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ANTIMICROBIAL AND ANTIOXIDANT ACTIVITY OF NEW TRANSITION METAL COMPLEXES DERIVED FROM 5-(2-(4-METHOXYPHENYL)-1H-BENZO [D] IMIDAZOL-1-YL) QUINOLIN-8-OL

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ABSTRACT: New pharmacologically active transition metal complexes of Co(II), Ni (II), Cu (II), and Zn(II) have been synthesized with the ligand 5-(2-(4-methoxyphenyl)-1H-benzo [d] imidazol-1-yl) quinolin-8-ol (2). Different analytical and spectroscopic tools were used to analyze the compounds, including elemental analysis, FTIR, ¹H-NMR, mass spectra, electronic spectra, magnetic measurement, and molar conductance techniques. FTIR confirmed that the ligand coordinates the metal ion to form a mononuclear complex via the oxygen and nitrogen atoms of the phenolic and quinoline rings. For Co(II) and Zn(II) complexes, tetrahedral geometry is recommended, whereas square-planar geometry is proposed for Ni(II) and Cu(II) complexes. The antibacterial activity of the ligand and its metal complexes were assessed using the disc diffusion method, and minimum inhibitory concentration (MIC) was determined in the broth dilution technique. The antimicrobial activity results showed that the metal complexes were shown to be more active than the free ligand. Besides, Cu(II) complex was shown to be the most potent antioxidant using the DPPH and hydroxyl radical scavenging methods, with IC₅₀ values of 17.3 and 21.5 µg/mL, respectively.

INTRODUCTION: In coordination chemistry, metal complexes with potentially bidentate ligands have sparked a lot of attention. Complexation of transition metals with heterocyclic ligands has played an important role in the development of

coordination chemistry¹. AS a result, a significant number of heterocyclic-based ligands and their transition metal complexes have been studied dynamically, not only for their biological applications, thermal analysis, and spectral analysis but also for their fascinating coordination chemistry.

Because of their industrial and biological uses, several heterocyclic-based metal complexes have been investigated². Because of their diverse biological actions, benzimidazole core compounds have emerged as a popular study subject among

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heterocyclic compounds in recent years³. In medicinal chemistry and agro-chemistry, benzimidazole is a valuable scaffold⁴. Several commercial fungicides based on the benzimidazole scaffold have recently been developed or released. The present study was motivated by the aforementioned facts and literature on pharmacologically active heterocyclic benzimidazole nucleus^{5, 6}, to develop a novel benzimidazole-based ligand and their transition metal complexes. The antimicrobial activity of the synthesized ligands and their transition metal complexes was evaluated against different bacterial and fungal species. DPPH and hydroxy free radical scavenging tests were used to assess antioxidant activity. As a result, the current research aims to develop novel synthetic antibacterial and antioxidant agents that are more active and less harmful.

MATERIALS AND METHOD: Reactants and reagents were purchased from commercial suppliers of analytical grade. The ¹H and ¹³C NMR spectra were recorded on Bruker Avance - 400 MHz NMR instrument using TMS as an internal solvent and DMSO (d₆) as a solvent. Chemical shift is given in part per million (δ -scale). Mass spectra were recorded on Perkin-Elmer LC-MS PE Sciex API/65 Spectrophotometer. Melting points were determined in one end open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. The Merck-made pre-coated TLC plates were used. Elemental analysis (C, H, and N) was undertaken with the Perkin-Elmer model 240 °C analyzer. A UV-Vis double beam spectrophotometer (Systronics 118, India) was used to record the UV-Vis spectra. A digital electronic conductivity meter was used to do the molar conductance measurements. At room temperature, magnetic measurements were made using the Gouy technique.

Synthesis of 2-(4-Methoxyphenyl)-1H-Benzo [D] Imidazole (1): 4-Anisaldehyde (5 mmol) was added to a stirred solution of 1, 2-phenylene diamine (5 mmol), and NH₄Cl (10 mmol) in THF and allowed to stir for 7 h at 60 °C. After completion of the reaction (TLC), the solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate to obtain

compound 1. Yield: 95%. Anal. calc. for C₁₄H₁₂N₂O: C, 74.98; H, 5.39; N, 12.49. found: C, 74.95; H, 5.36; N, 12.52. ¹H NMR (400 MHz, DMSO-d₆) δ : 3.83 (s, 3H, OCH₃), 5.09 (s, 1H), 7.23-7.64 (m, 8H, Ar-H), Mass: m/z: 225 (M+1).

