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Synthesis, Characterization, and Biological Activity of Transition Metal Complexes of Oxadiazole

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A new oxadiazole and its metal complexes have been synthesized and characterized. The ligand potassium 2-(2-phenylisonicotinoyl)hydrazinecarbodithioate $[K^+(H_2L)^-]$ (1) on reaction with transition metals in EtOH-H_2O medium undergoes cyclization and converted to 5-(2-phenyl-4-pyridyl)-1,3,4-oxadiazole-2-thione (ppot), which yielded a series of mononuclear transition metal complexes. Four transition metal complexes of ligand are prepared and characterized based on elemental analysis, IR, ^{1}H NMR, UV-vis spectra, and thermogravimetry-differential thermal analysis (TG-DTA). From the obtained data, the structure of complexes has the general formula $[M(ppot)_2Cl_2(H_2O)_2]$, where M = Cu(II), Co(II), Ni(II), Zn(II). The thermal behaviors of these complexes showed that the complexes lost coordinated water molecules in the first step followed by decomposition of the ligand molecule in the subsequent steps. The ligand and its transition metal complexes were screened against fungi and bacteria *in vitro*. Data obtained showed that the ligand itself showed moderate biological activity, whereas the metal complexes exhibited a higher inhibition towards both bacteria and fungi.

Keywords 1,3,4-oxadiazole, biological activity, complexes, metal complexes

INTRODUCTION

1,3,4-oxadiazoles are an important class of heterocyclic compounds whose chemistry and uses have been highlighted in numerous reports.[1–4] Their syntheses and transformations have been of interest for a long time as they demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. They have proven antimicrobial, anti-inflammatory, antimitotic, antiarrhythmic, and insecticidal activities,[5–8] and are among the most widely employed in several areas such as corrosion inhibition, molecular sensory systems, and organic light-emitting diodes (OLEDs).[9–12] The heterocyclic thiones represent an important type of compound in the field of coordination chemistry because of their potential multifunctional donor sites, viz either exocyclic sulfur or endocyclic nitrogen.[13–14]

The classical synthetic routes to substituted 1,3,4-oxadiazoles thione/thiolate involve ring-forming reactions. Their syntheses attracted considerable attention and a number of methods have been used for their synthesis. The widely used strategy involves the cyclization of acyldithiocarbate esters, N-aroylditiocarbazates, and their salts to 1,3,4-oxadiazoles in the presence of a base.[13,14] Several other reported methods for synthesis of oxadiazoles include oxidative cylization of acylhydrazones,[15] acylthiourea,[16–18] and acylthiosemicrbazide.[19–22] Cyclization of N^2-[bis(benzylsulfanyl)methylene] benzohydrazide (N^2-Hbmbh) to 2-benzylsulfanyl-5-(2-methoxyphenyl)-1,3,4-oxadiazole during complexation with metals under normal condition without the use of any other reagent viz. base or acid was reported by Sigh and coworkers.[23]

The wide spectrum of biological properties and other applications of oxadiazoles and their metal complexes prompted the study of the metal complexes of 5-(2-phenyl-4-pyridyl)-1,3,4-oxadiazole-2-thione obtained by the cyclization of potassium 2-(2-phenylisonicotinoyl)hydrazinecarbodithioate. We report herein the synthesis, spectroscopic characterization, thermogravimetric, and antimicrobial activity of the oxadiazole ligand and its Cu(II), Co(II), Ni(II) and Zn(II) complexes.

EXPERIMENTAL

Materials and Physical Measurement

Analytical grade (AR) chemicals with highest purity available were used. The analysis of CHNS/O contents of ligand and metal complexes were done on Euro elemental analyzer.

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IR spectra were recorded on (Thermo-Nicolet FT-IR, Nicolet IR-200, USA) spectrometer using KBr pellets. TG/DTA curves for the complexes were recorded on Nietzsche thermobalance (model-STA 40 g) with P_tV_s P_t 10% Rh thermocouple in dynamic air conditions between the room temperature (~20°C) and 1020°C (gradient 10K/min).

