [d]imidazol-2-yl)-2-hydroxyphenyl) (4-bromophenyl) methyl) acetamide (A3). Colour: Brwon, 76%, Rf = 0,76, Oily compound; FTIR (cm^{-1}): 3452 (OH), 3370 (NH of imidazole ring), 3184(NH of amide group), 2971&2893 (CH aliphatic), 1661 (C=O group), 1609 (C=N group), 1587&1498 (C=C group), 963 (C-Br group); ^{1}HNMR (DMSO-d_6, 400 MHz): δ 12.72 (s, 1H, NH of imidazole ring), 9.99 (s, 1H, phenolic), 8.14 (s, 1H, NH of amide group), 4.51 (s, 1H, CH proton between two aromatic rings), 1.21 (s, 3H, CH_3 group), 6.56-8.11 (m, 11H, proton of aromatic ring). The FTIR and ^{1}HNMR spectra of compound A3 are shown in Figures 7 and 8

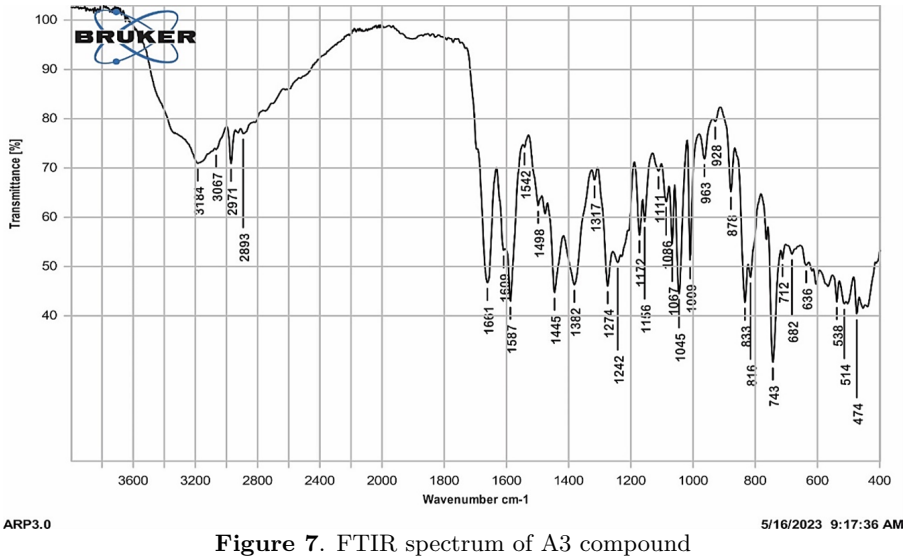

Figure 7. FTIR spectrum of A3 compound

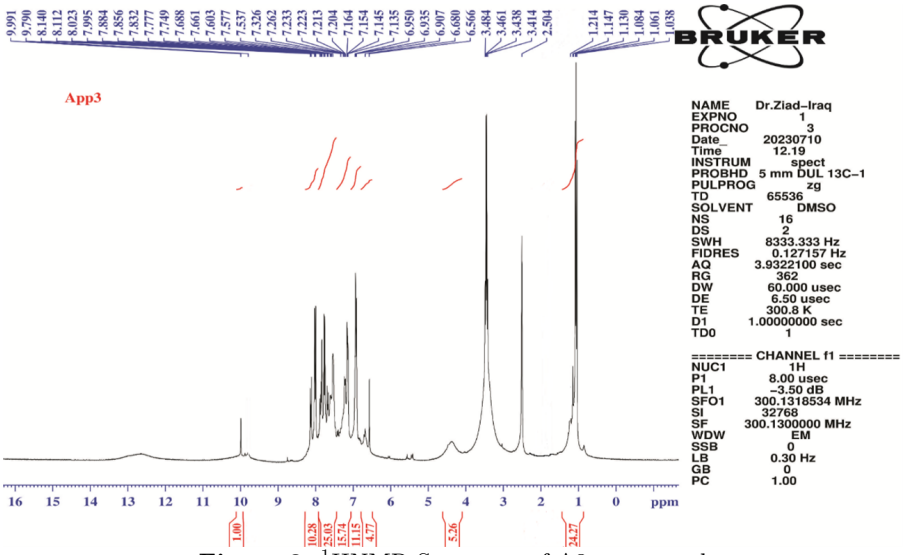

Figure 8. ^{1}HNMR Spectrum of A3 compound

N-((5-(1H-benzo [d]imidazol-2-yl)-2-hydroxyphenyl) (4-nitrophenyl) methyl) benzamide (A4). Colour: Brwon, 68%, Rf = 0.70, Oily compound; FTIR (cm^{-1}): 3366 (OH interference with NH of benzimidazole), 3166 (NH of amide group), 3063 (CH aromatic), 1658 (C=O group), 1606 (C=N group), 1590&1518 (C=C group), 1339&1576 (NO_2 group); ^{1}HNMR (DMSO-d_6, 400 MHz): δ 12.85 (s, 1H, NH of imidazole ring), 10.16 (s, 1H, phenolic), 8.43 (s, 1H, NH of amide group), 4.37 (s, 1H, CH proton between two aromatic rings), 6.90-8.40 (m, 11H, proton of aromatic ring). Figures 9 and 10 represent the spectra of FTIR and ^{1}HNMR of A4 compound

