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Synthesis, Characterization, And Antimicrobial Evaluation Of Metal Complexes Derived From A Novel Benzimidazole-Pyrazole-Quinoline Hybrid Ligand

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Abstract

A novel nitrogen-containing hybrid ligand, 5-((3-((1H-benzo[d]imidazol-1-yl)methyl)-5-(4-fluorophenyl)-1H-pyrazol-1-yl)methyl)-8-hydroxyquinoline (BIFPHQ), was synthesized by reacting 1-((5-(4-fluorophenyl)-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (BIFP) with 5-chloromethyl-8-hydroxyquinoline. This ligand was further complexed with divalent metal ions including Cu(II), Ni(II), Co(II), Zn(II), and Mn(II). The structural elucidation of the ligand and its metal complexes was accomplished through elemental analysis, FT-IR, NMR (^{1}H and ^{13}C), and mass spectroscopy. The analytical data confirmed a 1:2 (metal:ligand) stoichiometry for all complexes. Magnetic susceptibility measurements and electronic spectral studies suggested an octahedral geometry for the synthesized metal chelates. The thermal stability of the compounds was assessed by thermogravimetric analysis (TGA).

The ligand and its metal complexes were evaluated for their antimicrobial activity against a panel of Gram-positive and Gram-negative bacteria, as well as fungal strains, by determining the Minimum Inhibitory Concentration (MIC). The biological screening revealed that the metal complexes exhibited significantly enhanced antimicrobial potency compared to the free ligand. Notably, the copper(II) complex demonstrated the most promising activity, outperforming the standard drugs Amoxicillin and Nystatin in several cases. This study underscores the potential of metal complexation to enhance the biological efficacy of organic ligands and positions the BIFPHQ-Cu(II) complex as a particularly attractive candidate for further development.

Keywords: *8-Hydroxyquinoline, Pyrazole, Benzimidazole, Metal complexes, Spectral characterization, Antimicrobial activity, Minimum Inhibitory Concentration (MIC).*

INTRODUCTION

Metal complexes play a significant role in medicinal inorganic chemistry, propelling therapy development.[1, 2] Their pharmacological activities not only rely on the metal cation but also on the structure and character of the organic ligand, which influences specificity, bioavailability, and action[3]. Among the pharmacophores, the 8-hydroxyquinoline (8-HQ) draws special attention due to the high chelating capability and wide range of pharmaceutical activities, such as antimicrobial, anticancer, and antifungal activities.[4-13] Their derivatives give stable complexes with a wide range of metal ions, which frequently enhance the biological efficacy compared with the parent ligand.

Hybrid ligands by coupling disparate bioactive heterocycles offer a promising drug discovery strategy by enhancing the inherent pharmacological activities. The notable heterocycles, benzimidazole and pyrazole, with broad-based biological uses, when coupled with the 8-hydroxyquinoline framework, may give us new ligands with increased metal-chelating ability and increased biological efficacy. As a continuation of our studies on bioactive metal complexes [14], the current contribution involves the synthesis, characterization, and bioassay of a newly prepared hybrid ligand. The ligand, 5-((3-((1H-benzo[d]imidazol-1-yl)methyl)-5-(4-fluorophenyl)-1H-pyrazol-1-yl)methyl)-8-hydroxyquinoline (BIFPHQ), integrates the 8-hydro. In this paper, the complexes with divalent metal ions (Cu(II), Ni(II), Co(II), Zn(II), Mn(II)) of the ligand BIFPHQ are presented. The ligand and the complexes were characterized by the elemental analysis and spectroscopic techniques (IR, NMR, Mass), magnetic susceptibility and thermogravimetric analysis (TGA). The research concerned the investigation of the influence of the process of complexation upon the antimicrobial action. The ligand and the metal chelates were screened for the in vitro antibacterial activities against Gram-positive (Bacillus megaterium, Staphylococcus aureus) and Gram-negative (Escherichia coli, Pseudomonas aeruginosa) bacteria and the antifungal activities against P. expansum and F. oxysporium. The results were compared with standard drugs, Amoxicillin and Nystatin, for the evaluation of their possibilities as new sources.