Synthesis of 5-(2-(4-Methoxyphenyl)-1H-Benzo [D] Imidazol-1-Yl) Quinolin-8-Ol (2): The equimolar quantity (2 mmol) of compounds 1 and 5-chloro-8-hydroxyquinoline were taken in THF in the presence of triethylamine and potassium carbonate and allowed to be refluxed for 8 h. After completion of the reaction (TLC; hexane: ethyl acetate, 8:2 v/v), the resulting reaction mixture was cooled to room temperature and poured onto crushed ice, and extracted with dichloromethane. The combined organic layer was washed thoroughly with 5% NaHCO₃ and dried over Na₂SO₄, and concentrated in vacuo to obtain the desired product (2). Yield: 92%. m.p.: 231 °C. Anal. calc. for C₂₃H₁₇N₃O₂: C, 75.19; H, 4.66; N, 11.44. found: C, 75.13; H, 4.65; N, 11.47. IR (KBr, cm⁻¹), 3307.36 (-OH), 1670.00 (C=N), 1407.71 (CH), 1370.45 (C₆H₅), 825 (C-N), 783.36 (C=C), 739.23(C-C). ¹H NMR (400 MHz, DMSO-d₆) δ : 3.83 (s, 3H, OCH₃), 7.03-7.77 (m, 13H, Ar-H), 8.69 (s, 1H, OH). ¹³C NMR (100 MHz, DMSO-d₆) δ : 55.8, 111.2, 112.1, 113.1, 114.8, 118.4, 118.7, 120.1, 122.0, 123.0, 130.3, 131.9, 135.1, 135.5, 138.3, 144.0, 149.4, 150.2, 152.7, 160.6. Mass: m/z: 368 (M+1). UV-Visible: 296 nm (n- π *).

Co(II) Complex: Anal. calc. for C₄₆H₃₂CoN₆O₄: C, 69.78; H, 4.07; Co, 7.44; N, 10.61. found: C, 69.74; H, 4.05; Co, 7.42; N, 10.65. IR (KBr, cm⁻¹): 1575.15 (CH), 1498.21 (C=N), 535.15 (Co-N), 492.37 (Co-O). Mass: m/z: 792 (M+1).

Ni(II) Complex: Anal. calc. for C₄₆H₃₂NiN₆O₄: C, 69.81; H, 4.08; N, 10.62; Ni, 7.42. found: C, 69.80; H, 4.05; N, 10.67; Ni, 7.41. IR (KBr, cm⁻¹): 1573.65 (CH), 1495.41 (C=N), 526.42 (Ni-N), 489.17 (Ni-O). Mass: m/z: 792 (M+1).

Cu(II) Complex: Anal. calc. for C₄₆H₃₂CuN₆O₄: C, 69.38; H, 4.05; Cu, 7.98; N, 10.55. found: C, 69.35; H, 4.02; Cu, 7.95; N, 10.59. IR (KBr, cm⁻¹): 1576.08 (CH), 1495.68 (C=N), 543.29 (Cu-N), 499.14 (Cu-O). Mass: m/z: 797 (M+1).

Zn(II) Complex: Anal. calc. for C₄₆H₃₂ZnN₆O₄: C, 69.22; H, 4.04; N, 10.53; Zn, 8.19. found: C, 69.21;

H, 4.01; N, 10.57; Zn, 8.16. IR (KBr, cm^{-1}): 1573.32 (CH), 1496.18 (C=N), 525.13 (Zn-N), 483.12 (Zn-O). Mass: m/z : 799 (M+1).

Antimicrobial Activity: The newly synthesized ligand and its metal complexes were tested for antibacterial activity against a range of bacteria, including *Staphylococcus aureus* (NCIM 5021), *Bacillus subtilis* (NCIM 2999) and *Escherichia coli* (NCIM 2574), and fungi, *Candida albicans* (NCIM 3471). Microbial strains were cultivated overnight at 37 °C in nutrients and potato dextrose agar medium. The antibacterial activity and minimum inhibitory concentration (MIC) of the ligand and its metal complexes were assessed using agar disc diffusion⁷ and broth dilution techniques⁸, respectively. The inhibitory zone was measured in millimeters for all samples evaluated in triplicate. The MIC was determined to be the lowest chemical concentration that inhibited the development of the macroscopic microorganism

Antioxidant Activity:

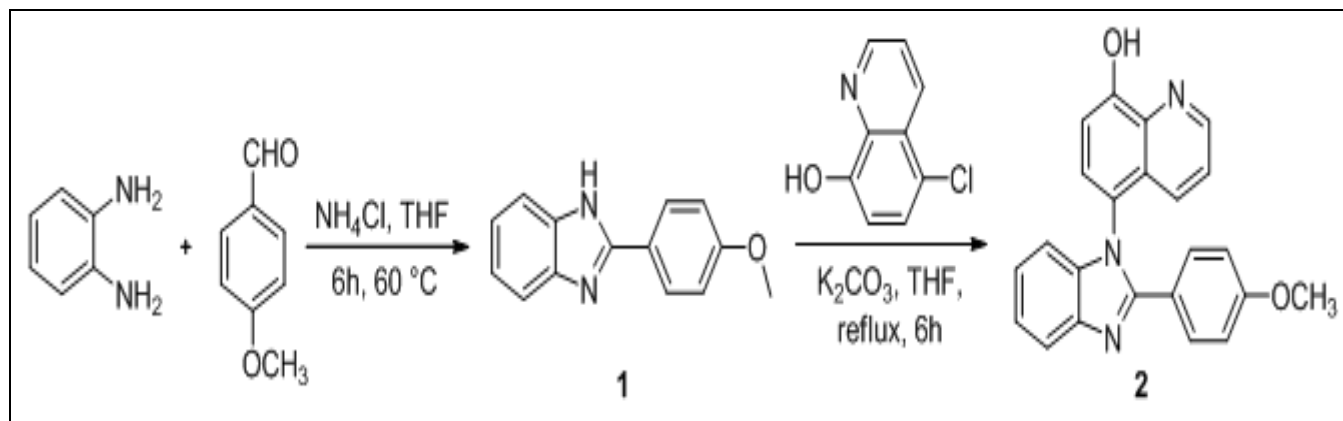
DPPH Free Radical Scavenging Activity: The Blois technique^{9, 10} was used to measure the ability to scavenge the stable free DPPH radical. Ligand IC_{50} values were determined, and their metal complexes were the sample concentration at which 50% of the DPPH radicals were scavenged. The tests were done three times, and the findings were

given as mean values with standard deviations. Ascorbic acid was used as a standard drug.

Hydroxyl Radical Scavenging Assay: The standard reported method was used to determine the scavenging activity of the ligand and its Co(II), Ni(II), Cu(II), and Zn(II) complexes on hydroxyl radical activity^{11, 12}. Spectroscopically, the intensity of the color produced was measured at 532 nm against a reagent blank. The ligand and its metal complexes IC_{50} values were determined. The results were reported as mean values with standard deviations for all samples and the control. BHA was used as a reference drug.

RESULTS AND DISCUSSION:

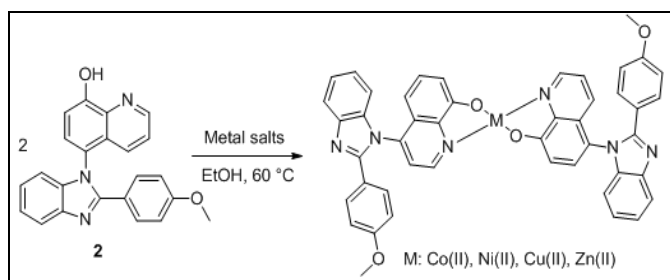
Synthesis: The condensation reaction between 1, 2-phenylenediamine, and 4-anisaldehyde was carried out using NH_4Cl in ethanol solvent at 60°C for 6 h to produce the intermediate substituted benzimidazole (1) (Scheme 1). The intermediate 2-(4-methoxyphenyl)-1H-benzo [d] imidazole (1) was then treated with 5-chloro-8-hydroxy quinoline in THF to give the required ligand 5-(2-(4-methoxyphenyl) -1H-benzo [d] imidazol-1-yl) quinolin-8-ol (2) in 92% yield. Elemental and spectroscopic analysis revealed the structure of the title compound. The newly synthesized ligand elemental and spectroscopic analysis agree well with its molecular formula.



SCHEME 1: SYNTHESIS OF LIGAND

In Scheme 2, the formation of transition metal complexes with ligand (2) in a 1:2 ratio is shown. The complexes were formed by ligand (2) reacting with metal ions, with the ligand acting as a bidentate ligand due to its oxygen and nitrogen atoms. The complexes analytical results match their molecular structures, with a molar metal to ligand

ratio of 1:2. All of the complexes molar conductance and magnetic moment were calculated and the results are shown in **Tables 1** and **2**, respectively. The magnetic moment data reveals that Co(II) and Cu(II) complexes are paramagnetic, whereas Ni(II) and Zn(II) complexes are diamagnetic.