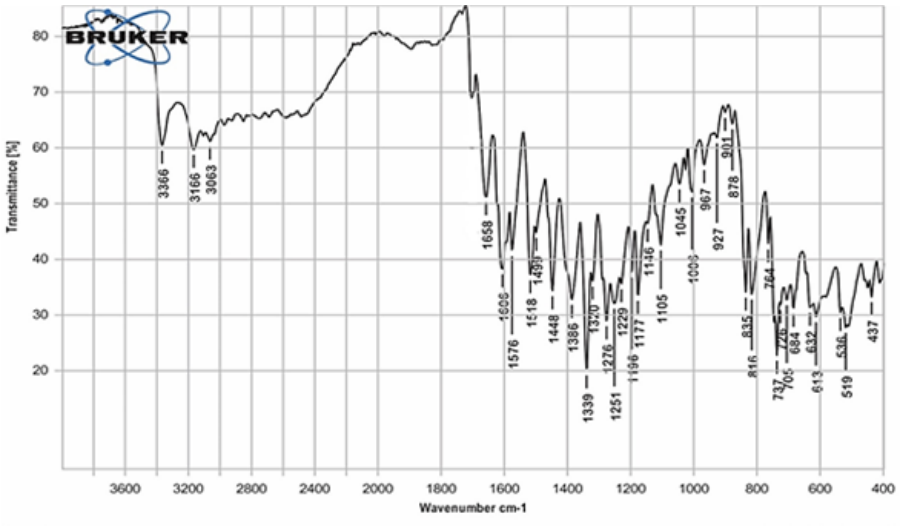

Figure 9. FTIR Spectrum of A4 compound

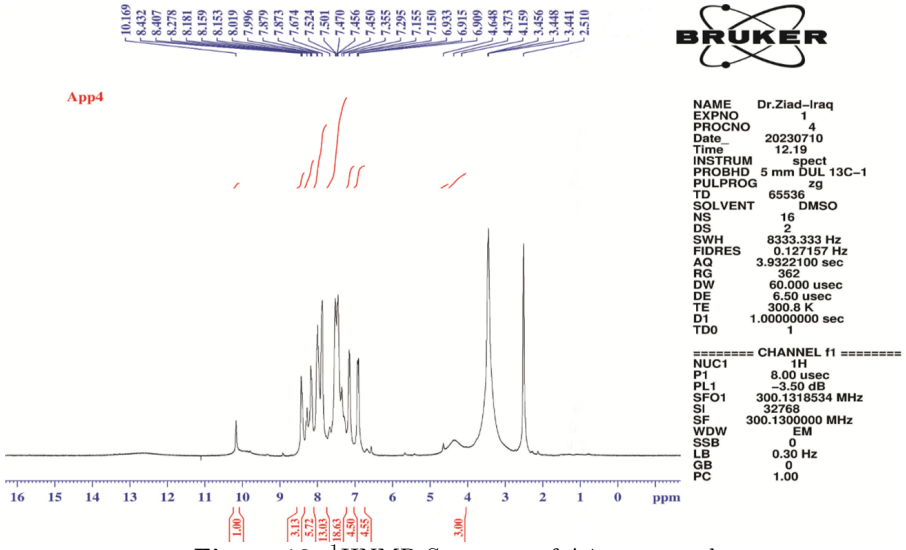

Figure 10. ^{1}HNMR Spectrum of A4 compound

N-((5-(1H-benzo [d]imidazole-2-yl)-2-hydroxyphenyl) (4-bromophenyl) methyl) benzamide (A5). Colour: Brwon, 90%, Rf = 0,71 Oily compound; FTIR (cm^{-1}): 3522 (OH), 3380 (NH of imidazole ring), 3171 (NH of amide group), 1660 (C=O group), 1607 (C=N group), 1587&1542 (C=C group), 928 (C-Br group); ^{1}HNMR (DMSO-d_6, 400 MHz): δ 12.87 (s, 1H, NH of imidazole ring), 9.98 (s, 1H, phenolic), 8.15 (s, 1H, NH of amide group), 4.35 (s, 1H, CH proton between two aromatic rings), 6.58-8.12 (m, 11H, proton of aromatic ring). The spectra of FTIR and ^{1}HNMR of compound A5 are shown in the Figures 11 and 12.