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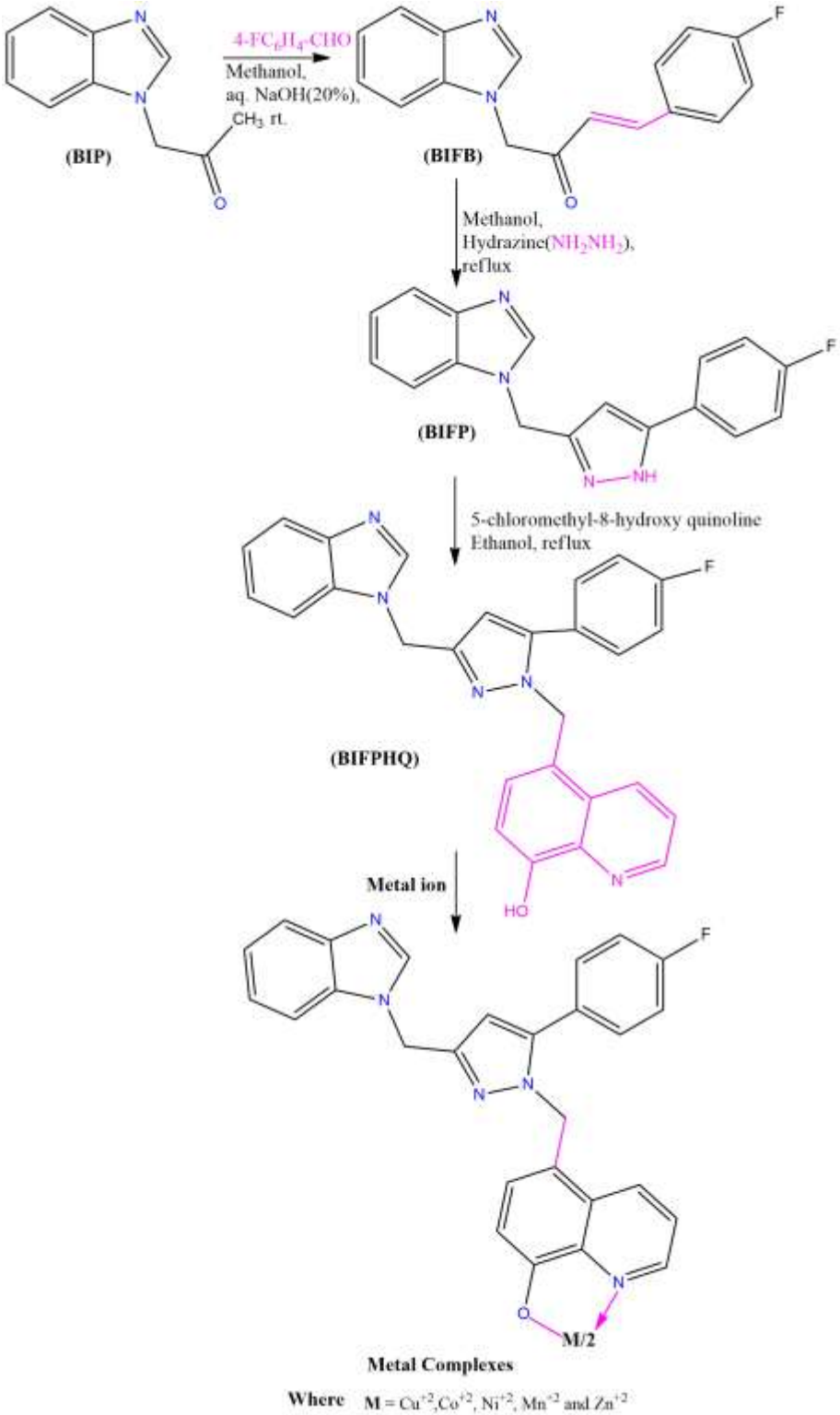

Figure-1 Synthesis pathway of metal complxes of BIFPHQ

Experimental

The chemicals were used laboratory grade. Elements and Metals compositions were examined by standard methods[15]. For spectroscopic analysis carried out standard instruments. The standard Broth method applied for biological study[16,17]. Same conditions using Amoxillin and Nystatin were used standard for comparison.

