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Synthesis, Characterization and Antimicrobial Activity of Ni(II), Zn(II), and Cd(II) Complexes of 3/4-Bromo-Benzoic Acid (Phenyl-Pyridine-2-yl-Methylene)-Hydrazide Ligand

Someshwar Bhale [1], Vishnu Gore [2], Sunil Tekale [2], Rajendra P. Pawar [2,*]

[1] Department of Chemistry, Smt. G. G. Khadse College, Muktainagar 425 306, Dist. Jalgaon, Maharashtra, India
[2] Department of Chemistry, Deogiri College, Aurangabad 431 005, Maharashtra, India
* Correspondence: rppawar@yahoo.com;

Scopus Author ID 56095571700
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Abstract: New transition metal complexes $[Ni(L)_2]$, [Zn(L)Cl], $[Zn(L)_2]$ and $[Cd(L)_2]$ were synthesized from 3-bromo-benzoic acid (phenyl-pyridin-2-yl-methylene)-hydrazide (3Bbpph) and 4-bromo-benzoic acid (phenyl-pyridin-2-yl-methylene)-hydrazide (4Bbpph) ligands and were characterized by different physicochemical and spectral studies - IR, elemental, UV Visible, ^{1}H NMR spectra and mass analysis. The data revealed the presence of tetra-coordinate [Zn (L)Cl], whereas $[Ni(L)_2]$, $[Zn(L)_2]$, and $[Cd(L)_2]$ complexes consist of metal ion coordinated with two molecules of ligand to form octahedral geometry. The ligands act as monobasic, tridentate, and coordinated through enolate-O, azomethine-N, and pyridyl-N atoms. The antimicrobial activity of the ligands and metal complexes was investigated against *Staphylococcus Aureus, Streptococcus Pyogenes, Escherichia coli, Salmonella typhi, Candida Albicans* and *Trichophyton Rubrum* which revealed that the metal complexes exhibit greater activity than the parent ligands.

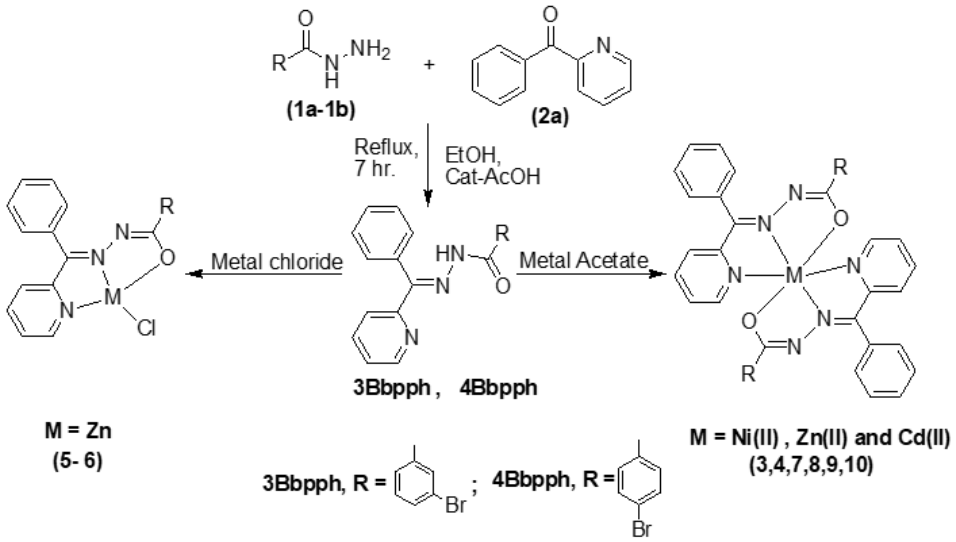
Keywords: Antimicrobial; Metal complexes; NNO donor ligand; Spectral analysis.

1. Introduction

The interest of aryl hydrazone ligands in coordination chemistry has been increased in recent years due to their bonding mode variation towards transition metal ions and an extensive range of biological properties. The presence of lone pair of electrons in a sp^2 hybridized orbital of the nitrogen atom of the Schiff base or azomethine group has considerable biological and chemical importance.