Synthesis of Ligand $[K^+(H_2L)^-]$ (1)

$K^+(H_2L)^-$ was synthesized by the drop wise addition of CS_2(6.09 mL 0.1012 mol) to a solution of 2-phenylisonicotinohydrazide (6 g 0.0225 mol) and KOH (2.53 g 0.0451 mol) in 50 mL MeOH. The solution was stirred continuously for 3h at room temperature. The precipitated product was filtered off and washed with diethyl ether. Color: Yellow. Yield: 0.76 g 86 %. m.p.: 134°C. Anal. calc. for $C_{13}H_{10}KN_3OS_2$: C, 47. 68; H, 3.08; N, 12.83; S, 19.58%. Found: C, 47.02; H, 2.98; N, 11.98; S 19.34%. FTIR (KBr, cm^{-1}): υ(NH) 3174m; υ(C=O) 1647; [β(NH) +υ (CN)] (thioamide I) 1454; [υ (CN) + β(NH)] (thioamide II) 1374;υ(N-N) 1060 m; υ(C=S) 997s; pyridine ring 654.^{1}H NMR (DMSO-d_6) s,singlet; m, multiplet): δ 10.95 (s, 1H secondary amide), δ 2.5 (s, 1H amine), δ 7.31 – 8.20 (m, Ar H's). UV-Vis spectrum [λ_{max} DMF, cm^{-1}]: 37453, 31847, 24875 cm^{-1}.

Synthesis of Metal Complexes

All the metal complexes **(2–5)** were prepared by a general procedure. Hot solution (60°C) of the appropriate metal chlorides (1.05 mmol) in an ethanol water mixture (1:1, 25 mL) was added to the hot solution (60°C) of the carbodithioate (0.4 g, 1 mmol) in the same solvent (25 mL).The resulting mixture was stirred under reflux for 1 h, the precipitate was filtered off, washed twice with a 1:1 ethanol: water mixture.

*$[Cu(ppot)_2Cl_2(H_2O)_2]$ (**2**)*

Color: Brown. m.p.: 232°C. Anal. calc. for $C_{26}H_{16}N_6O_4S_2CuCl_2$: C, 48. 56; H, 2.51; N, 13.07; S, 9.97, Cu, 9.88 %. Found: C, 45.60; H, 2.42; N, 12.98; S, 9.34, Cu, 9.78%. FTIR (KBr, cm^{-1}): υ(OH) 3371 m; υ(C=N) 1604s; υ_{as}(C-O-C) 1233; υ_s(C-O-C) 1154; υ(N-N) 1094m; υ(C-S) 840 s. UV-Vis spectrum [λ_{max} DMF, cm^{-1}]: 24682, 37453, 31545.

*$[Co(ppot)_2Cl_2(H_2O)_2]$ (**3**)*

Color: Black. m.p.: 201°C. Anal. calc. for $C_{26}H_{16}N_6O_4S_2CoCl_2$: C, 48. 91; H, 2.53; N, 13.16; S, 10.05; Co, 9.23%. Found: C, 48.89; H, 2.51; N, 13.10; S, 10.02, Co, 9.12 %. FTIR (KBr, cm^{-1}): υ(OH) 3215m; υ(C=N) 1606s; υ_{as}(C-O-C) 1236; υ_s(C-O-C) 1156; υ(N-N) 1096m; υ(C-S) 843 s. UV-Vis spectrum [λ_{max} DMF, cm^{-1}]: 24691, 33112, 34722, 40160.

*$[Ni(ppot)Cl_2(H_2O)_2]$ (**4**)*

Color: Green Yellow.. m.p.: 243°C. Anal. calc. for $C_{26}H_{16}N_6O_4S_2NiCl_2$i: C, 48. 93; H, 2.53; N, 13.17; S, 10.05; Ni, 9.20 %. Found: C, 49.01; H, 2.48; N, 13.08; S, 10.04, Ni, 9.18%. FTIR (KBr, cm^{-1}): υ(OH) 3371m; υ(C=N) 1607s; υ_{as}(C-O-C) 1233; υ_s(C-O-C) 1154; υ(N-N) 1097m; υ(C-S) 842 s. UV-Vis spectrum [λ_{max} DMF, cm^{-1}]: 24813, 32786, 34843, 37594.