Synthesis of 1-(1H-benzo[d]imidazol-1-yl)-4-(4-fluorophenyl)but-3-en-2-one(BIFB)[18,19]:
The 4-fluro benzaldehyde and BIP mixed in sufficient ethanol with aq.KOH (10%, 5ml) and stirred for one day. Then pour it into ice, the solid precipitate was formed. The solid crystallized by R-sprit. The Yield was 71% and m.p was 136-137°C. The elemental analysis for $C_{17}H_{13}N_2OF$ (280 gm/mol), Cal.(Found) %C-72.85 (72.8); %H-4.67(4.6),%F-6.78(6.7) and %N-9.99(9.9). IR spectra KBr (cm^{-1}): 3048 (Aromatic C-H Str.), 2960, 2835, 1465, 1365(C-H Str.), 1670(C=O), 1600 (C=N) and 1250(C-F). 1H NMR (ppm): 7.29-8.18 (m, 9H, benzimidazole, Aromatic-H), 4.95 (s, 2H, -N-CH_2-CO-), 6.55, 8.40 (d, 2H, ethylene); 13C NMR (ppm): 194.5(CO), 112.1-162.3(Ar-C), 58.3(CH_2), 150.2, 156.0 (C=C). Mass (m/z) : 281.1 (M^+).

Synthesis of 1-((5-(4-fluorophenyl)-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (BIFP) [19,20] :
Refluxed 1-(1H-benzo[d]imidazol-1-yl)-4-(4-fluorophenyl) but-3-en-2-one **(BIFB)** (0.01 mol), hydrazine hydrate(0.01 mol) for 6 hrs in EtOH. Then cooled it and kept at 0°C overnight. The residue filtered, washed and dried on air and crystallized by ethanol. yield was 73% and m. p. was 172–173°C. The elemental analysis for $C_{17}H_{13}N_4F$ (292 gm/mol),Cal.(Found) %C-69.85 (69.8);%H-4.48(4.4),%F-6.50(6.4) and %N-19.17(19.1). IR spectra KBr (cm^{-1}) 3425 (NH), 3050 (Aromatic C-H Str.), 2930, 2850, 1500, 1385(C-H Str.),1599 (C=N) and 1250(C-F). 1H NMR (CDCl3,TMS): δ 7.30-8.25 (m,9H,Ar-H), 6.10 (s, 1H, NH), 4.83(s,2H,CH_2), 5.22 (s, 1H, H-pyrazole). 13C NMR : δ 112.8-153.5(Ar-C), 58.3(CH2),Mass (m/z):293.4 (M^+).

Synthesis of 5-((3-((1H-benzo[d]imidazol-1-yl)methyl)-5-(4-fluorophenyl)-1H-pyrazol-1-yl) methyl)-8-hydroxy quinoline (BIFPHQ) [19]:
In 1-((5-(4-fluorophenyl)-1H-pyrazol-3-yl)methyl)-1H-benzo[d] imidazole **(BIFP)**(0.01 mol) in dry acetone (5 ml) cooled at 0°C, was added triethylamine (0.1 mmol), 5-chloromethyl-8-hydroxy quinoline (0.1 m mol) dropwise added at 0°C. Stir this mixture for 180 mins. The solid ppt. was filtered and crystallized by EtOH. yield was 66% and m.p. was 178–79°C. The compositions study for $C_{27}H_{20}N_5OF$ (449 gm/mol), Cal.(Found) %C-72.15(72.1);%H-4.48(4.4),%F-4.23(4.2) and %N-15.58(15.5). IR spectra KBr (cm^{-1}) : 3400(-OH), 2920(CH2), 3030 (Ar. C-H str.), 2920, 2850,1508(C-H Str.), 1648, 1575, 1698, 1435 (8-HQ moiety),1275-1298(C-N) and 1250(C-F). 1H NMR (CDCl3,TMS): δ 7.30-8.50 (m, 14H,Ar-H), 4.80,4.42 (s,4H, CH_2), 5.10 (s, 1H, H-pyrazole), 9.50(s,1H,-OH). 13C NMR: δ 116.0-163.2(Ar-C), 52.8,58.8 (CH_2). Mass (m/z) : 450.1 (M^+).