Acylhydrazone Schiff bases easily coordinate with different transition metal ions, which can exhibit interesting physicochemical and biological properties. Transition metal complexes of aroyl hydrazones are known to provide suitable models for elucidation of the mechanism of enzyme inhibition by hydrazine derivatives and their pharmacological applications [1]. The biological activity associated with these compounds is mainly due to the presence of -CONHN=CH- moiety [2] and their ability to form stable chelates as well as multi-coordination centers with essential metal ions.

A number of aryl hydrazone metal complexes have been reported for different biological activities such as antimicrobial [3-5], anticonvulsant [6-7], anti-inflammatory [8-9], antitubercular [10-12] and antiproliferative [13-14] activities. The cadmium (II) ion complex also served as the catalytic center in the carbonic anhydrase enzyme [15]. In addition, the zinc (II) complexes with salicylaldehyde-derived hydrazones [16] proved to present a wider pharmacological profile as anti-inflammatory agents than their hydrazone ligands [17]. Furthermore, copper (II) complex of 2-acetylpyridine and 2-benzoylpyridine-derived hydrazones serve as an effective strategy for antimicrobial activity [18]. The aryl hydrazone of 2-benzoylpyridine acts as tridentate monobasic or neutral ligands due to keto-enol tautomerization. The tridentate binding modes of these ligands make them suitable as mononuclear bis-chelating agents towards central metal ions, forming six coordinated octahedral geometry. The presence of the heterocyclic ring in synthesized ligands extends their pharmacological properties as well as provide an additional binding site to the metal ions [19]. In view of the important role of metal complexes of 2-benzoyl pyridine Schiff bases in biological systems, their structural properties [20-23] and in continuation of our efforts in the development of new metal complexes [24]; in the present article, we report synthesis, characterization and antimicrobial activity of $[Ni(L)_2]$, [Zn(L)Cl], $[Zn(L)_2]$, and $[Cd(L)_2]$ complexes with 3,4-bromo-benzoic acid (phenyl-pyridin-2-yl-methylene)-hydrazide ligand (Scheme 1).



Scheme 1. Preparation of the Ligands 3Bbpph, 4Bbpph, and their metal complexes.

2. Materials and Methods

All common analytical reagent grade chemicals were obtained from commercial sources and used without purification. The chemicals used were Spectrochem, or Sigma Aldrich made. 3 and 4-Bromobenzhydrazides were synthesized by using the reported method [25]. IR spectra of the samples were recorded on Thermo-Nicolet Nexus 670 FT-IR and IR-Affinity-1 spectrometer in the range 4000-400 cm^{-1}. The ^1H NMR spectra of ligand and metal complexes were recorded on Bruker (advance 200) spectrometer in $CDCl_3$ and DMSO-d_6 at 200 MHz. Mass spectra of the ligand and complexes were measured on HRMS-Q Exactive (ORBITRAP) mass spectrometer and Acquity water hyphenated TSQ LCMS, respectively. UV-visible spectra of the complex were recorded on Shimadzu UV-1800 spectrometer. The thermal behavior of the metal complexes was studied with Shimadzu TGA-50, under a nitrogen

atmosphere at a heating rate of 10 °C per minute. The carbon, hydrogen, and nitrogen contents were determined on the Perkin Elmer CHNS analyzer.

Antimicrobial activity of the synthesized ligand and metal complexes were tested *in vitro* against four bacterial and two fungal species by the Petri plate method. The stain was containing solidified 15 ml Muller Hinton Agar was used and Potato Dextrose Agar medium for bacterial and fungal sensitivity, respectively, at 500 ppm concentration in DMSO. The results were compared with known standard antibiotics viz. azithromycin for antibacterial and clotrimazole for antifungal activity, respectively. The plates were incubated at 37℃ for 24 and 48 hr for bacterial and fungal sensitivity, respectively. The activity of compounds was measured in terms of the zone of inhibition in mm.