SCHEME 2: SYNTHESIS OF TRANSITION METAL COMPLEXES

TABLE 1: PHYSICAL PROPERTIES AND MOLAR CONDUCTANCE OF METAL COMPLEXES

Complexes	M.P. (°C)	Yield (%)	Λ_m (Ohm ⁻¹ cm ² mol ⁻¹)
Co(II) complex	328	77	13.7
Ni(II) complex	341	76	10.8
Cu(II) complex	297	83	17.3
Zn(II) complex	285	79	10.1

TABLE 2: ELECTRONIC SPECTRAL ASSIGNMENTS, MAGNETIC MOMENT VALUES AND GEOMETRY OF METAL COMPLEXES

Complexes	λ_{max}	Band assignments	Magnetic moment (BM)	Geometry
Co(II) complex	364, 638	$^4A_{2f} \rightarrow ^4T_{1p}$	4.26	Tetrahedral
Ni(II) complex	319, 338, 512	$^1A_{1g} \rightarrow ^1A_{2g}$ $^1A_{1g} \rightarrow ^1B_{1g}$	Diamagnetic	Square Planar
Cu(II) complex	329, 351, 645	$^2B_{1g} \rightarrow ^2A_{1g}$	1.83	Square Planar
Zn(II) complex	-	-	Diamagnetic	Tetrahedral

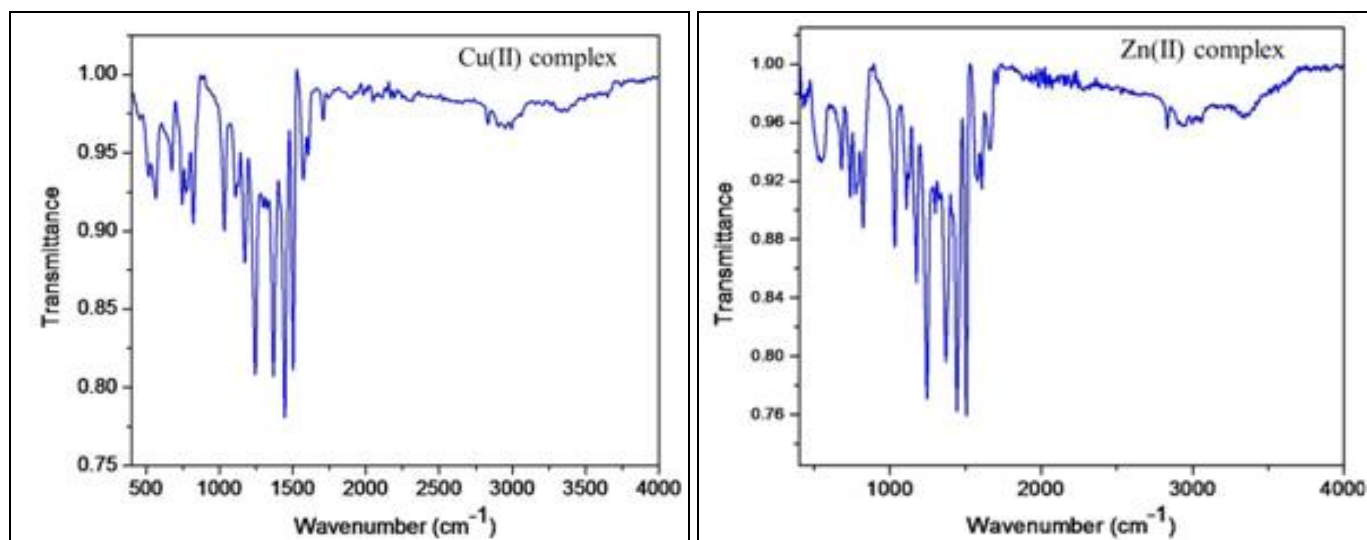


FIG. 1: IR SPECTRUM OF Cu(II) AND Zn(II) COMPLEXES

Antimicrobial Activity: Using the disc diffusion technique, the newly synthesized ligand and its Co(II), Ni(II), Cu(II), and Zn(II) metal complexes were tested for antibacterial and antifungal activity against *S. aureus*, *B. subtilis* and *E. Coli* strain *in-vitro*. The broth dilution technique was used to determine the minimum inhibitory concentration (MIC). **Table 3.** shows the antimicrobial activity of the ligand and its Co(II), Ni(II), Cu(II) and Zn(II) complexes. The antibacterial activity of metal