Table-1 Analysis of BIFPHQ and Metal complex

Ligand and Metal Complex	Elemental analysis (%)						
	Color	Yield %	C% Cald. Found	H% Cald. Found	F% Cald. Found	N% Cald. Found	M%
$C_{27}H_{20}N_5OF$	off White	66	72.15 72.1	4.48 4.4	4.23 4.2	15.58 15.5	- -
$C_{54}H_{38}N_{10}O_2F_2Cu^{(II)}.2H_2O$	bluish white	66	65.09 65.0	4.22 4.2	3.82 3.8	14.06 14.0	6.38 6.3
$C_{54}H_{38}N_{10}O_2F_2Ni^{(II)}.2H_2O$	greenish white	64	65.41 65.4	4.24 4.2	3.84 3.8	14.13 14.1	5.93 5.9
$C_{54}H_{38}N_{10}O_2F_2Co^{(II)}.2H_2O$	pale white	62	65.39 65.3	4.24 4.2	3.83 3.8	14.13 14.1	5.95 5.9
$C_{54}H_{38}N_{10}O_2F_2Zn^{(II)}.2H_2O$	off white	63	64.97 64.9	4.21 4.2	3.81 3.8	14.04 14.0	6.56 6.5
$C_{54}H_{38}N_{10}O_2F_2Mn^{(II)}.2H_2O$	pale white	60	65.66 65.6	4.26 4.2	3.85 3.8	14.19 14.1	5.57 5.5

Synthesis of metal complex of 5-((3-((1H-benzo[d]imidazol-1-yl)methyl)-5-(4-fluoro phenyl)-1H-pyrazol-1-yl)methyl)-8-hydroxy quinoline (BIFPHQ)) :

A hot liquid of Metal salt (0.25 mol) and 50% aq. HCOOH (2.5 ml) was added drop-wisely to the hot 20% aq.HCOOH (20ml) of BIFPHQ (0.05mol). Adjust the pH (~8.5) using 50% NH_4OH

solution, then digested it for 4 hours in the water bath. Then filtered, washed with hot water, and subsequently with small quantity of ethanol, acetonitrile.

Table – 2 Spectral Features and Magnetic Moment of BIFPHQ- Metal Chelates

Metal Chelates	μ_{eff} (BM)	Electronic spectral data(cm^{-1})	Transition
BIFPHQ-Cu(II)	1.92	23985 15760	CT $^2B_{1g} \rightarrow {}^2A_{1g}$
BIFPHQ-Ni(II)	3.20	22245 15793	$^3A_{2g} \rightarrow {}^3T_{1g}$ (P) $^3A_{2g} \rightarrow {}^3T_{1g}$ (F)
BIFPHQ-Co(II)	4.76	23952 18125 8745	$^4T_{1g}(F) \rightarrow {}^6T_{2g}(\upsilon_1)$ $^4T_{1g}(F) \rightarrow {}^4A_{2g}(\upsilon_2)$ $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$
BIFPHQ-Mn(II)	5.50	23890 18340 16838	$^6A_{1g} \rightarrow {}^6A_{1g}(^4E_g)$ $^6A_{1g} \rightarrow {}^4T_{2g}(^4G)$ $^6A_{1g} \rightarrow {}^4T_{1g}(^4G)$
BIFPHQ-Zn(II)	D	-	-

D*=Diamagnetic

Thermogravimetric analysis of BIFPHQ and its metal chelates was investigated by conducting thermogravimetric analysis (TGA). TGA was carried out in a slow stream of air at 10°C/min. heating rate. Du point thermogravimetric analyzer (TC-10ATA-3000) was used.

Table-3 Thermo-gravimetric analysis of BIFPHQ and its metal chelates

Ligand/ Metal chelates	Percentage Wt. loss at various temperature(°C)						
	100	200	300	400	500	600	700
BIFPHQ	-	8.88	10.36	24.6	29.82	32.12	35.29
BIFPHQ-$Cu^{+2}.2H_2O$	0.05	6.02	19.78	28.51	34.38	37.94	45.23
BIFPHQ-$Ni^{+2}.2H_2O$	3.24	16.47	20.11	37.74	54.00	66.37	69.64
BIFPHQ-$Co^{+2}.2H_2O$	2.56	13.72	25.33	39.84	53.68	65.34	68.89
BIFPHQ-$Zn^{+2}.2H_2O$	7.44	16.03	32.12	37.55	56.31	67.39	70.20
BIFPHQ-$Mn^{+2}.2H_2O$	3.29	10.55	14.61	35.9	54.49	66.98	69.62