2.1. General procedure for the synthesis of 3Bbpph & 4Bbpph ligands.

For the synthesis of ligands, equimolar quantity (10 mmol) of 3 or 4-bromobenzhydrazide (1a-1b) and 2-benzoyl pyridine (2a) (10 mmol) was dissolved in 30 mL ethanol, and a catalytic amount of acetic acid was added to the mixture. The resulting mixtures were refluxed for 7 hr with constant stirring. After completion of the reaction, the crude product was poured on crushed ice, filtered off, and finally recrystallized from absolute ethanol, as mentioned in Scheme 1.

Table 1. Physical & analytical data of the synthesized ligand and metal complexes.

Sr. No.	Compound	Mol. Formula (F.W.)	M.P.℃	Color	Elemental Analysis(%):Found (Calcd)			
					% C (cal.)	% H (cal.)	% N (cal.)	% M (cal.)
1	Ligand (3Bbpph)	$C_{19}H_{14}BrN_3O$ (379.032)	156℃	White	60.07 (60.02)	3.70 (3.71)	11.01 (11.05)	-
2	Ligand (4Bbpph)	$C_{19}H_{14}BrN_3O$ (379.032)	161℃	Bright yellow	60.10 (60.02)	3.65 (3.71)	15.03 (11.05)	-
3	[Ni(3Bbpph)$_2$]	$C_{38}H_{26}Br_2N_6NiO_2$ (817.15)	>250℃	Brown	15.91 (15.85)	3.30 (3.21)	10.15 (10.28)	7.20 (7.18)
4	[Ni(4Bbpph)$_2$]	$C_{38}H_{26}Br_2N_6NiO_2$ (817.15)	>250℃	Brown	15.80 (15.85)	3.26 (3.21)	10.20 (10.28)	7.25 (7.18)
5	[Zn(3Bbpph)Cl]	$C_{19}H_{13}BrClN_3OZn$ (480.073)	>250℃	Yellow	47.60 (47.54)	2.71 (2.73)	8.86 (8.75)	13.65 (13.62)
6	[Zn(4Bbpph)Cl]	$C_{19}H_{13}BrClN_3OZn$ (480.073)	>250℃	Yellow	47.57 (47.54)	2.71 (2.73)	8.78 (8.75)	13.80 (13.62)
7	[Zn(3Bbpph)$_2$]	$C_{38}H_{26}Br_2N_6O_2Zn$ (819.97)	>250℃	Yellow	55.40 (55.40)	3.20 (3.18)	10.16 (10.20)	7.99 (7.94)
8	[Zn(4Bbpph)$_2$]	$C_{38}H_{26}Br_2N_6O_2Zn$ (819.97)	>250℃	Yellow	55.47 (55.40)	3.15 (3.18)	10.24 (10.20)	7.91 (7.94)
9	[Cd(3Bbpph)$_2$]	$C_{38}H_{26}Br_2CdN_6O_2$ (870.87)	>250℃	Cream yellow	52.46 (52.41)	3.12 (3.01)	9.52 (9.65)	12.96 (12.91)
10	[Cd(4Bbpph)$_2$]	$C_{38}H_{26}Br_2CdN_6O_2$ (870.87)	>250℃	Cream yellow	52.48 (52.41)	3.00 (3.01)	9.61 (9.65)	12.95 (12.91)

2.2. Spectral data of the synthesized ligands.

2.2.1. 3-Bromo-benzoic acid (phenyl-pyridin-2-yl-methylene)-hydrazide (3Bbpph).