The appearance of new distinctive bands in the IR spectra of complexes verified the formation of complexes **Fig. 1**. The absence of OH bands in the 3307 cm⁻¹ region shows that the complexation of the ligand with metal ions. M–N and M–O bonds are responsible for new bands at 525-543 cm⁻¹ and 483-499 cm⁻¹, respectively¹³. The absorption maximum of the Co(II) complex was found at 638 nm **Fig. 2**, which corresponds to the $^4A_{2f} \rightarrow ^4T_{1p}$ transition, confirming the tetrahedral geometry¹⁴. The absorption spectra of Ni(II) complexes revealed a band 512 nm that corresponded to the $^1A_{1g} \rightarrow ^1B_{1g}$ transition, confirming a square planar geometry. The Cu(II) complex spectrum exhibits square planar geometry, with a peak at 645 nm corresponding to the $^2B_{1g} \rightarrow ^2A_{1g}$ transition¹⁵.

complexes was shown to be higher than that of their ligand alone (2). Metal chelates have antibacterial action due to the lipophilic nature of the metal ions in complexes. Cu(II) complexes were shown to be more active against both bacterial and fungal strains than the other three tested complexes. Due to the protein denaturation of the sulfhydryl group, metal complexes containing copper ions enter the bacterial cell wall more easily, damaging the bacterial cell wall¹⁶.