*$[Zn(ppot)_2Cl_2(H_2O)_2]$ (**5**)*

Color: Light Yellow. m.p.: 235°C. Anal. calc. for $C_{26}H_{16}N_6O_4S_2ZnCl_2$: C, 48. 42; H, 2.50; N, 13.03; S, 9.94; Zn, 10.14 %. Found: C, 48.50; H, 2.48; N, 13.01; S, 9.84, Zn, 10.03%. FTIR (KBr, cm^{-1}): υ(OH) 3218m; υ(C=N) 1607s; υ_{as}(C-O-C) 1233; υ_s(C-O-C) 1158; υ(N-N) 1098m; υ(C-S) 841 s. UV-Vis spectrum [λ_{max} DMF, cm^{-1}]: 25773, 31645, 37453.

Biological Activity

The antibacterial activity of the ligand and its metal complexes (**1–5**) was tested *in vitro* against test bacteria *S. aureus* (Gram-positive) and *E. coli* (Gram-negative) at different concentrations by disc diffusion technique.[24,25] Twenty-five milliliters of sterilized nutrient agar media (NA) was poured in each petriplate. After solidification, 0.1 mL of test bacteria was spread over the medium using a spreader. The test compounds in measured quantities were dissolved in DMF to get concentration of 200, 100, and 50 μg mL^{-1}. The disc Whatmann No. 1 filter paper having the diameter 5.00 mm each containing (1.5 mg cm^{-1}) of compounds were placed at four equidistant places at a distance of 2 cm from the center in the inoculated petriplates. Filter paper disc treated with DMF served as control and pencillin was used as a standard drug. All determinations were made in duplicate for each of the compounds. Average of two independent readings for each compound was recorded. These petriplates were kept in refrigerator for 24 h for pre-diffusion. Finally petriplates were incubated at 30°C for 24 h.

The *in vitro* antifungal activity of the ligand and their corresponding complexes was tested by the food poison technique using potato-dextrose-agar (PDA) medium at 200, 100, and 50 μg mL^{-1}. *R. bataticola* and *A. alternate* were used as test organism. Stock solutions of compounds were prepared by dissolving the compounds (0.064 mg) in DMF. Chlorothalonil was used as commercial fungicide and DMF served as control. Appropriate quantities of the compounds in DMF was added to potato dextrose agar medium in order to get a concentrations 200, 100, and 50 μg mL^{-1} of compounds in the medium. The medium was poured into a set of two petriplates under aspartic conditions in a laminar flow hood. When the medium in the plates was solidified, a mycelial disc of 0.5 cm in diameter was cut from the periphery after 7 days old culture, and it was aseptically inoculated upside down and incubated at 25 ± 1°C until fungal growth in the control petriplates was almost complete. All the measurements were carried out in triplicates.

RESULTS AND DISCUSSION

Potassium 2-(2-phenylisonicotinoyl)hydrazinecarbodithioate (**1**) was synthesized from 2-phenylisonicotinohydrazide and its