Yield: 81(%), Color: white, M.P.-156℃. IR (KBr, cm^{-1}): 3449 (NH), 1689 (C=O), 1580 (C=N), 1077 (N-N), 713 (C-Br); ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm :15.37 (br. s, 1H, -NH), 8.89- 8.76 (m, 1H, Ar-H), 8.15 (t, *J* = 1.7 Hz, 1H, Ar-H), 7.91 (dd, J = 1.2, 8.0 Hz, 1H, Ar-H), 7.82 (dd, *J* = 1.9, 7.8 Hz, 1H, Ar-H), 7.73-7.55 (m, 3H, Ar-H), 7.50-7.32 (m, 6H, Ar-H); ^{13}C NMR (200 MHz, $CDCl_3$) δ ppm : 162.73, 152.99, 147.76, 137.66, 137.50,134.75,134.74, 130.78, 130.26, 129.41, 129.14, 128.35, 126.91, 126.06, 124.39, 122.85; HRMS: m/z (%): 380.0393 $(M+H)^+$.

2.2.2. 4-Bromo-benzoic acid (phenyl-pyridin-2-yl-methylene)-hydrazide (4Bbpph).

Yield: 85(%). Color: Bright yellow, M.P.: 160-162°C. IR (KBr, cm^{-1}): 3449 (NH), 1682 (C=O), 1581 (C=N), 1003 (N-N), 712 (C-Br). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 15.20 (br., s., 1H, NH), 8.77-8.89 (m, 1H, Ar-H), 7.82-7.90 (m, 3H, Ar-H), 7.54-7.72 (m, 4H, Ar-H), 7.39-7.48 (m, 5H, Ar-H); ^{13}C NMR (200 MHz, $CDCl_3$) δ pm: 163.42, 153.06, 148.24, 147.77, 137.63, 137.58, 137.56, 132.68, 131.94, 129.41, 129.14, 128.37, 126.90, 126.60, 124.32; HRMS : m/z (%) 380.0393 $(M+H)^+$.

2.3. General procedure for the synthesis of metal complexes (3-10).

The complexes of [Ni (II), Zn (II), and Cd (II)] were synthesized by mixing 1:2 molar ratio of the corresponding metal acetate to the ligand, and Zn (II) complexes were synthesized by mixing 1:1 molar ratio of zinc chloride to the ligand in methanol. The basic pH of the resulting solution was maintained by adding alcoholic ammonia and refluxed for 10 hr. After the completion of the reaction, the reaction mass was filtered in the hot condition and washed with methanol. The physical and analytical data of the synthesized ligand and metal complexes are mentioned in Table 3. The ^{1}H NMR and mass spectra of the synthesized Zn metal complexes are shown in Figures 1-4.

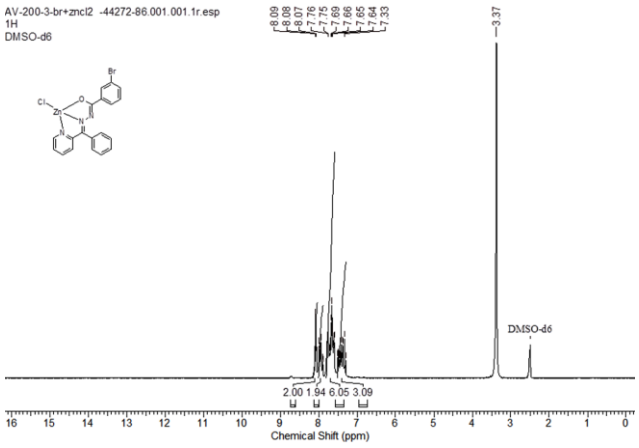


Figure 1. ^{1}H NMR of [Zn(3Bbpph)Cl].