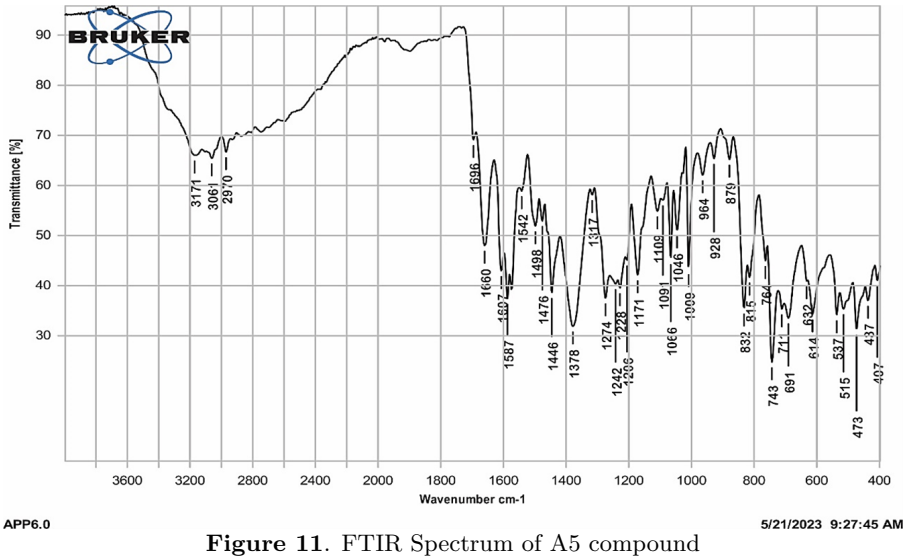

Figure 11. FTIR Spectrum of A5 compound

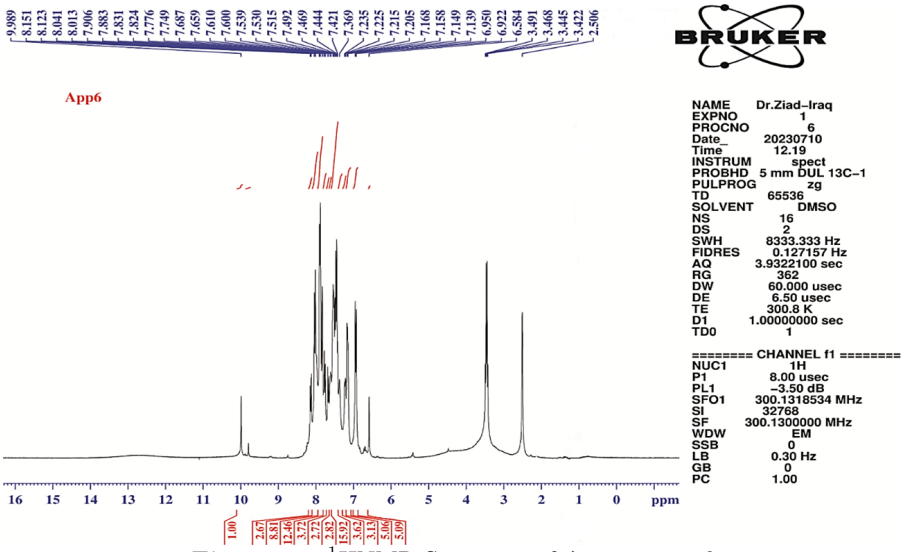

Figure 12. ^{1}HNMR Spectrum of A5 compound

The biological efficacy of some of the formulated compounds, which include benzimidazole derivatives, was evaluated. They were tested against Gram-positive bacteria such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, as well as Gram-negative bacteria like *Escherichia coli* and *Klebsiella pneumoniae*. Furthermore, their antifungal activity was assessed against *Candida albicans*. The findings from these antimicrobial activity tests can be found in Table 1 and shown in Figures 13 and 14. For the investigation of anti-bacterial properties, a good diffusion test was utilized in the *in vitro* study. This technique involves the creation of an inhibition zone that curbs the diffusion of derivative compounds on agar plates [26], [27]. These plates were then incubated for 24 hours at 37 °C, and the diameter of the inhibition zone was quantified in millimeters. Notably, the DMSO control did not exhibit any antimicrobial activity against the tested bacterial strains. However, the compounds that were tested demonstrated active antimicrobial properties. The data on the antibacterial activities of novel benzimidazole derivatives (A1-A5) show good antibacterial activity. The biological activity of these compounds from the presence of imidazole ring which imports in elucidating the mechanism of transformation reaction in biological systems. However, the antifungal results of benzimidazole derivatives show suitable antifungal activity, except for the A2 compound due to the presence of the hydroxy group in this compound. The benzimidazole derivatives generally show high activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Candida albicans*, these results agree with previous studies [28]–[30].

Table 1. Antibacterial and antifungal activities of some of the synthesized compounds

Comp.	Conc. mg/L	Inhibition Zone (mm)				
		Escherichia coli	***Klebsiella pneumoniae***	***Staphylococcus aureus***	***Staphylococcus epidermidis***	***Candida albicans***
	250	10	12	20	21	5
A1	500	12	11	15	18	7
	1000	8	12	15	18	10
	250	15	10	18	20	-
A2	500	12	8	15	15	-
	1000	12	10	5	16	-
	250	15	13	15	17	7
A3	500	20	13	20	22	6
	1000	15	13	20	23	9
	250	15	10	15	18	9
A4	500	12	12	15	14	10
	1000	12	12	12	15	10
	250	15	16	23	22	7
A5	500	12	17	15	23	8
	1000	15	17	20	23	10
Fluconazole	500	-	-	-	-	21
Chloramphenicol	500	17	15	13	13	-

*1-9 (low); 10-19 (medium); 20 and above (good)