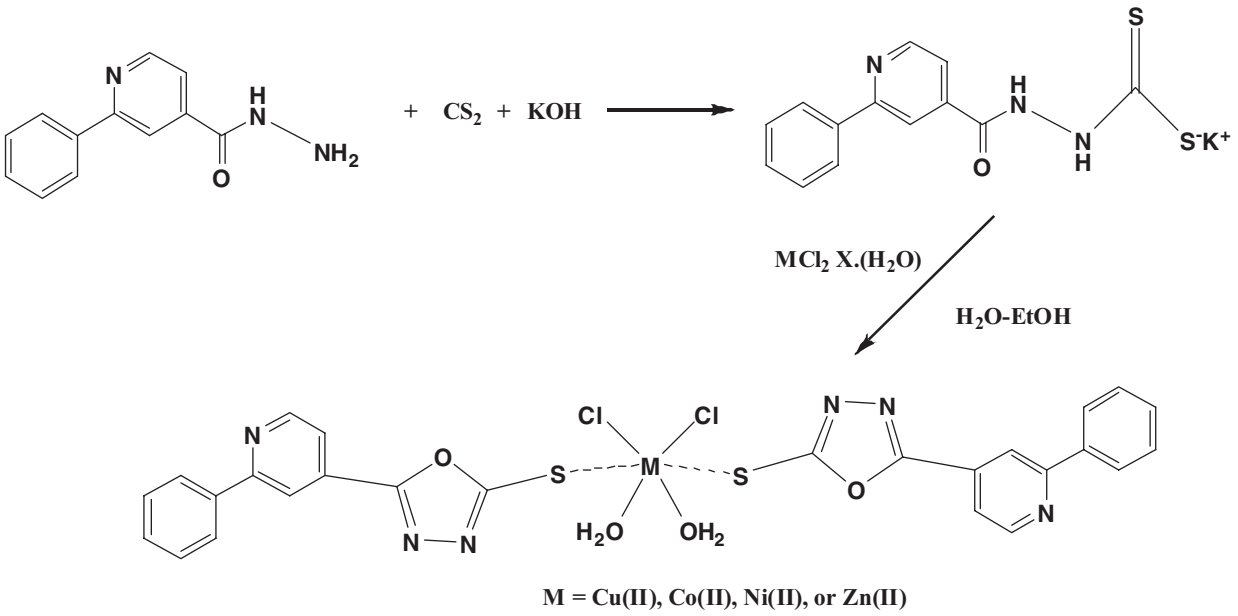

FIG. 1. Synthesis of the ligand $[K^+(H_2L)^-]$ (**1**) and its metal complexes (**2–5**).

metal complexes were prepared, as shown in the Figure 1. The transition metal complexes were obtained by substitution reaction of metal halide with bidentate ligand, in 1:2 molar ratios. Microanalytical data (CHNS), FT-IR, Uv-vis spectroscopy, ^{1}H NMR, and TG/DTA were used to characterize the complexes and are consistent with the proposed formula (Table 1). The room temperature molar conductivity measurement (10^{-3}) in DMSO indicated that the complexes are non-electrolytes. All the complexes (**2–5**) are non-hygroscopic and are stable in air, but are insoluble in common organic solvents.

IR Spectra

The characteristic IR absorption bands of the functional groups of the complexes showed significant changes when compared with that of the parent free ligand. Shift of IR absorption of some of characteristic vibrational frequencies of the functional groups of the ligand upon complexation provides evidence for the mode of binding of the ligand and to the metal ion. The IR spectra of the complexes are very similar to each other, except some slight shifts and intensity change of a few vibration bands caused by different metal ions, which indicate that the complexes have similar structures. Representative IR spectra of the ligand (**1**) and complex (**4**) are shown in Figure 2.

The IR spectrum of $[K^+(H_2L)^-]$ exhibited a medium band at 3174 cm^{-1} due to ν(N-H) and the band at 1647 cm^{-1} was assigned to υ(C=O) vibrations. The characteristic bands due to υ(C=O), thioamide I, thioamide II, υ(C=S),υ(N-N), observed at 1647, 1454, 1374, 1060 and 997 cm^{-1}, respectively. The band at 654 cm^{-1} is due to the pyridine ring.

A comparative study of the IR spectra of **2**, **3**, **4**, and **5** with that of $[K^+(H_2L)^-]$ (**1**) indicated that bands due to υ(C=O), thioamide I, thioamide II and υ(C=S) were absent. Appearance of new bands at 1604–1609 cm^{-1} (endocyclic C=N), 1408–1412 cm^{-1} for υ_{as}(C-O-C), and 1279–1280 cm^{-1} for υ_s(C-O-C) suggest cyclization of acyclic dithiocarbazate (**1**). The IR data are consistent with the presence of a 1,3,4-oxadiazole moiety.[26] The spectra of all complexes exhibited intense broad bands at 3400–3200 cm^{-1} due to υ(OH) of the coordinated water molecule(s).[27] The presence of coordinate water molecules also confirmed by elemental and thermogravimetric analyses.