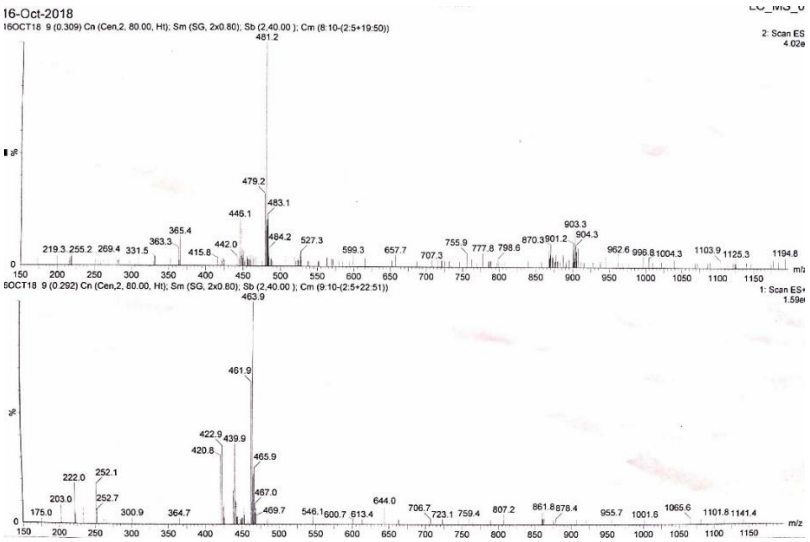


Figure 2. LCMS of [Zn(3Bbpph)Cl].

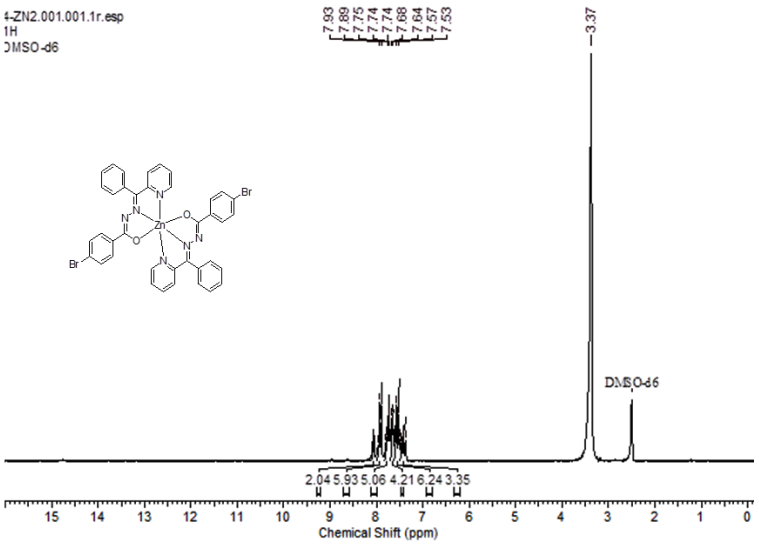


Figure 3. ^{1}H NMR of [Zn(4Bbpph)$_2$].

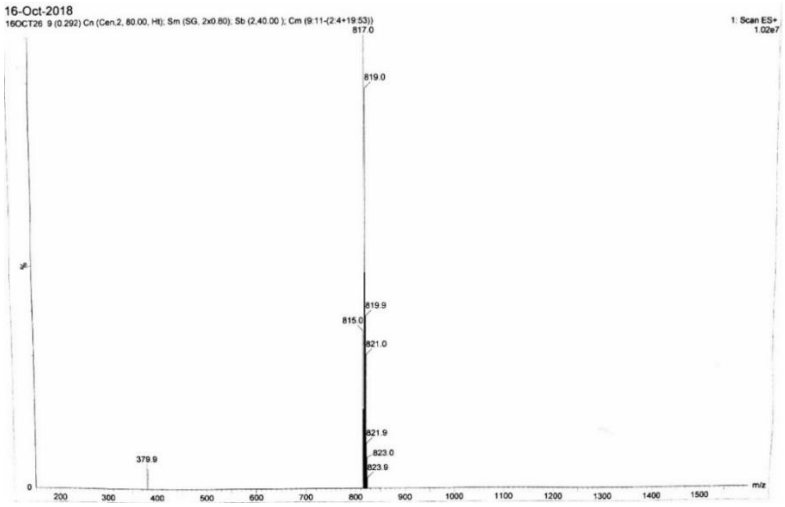


Figure 4. LCMS of [Zn(4Bbpph)$_2$].