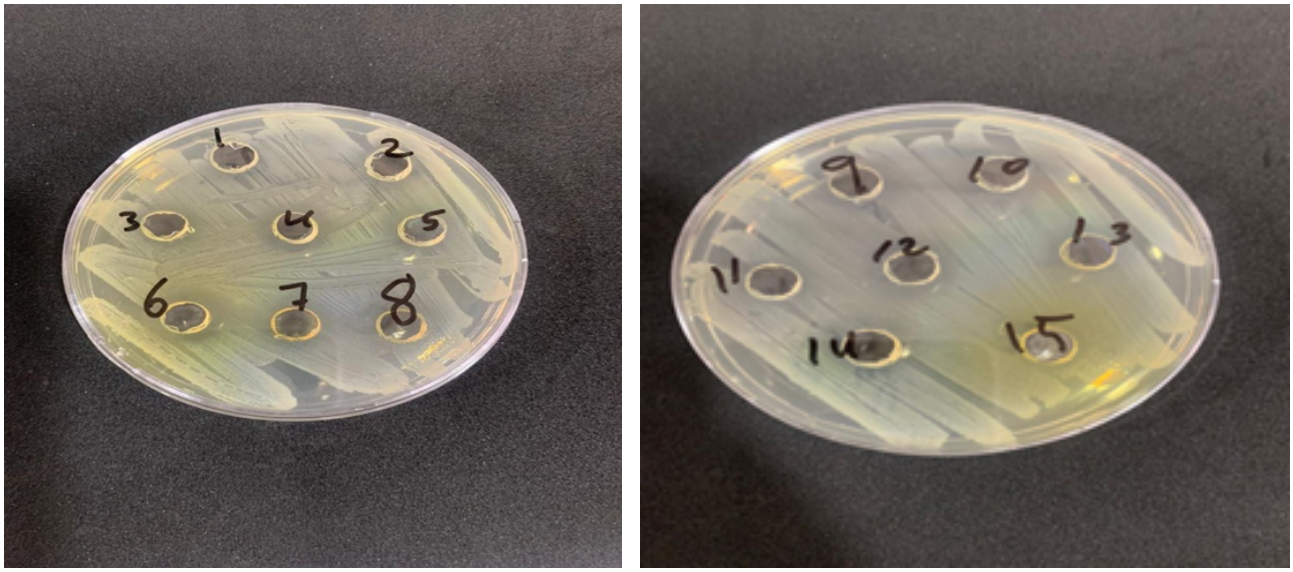

Figure 13. Inhibition zone of the compounds (A1-A5) on (-ve) bacteria E. coli

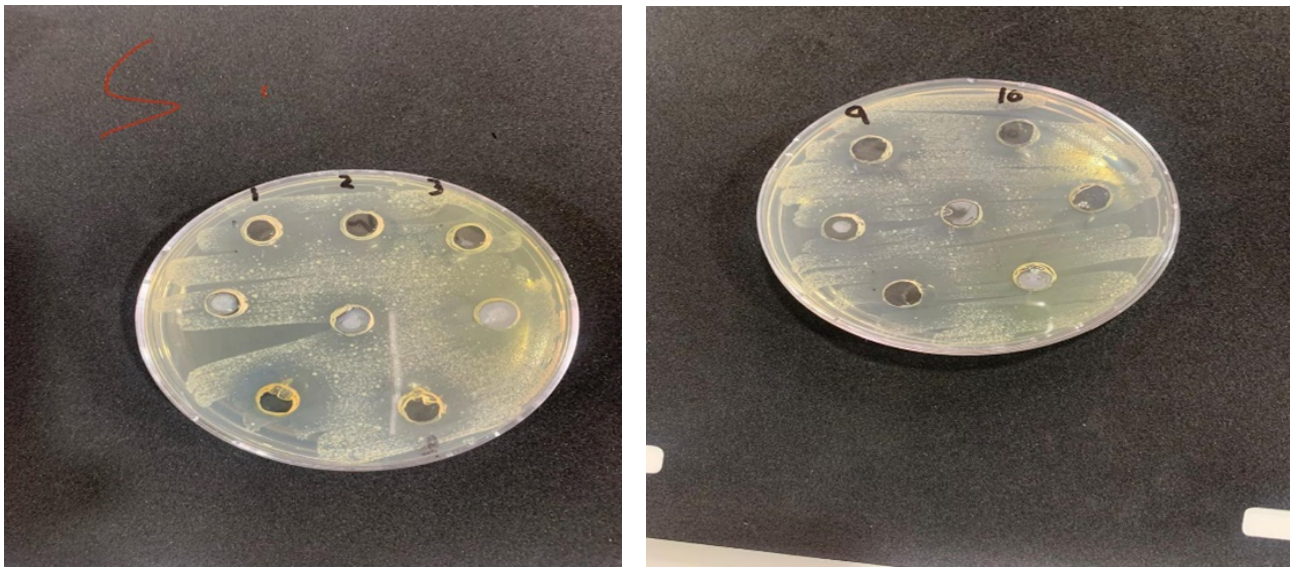

Figure 14. Inhibition zone of the compounds(A1-A5) on (+ve) bacteria *Staphylococcus aureus*

CONCLUSION

In conclusion, benzimidazole derivatives (A1-A5) were synthesized by condensing 2-(4-hydroxyphenyl) benzimidazole with various aldehydes and amides, using CdO nanoparticles as a catalyst. The antimicrobial and antifungal activities of these synthesized derivatives were evaluated, showing satisfactory antimicrobial and appropriate antifungal activity for all except the A2 compound. Further research and structural modifications of these derivatives are recommended to develop more potent benzimidazole derivatives.

SUPPLEMENTARY MATERIAL

None.

AUTHOR CONTRIBUTIONS

Asmaa M. Abdullah: Performed all experiments and wrote the original draft. Abdull Jabar Kh. Attia: Conducted the calculations and analysis. Sergei N. Shtykov: Methodology and reviewed the revised manuscript.

FUNDING

None.

DATA AVAILABILITY STATEMENT

None.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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