UV-Vis Absorption Spectra

The electronic absorption spectra (not shown) of the ligand (**1**) and its metal complexes (**2–5**) were recorded in DMF

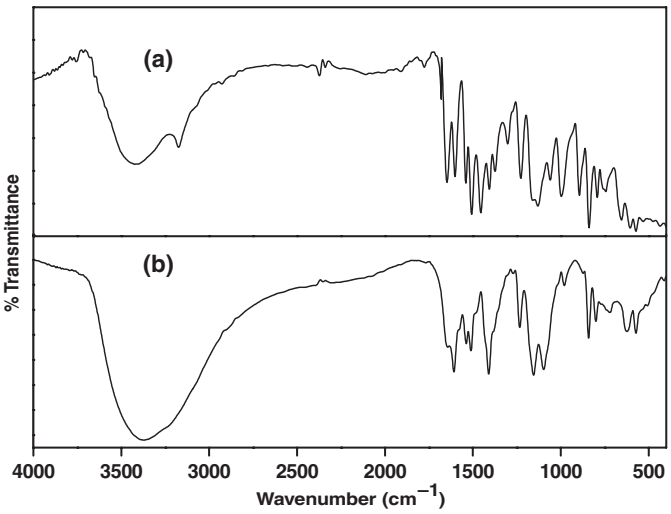

FIG. 2. FTIR spectra of (a) $[K^+(H_2L)^-]$ and (b) $[Ni(ppot)_2Cl_2(H_2O)_2]$.

TABLE 1
Analytical data and other details of the compounds **1–5**

S. No.	Molecular formula	Formula weight	Color (% yield)	M. p. (°C)	Elemental analysis % found [calculated]					Molar conductance ($ohm^{-1}mol^{-1}cm^2$)
					C	H	N	S	M	
1	$C_{13}H_{10}KN_3OS_2$	327.47	Yellow	134	47.02 (47.68)	3.08 (2.98)	12.83 (11.98)	19.58 (19.34)	–	–
2	$C_{26}H_{16}N_6O_4S_2CuCl_2$	640.94	Brown	232	45.60 (48.56)	2.42 (2.51)	12.98 (13.07)	9.34 (9.97)	9.78 (9.88)	18
3	$C_{26}H_{16}N_6O_4S_2CoCl_2$	638.41	Black	201	48.89 (48.91)	2.51 (2.53)	13.10 (13.16)	10.02 (10.05)	9.12 (9.23)	17
4	$C_{26}H_{16}N_6O_4S_2NiCl_2$	638.17	Green	243	49.01 (48.93)	2.48 (2.53)	13.08 (13.17)	10.04 (10.05)	9.18 (9.20)	27
5	$C_{26}H_{16}N_6O_4S_2ZnCl_2$	644.89	Light Yellow	235	48.50 (48.42)	2.48 (2.50)	13.01 (13.03)	9.84 (9.94)	10.03 (10.14)	22

solution. The electronic spectra of **1** shows bands at 37453 cm^{-1} and 31847 cm^{-1} due to $\pi \rightarrow \pi^*$ transition and a band at 24875 cm^{-1} due to $n \rightarrow \pi^*$ transition. These bands may be attributed to the intraligand charge transfer of the NCS_2^- group.[28] The band at 24875 cm^{-1} is assignable to the $n \rightarrow \pi^*$ transition of the pyridine ring. A comparison of the spectra of the free ligands and their complexes showed the $\pi \rightarrow \pi^*$ presence of the bands of the ligand in all complexes. On complexation, these bands suffer considerable shifts due to coordination to respective metal ions. The absorption bands of the complexes **2–5** in the same solvent are exhibited bands at 24500–28500 cm^{-1} and at 32300–32500 cm^{-1}, which are assigned to the d $\rightarrow$ d transitions. The absorption in the ultraviolet region are assignable to transitions within the ligand orbitals, and that in the visible region is probably due to charge transfer transition involving ligand and metal orbitals, transition from S$\rightarrow$M.[29] The strong band at about 24690–28500 cm^{-1} is assignable to a combination of metal-ligand charge transfer (M $\rightarrow$ LCT) and d-d bands.[30] The nature of electronic spectra of **2–5** were similar to those observed for other octahedral transition metal complexes.[31]

^{1}HNMR Spectra

The ^{1}HNMR spectra of the ligand (Figure 3) showed two singlets at δ =10.95, 2.5 due to the presence of secondary amide and primary amine protons, respectively, as they disappeared on duteration. These two signals are absent in the spectra of the complexes supports the ring cyclization. The free ligand exhibited mulitiplet signals at δ =7.31 – 8.20 are due to the protons of the aromatic ring of the ligand.