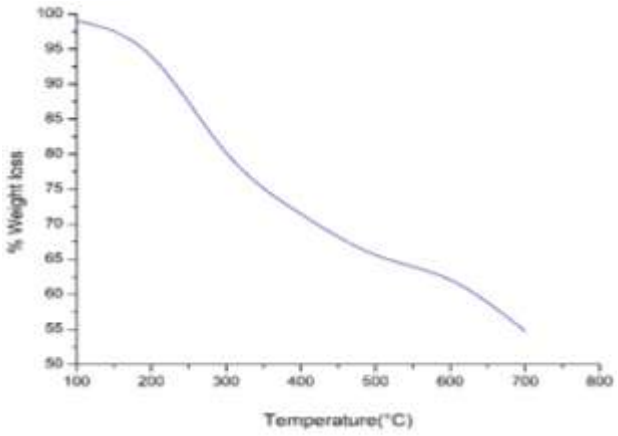

Figure-2 TGA Thermogram of BIFPHQ-$Cu^{+2}.2H_2O$

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RESULT AND DISCUSSION

The 5-((3-((1H-benzo[d]imidazol-1-yl)methyl)-5-(4-fluorophenyl)-1H-pyrazol-1-yl)methyl)-8-hydroxyquinoline (**BIFPHQ**) synthesisd from 5-chloromethyl-8-hydroxy quinoline and 1-((5-(4-fluorophenyl)-1H-pyrazol-3-yl)methyl)-1H-benzo [d] imidazole (BIFP). Table-1 present the elemnetal analysis, which are consistent with the structure predicted(Scheme-1). The BIFPHQ infrared spectra comprises the mostly same bands of hydroxy quinoline, particlurly for 3400 (-OH), 2920(CH_2) and 1250 (C-F) cm^{-1}. BIFPHQ shows NMR singlet of 1H at 9.50 for -OH. The methylene proton shows singlet at 4.80,4.42 ppm. These all prove the BIFPHQ structure.

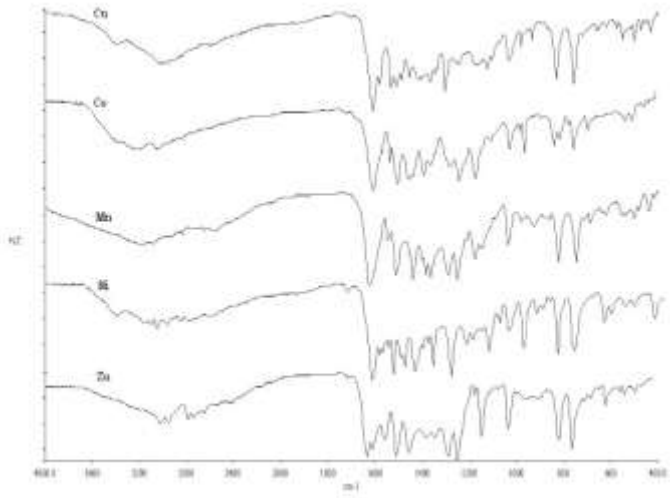

Figure-3 BIFPHQ- Metal Chelate infrared specta

The element analysis of BIFPHQ- metal chelates as seen in Table- I are confirmed the expected structures, they also indicated that the metal to ligand ratio is 1: 2. Metal complex donot shows the bands of hydroxy group that is shown in ligand, because of metal complextion[21,22].(Figure-3).