3. Results and Discussion

3.1. IR spectra.

The IR spectral data of the ligands and their metal complexes are presented in Table 2. In IR spectra, characteristic bands were found in the range of 3449-3450, 1682-1689, and 1580-1581 cm^{-1} in ligands corresponding to ν(NH), ν(C=O) and ν(C=N) functional group respectively. The disappearance of ν(NH) and ν(C=O) bands in metal complexes indicates that the ligand binds through enolate- 'O' during complexation via keto-enol tautomerism [26]. A new band appearing in the range between 1343-1359 cm^{-1} for (C-O) in metal complexes confirms the bonding of oxygen through deprotonation. The bands for ν(C=N) stretching in ligands were shifted to lower frequencies in metal complexes implying the involvement of nitrogen of azomethine group upon complexation [27].

Metal complexes show additionally non-ligand band in the range 449-470 cm^{-1} and 496-518 cm^{-1}, which are tentatively assigned to ν(M-N) and ν(M–O), respectively.

Table 2. IR spectral data of ligand (3Bbpph and 4Bbpph) and metal complexes.

Ligand / Complex	ν(HC=N)	ν(NH)	ν(M-N)	ν(M-O)
Ligand (3Bbpph)	1580	3449	-	-
Ligand(4Bbpph)	1581	3449	-	-

Ligand / Complex	ν(HC=N)	ν(NH)	ν(M-N)	ν(M-O)
[Ni(3Bbpph)$_2$]	1552	-	453	518
[Ni(4Bbpph)$_2$]	1577	-	468	503
[Zn(3Bbpph)$_2$]	1562	-	449	515
[Zn(4Bbpph)$_2$]	1579	-	470	496
[Zn(3Bbpph)Cl]	1560	-	449	514
[Zn(4Bbpph)Cl]	1579	-	468	496
[Cd(3Bbpph)$_2$]	1570	-	445	513
[Cd(4Bbpph)$_2$]	1579	-	470	492

3.2. ^{1}H NMR spectra.

^{1}H NMR spectra of the metal complex were examined in comparison with that of ligands. The spectra of ligands show singlet at 15.37 and 15.20 ppm for 3Bbpph and 4Bbpph ligands, respectively, which was assigned to -NH proton of hydrazide. The -NH proton appears at a higher region due to intramolecular hydrogen bonding between amide proton and pyridyl-N [28]. The disappearance of -NH proton of hydrazide in metal complexes confirms the involvement of oxygen in coordination by deprotonation via enolate. The aromatic protons (13 hydrogens) of ligand (3Bbpph) appear in the range 7.38-8.85 ppm, which were shifted to upfield in [Zn(3Bbpph)Cl] complex in the range 7.33-8.09 ppm. On the other hand, the aromatic proton (13 hydrogens) of ligand (4Bbpph) were observed in the range 7.43-8.83 ppm, which were shifted to upfield in [Zn(4Bbpph)$_2$] complex in the range 7.53-7.93 ppm.

3.3. Mass spectra.

HRMS mass spectra of ligands (3Bbpph & 4Bbpph) showed peaks at 380.0393 and 380.0392, respectively, which corresponds to M+H, confirming the suggested molecular formula $C_{19}H_{14}BrN_3O$ for the ligands. The mass spectra of [Zn(4Bbpph)Cl] and [Zn(3Bbpph)$_2$] metal complexes showed peaks at 481.2,483.1 and 821.0,823.0 amu which correspond to molecular ion peaks at M+1, M+2 in 3:1 ratio in case of chlorine and 1:1 in case of bromine (Figure 2 and Figure 4). The molecular ion peaks confirm the proposed molecular formula of metal complex $C_{19}H_{13}BrClN_3OZn$ and $C_{38}H_{26}Br_2N_6O_2Zn$, respectively (Figure 2, 4).

3.4. UV -Visible spectra.

The UV-visible spectra of metal complexes (3)-(4) and (7)-(8) were recorded in DMSO solvent, which showed regular octahedral geometry. The bands in the range 320-340 nm representing the imino group were detected in some complexes. The bands observed in the range of 390-415 nm can be attributed to the ligand to metal charge transfer transition [29]. Nickel (II) complex gives to rise three absorption bands at 10405, 16850 and 25608 cm^{-1}, attributable to $^3A_{2g}(F) \longrightarrow {}^3T_{2g}(F)$ (ν_1), $\longrightarrow {}^3T_{1g}(F)$ (ν_2) and $\longrightarrow {}^3T_{1g}(P)$ (ν_3) transitions in an octahedral field [30].