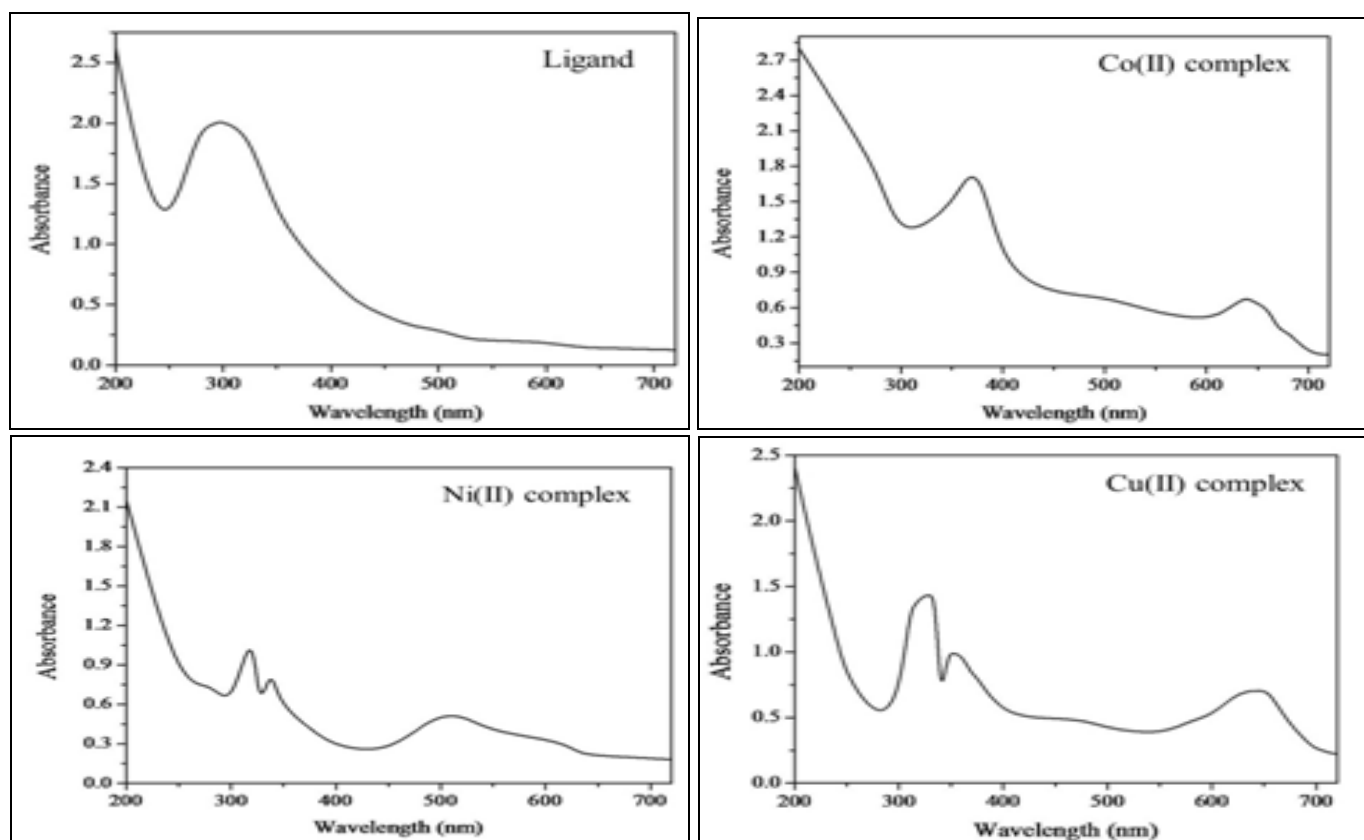


FIG. 2: ABSORPTION SPECTRUM OF LIGAND AND ITS METAL COMPLEXES

TABLE 1: *IN-VITRO* ANTIMICROBIAL ACTIVITY OF LIGANDS AND THEIR METAL COMPLEXES

Compound	Minimum inhibitory concentration (MIC) ^a in μM			
	Gram-positive		Gram-negative	Fungi
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>C. albicans</i>
Ligand	>128	>128	>128	>128
Co(II) Complex	82.7 \pm 1.15	89.3 \pm 1.09	98.1 \pm 1.95	96.1 \pm 0.74
Ni(II) Complex	75.3 \pm 1.22	73.8 \pm 1.95	89.5 \pm 1.04	86.2 \pm 1.36
Cu(II) Complex	41.5 \pm 0.95	40.3 \pm 0.26	57.8 \pm 1.29	49.6 \pm 1.21
Zn(II) Complex	50.3 \pm 1.07	54.8 \pm 1.77	68.2 \pm 1.03	61.8 \pm 1.44
Rifampicin	0.5 \pm 0.08	0.5 \pm 0.18	4.1 \pm 1.06	Nt ^b
Flucanazole	-	-	-	4.2 \pm 1.18

A The values given are means of three experiments

Antioxidant Activity: The ligand and its complexes were tested for DPPH and hydroxyl radical scavenging activities against ascorbic acid and BHA, respectively as a reference drug. **Table 1** shows the radical scavenging action of the ligands and their metal complexes.

In comparison to the norms, all of the complexes showed reduced activity (ascorbic acid and BHA). Based on the quantity of chemicals necessary for a 50% reduction in the initial DPPH radical concentration, the antioxidant activity was represented as the 50% inhibitory concentration (IC₅₀). Cu(II) complex has substantially greater DPPH and hydroxyl radical scavenging activity

than the free ligand, indicating that it is a lot better free radical scavenger and antioxidant than the ligand but lower than ascorbic acid as a reference.

TABLE 2: ANTIOXIDANT ACTIVITY OF THE LIGAND AND THEIR METAL COMPLEXES

Compound	IC ₅₀ ($\mu\text{g/mL}$) ^a	
	DPPH	$\cdot\text{OH}$
Ligand	18.7 \pm 1.23	26.1 \pm 1.07
Co(II) Complex	21.9 \pm 1.38	33.7 \pm 1.29
Ni(II) Complex	21.5 \pm 1.05	31.8 \pm 0.44
Cu(II) Complex	17.3 \pm 0.69	21.5 \pm 1.26
Zn(II) Complex	19.4 \pm 1.36	29.3 \pm 0.24
AA ^b	12.3 \pm 0.43	nt
BHA ^c	nt	15.3 \pm 0.68

A The values given are means of three experiments, B Ascorbic acid, cButylatedhydroxy anisole, nt: not tested

CONCLUSION: Co(II), Ni(II), Cu(II) and Zn(II) complexes of 5-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) quinolin-8-ol (2) were synthesized and characterized by utilizing a variety of analytical and spectroscopic techniques in this work. The antioxidant and antibacterial properties of the newly synthesized complexes were evaluated. All of the metal complexes examined showed promising antibacterial efficacy against the bacterial and fungal strains tested. Cu(II) shown substantial antibacterial activity when compared to other test compounds. Furthermore, the Cu(II) complex was discovered to have strong antioxidant activity when compared to the other examined complexes and ligand alone.

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CONFLICTS OF INTEREST: The authors declare that they have no known competing financial interests.

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