Table-4 BIFPHQ and metal chelates antibacterial study

compounds	MIC (μgmL^{-1})			
	Gram +Ve		Gram -Ve	
	B.Megaterium	*S.Aureus*	*E.Coli*	*Ps.Aeruginosa*
BIFPHQ	175	150	125	125
BIFPHQ -Cu$^{(II)}$	**25**	**25**	**50**	**25**
BIFPHQ -Ni$^{(II)}$	50	75	100	125
BIFPHQ -Co$^{(II)}$	75	75	50	50
BIFPHQ -Zn$^{(II)}$	75	50	50	50
BIFPHQ -Mn$^{(II)}$	125	100	100	100
Amoxillin	250	150	250	200

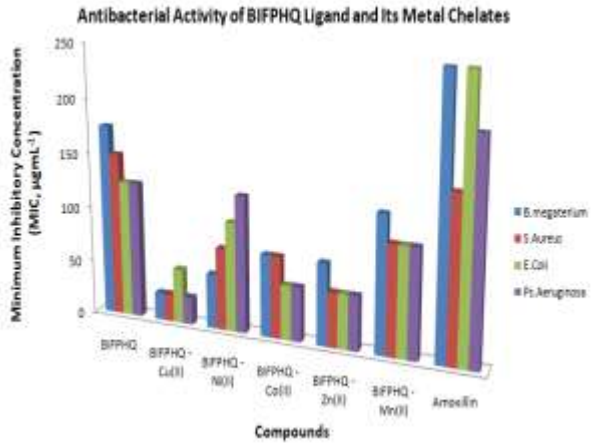

Figure-4 BIFPHQ and metal chelates antibacterial study

The magnetic moment are expceted according to structures. The value of magnetic moments and reflectance spectral data of each complexes co-relates with structure assigned as the octahedral geometry[21-23].

Table – 5 BIFPHQ and metal chelates antifungal study

compounds	MIC (μgmL^{-1})			
	P.Expansum	*B.Thiobromine*	*Nigrospora Sp.*	*F.Oxyporium*
BIFPHQ	125	125	100	125
BIFPHQ-$Cu^{(II)}$	**25**	**50**	**25**	**25**
BIFPHQ -$Ni^{(II)}$	100	125	125	125
BIFPHQ -$Co^{(II)}$	75	50	100	75
BIFPHQ -$Zn^{(II)}$	50	75	75	50
BIFPHQ-$Mn^{(II)}$	75	100	75	75
Nystatin	**300**	**200**	**250**	**200**

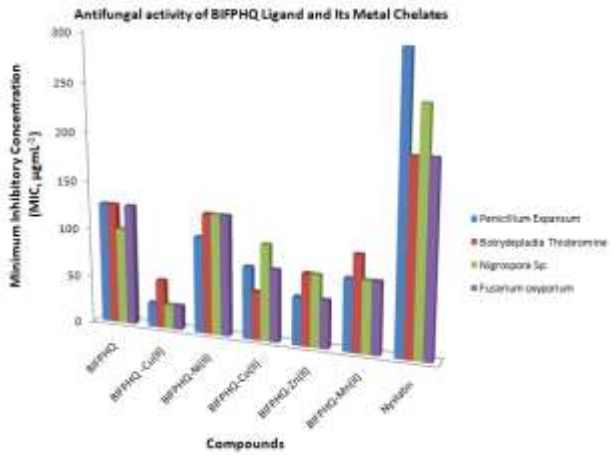

Figure-5 BIFPHQ and metal chelates antifungal study

The screening of biological activity BIFPHQ and metal chelates (Table-3 and 4 and Figure-4 and 5) indicated that the ligand and all the complexes are toxic, the chelates of copper(II) shows highest toxicity.

CONCLUSION

The hybrid ligand BIFPHQ, containing the pharmacophores of pyrazole, benzimidazole, and 8-hydroxyquinoline, was synthesized and characterized. The ligand effectively chelated Cu(II), Ni(II), Mn(II), Co(II), and Zn(II) ions. Elementary characterization, NMR spectroscopy, mass spectroscopy, magnetic susceptibility, and electron data determined the structures. The research established a significant rise in the antimicrobial activity by means of complexing. The whole set of the metal complexes revealed a higher potency than the free form of the ligand, BIFPHQ, against Gram-positive and Gram-negative bacteria as well as against fungi. The copper(II) derivative possessed the highest level of the antimicrobial action and surpassed the efficiencies of the following drugs: Amoxicillin. It illustrates the feasibility of synthesizing a hybrid ligand and coordinating the ligand with the metal ions for the generation of new drugs for the treatment of bacterial infections. The intense activity of the BIFPHQ-Cu(II) complex render it a potential candidate for carrying out further pharmacological studies and investigation of the mechanism.

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