3.5. TGA analysis.

Thermal analysis of metal complexes was studied under the nitrogen atmosphere at a heating rate of 10 °C/min within the temperature range of 25-700 °C. The [Zn(3Bbpph)$_2$] complex was decomposed in one stage between the temperature range 375-425 °C, which finally forms the corresponding metal oxide. Besides that the [Cd(4Bbpph)$_2$] complex decomposed in two stages, in the first stage there was the loss of some part of ligand and in the second stage complete loss of ligand and formation of the metal oxide. The test for halide ion

with the $AgNO_3$ solution was negative, indicating that the halide ion is inside the coordination sphere.

3.6. Antimicrobial screening.

The results of antimicrobial screening showed that the metal complexes were more active than the parent ligands (Table 3) against the same microbe under identical conditions. Increasing activity of metal complexes can be attributed due to the suspected factors such as dipole moment, stability, the bond length between metal and ligand, and cell permeability mechanism influenced by the presence of metal ion. Only the $[Zn(3Bbpph)_2]$, $[Cd(3Bbpph)_2]$, and $[Cd(4Bbpph)_2]$ complexes exhibited moderate activity, but less than the standard against all the tested microbes. The remaining complexes were totally inactive against the employed microbes.

Table 3. Antimicrobial screening of the synthesized compounds.

Compounds		Antibacterial Activity (Zone of inhibition in mm)				Antifungal Activity (Zone of inhibition in mm)	
		S. Aureus	*S. Pyogenes*	*E. Coli*	*S. Typhi*	*C. Albicans*	*T. Rubrum*
1	Lig.(3Bbpph)	-	-	-	-	-	-
2	Lig.(4Bbpph)	-	-	-	-	-	-
3	$[Ni(3Bbpph)_2]$	-	-	-	-	-	-
4	$[Ni(4Bbpph)_2]$	-	-	-	-	-	-
5	[Zn(3Bbpph)Cl]	-	-	-	-	-	-
6	[Zn(4Bbpph)Cl]	-	-	-	-	-	-
7	$[Zn(3Bbpph)_2]$	-	-	10	10	-	-
8	$[Zn(4Bbpph)_2]$	-	-	-	-	-	-
9	$[Cd(3Bbpph)_2]$	14	16	-	10	16	16
10	$[Cd(4Bbpph)_2]$	14	-	-	11	-	12
Antibiotic (AB) (Azithromycin)		**26**	**24**	**25**	**20**	**-**	**-**
Antifungal (AF) (Clotrimazole)		**-**	**-**	**-**	**-**	**18**	**25**

4. Conclusions

In the present study, two 3 or 4-bromo-benzoic acid (phenyl-pyridin-2-yl-methylene)-hydrazide ligands and their Ni(II), Zn(II) and Cd(II) complexes were synthesized and characterized by various spectral techniques. The spectral data indicate that the monoanionic tridentate behavior for ligands, which were coordinated via azomethane-nitrogen, pyridyl-nitrogen, and deprotonated carboxylate-oxygen atom to the central metal ions. Besides that, all-metal complexes except [Zn(3Bbpph)Cl] and [Zn(4Bbpph)Cl] were tetra coordinated & the others were octahedral around the central metal ion. The synthesized complexes are air-stable, non-hygroscopic, insoluble in most organic solvents but soluble in DMSO. The results of elemental analysis for all the metal complexes were in good agreement with the theoretical requirement of their compositions. Infrared, UV-Visible, ^{1}H-NMR, and mass spectrometry support the formation of the above compounds. Almost all the metal complexes had moderate to good antimicrobial activity as compared to the standard drugs.

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Conflicts of Interest

The authors declare no conflict of interest.

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