TG-DTA

Thermogravimetric (TG) and differential thermal (DTA) analyses were used to describe thermal behavior of the prepared complexes **2–5**. The typical TG-DTA analysis of the complexes was performed from 20 to 1020°C at a heating rate of 10 K min^{-1} under dynamic air condition. The TG and DTA study of complex (**2**) presents two steps of decomposition, shown in Figure 4. The first decomposition step occured at 70–180°C. In the first step, the complex loses the water molecules coordinated to the metal atom. This process is confirmed by two small endo-effects at 70 and 170°C. Second decomposition step occured between 210–700°C, due to the pyrolysis of the whole oxadiazole molecule. The degradation of this complexes was confirmed by two exo-effects, one at 360°C and another broad exothermic peak at 520°C. The TG curve for **3** showed two steps of decomposition. The first decomposition step occurred with a narrow temperature range between 90–140°C, which may be attributed to the loss of two coordinated water molecules. One endothermic peak centered at about 120°C is observed in the DTA curve. The second decomposition step occured at the temperature range 300 to 770°C. This may be due to the loss of oxadiazole moiety. A broad exothermic peak centered at about 620°C is noticed. The remaining residue is the metal oxide. The

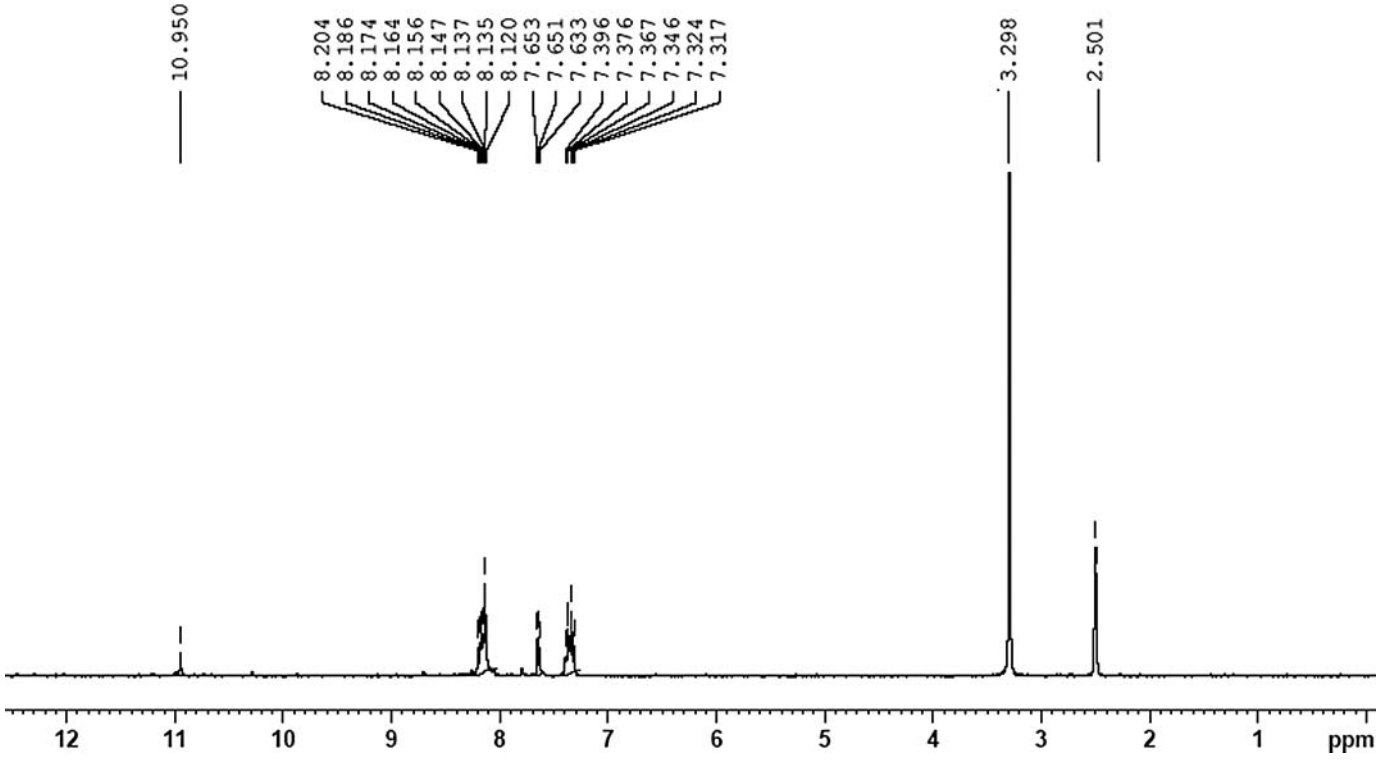

FIG. 3. H^{1}NMR spectrum of compound **1**.

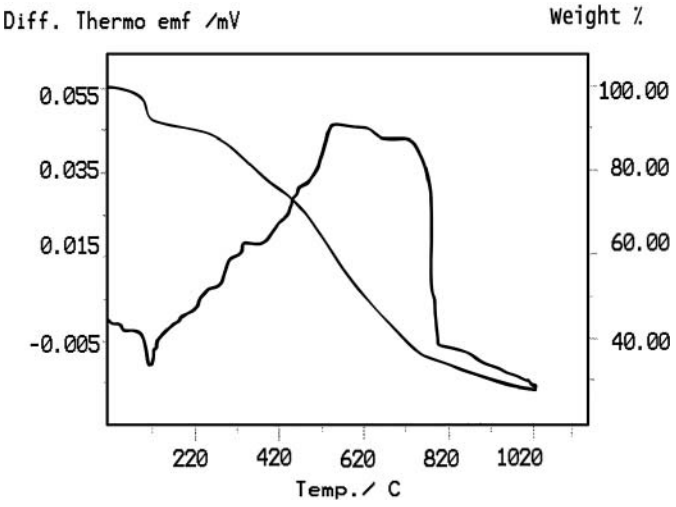

FIG. 4. TG and DTA thermograms of the complex **2**.

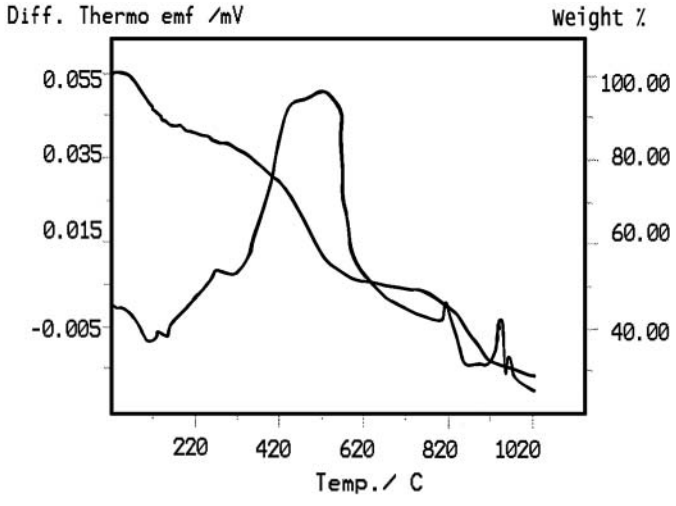

FIG. 5. TG and DTA thermograms of the complex **4**.

TG curve for complex **4** showing three decomposition steps is shown in Figure 5. The first decomposition step occurred at the temperature range 60 to 165°C, which corresponds to loss of two coordinated water molecules. A small endo-effect is observed at 110°C. Second decomposition step occurred at 330–570°C, and the third decomposition step occured at the temperature range 800–960°C. Three exothermic peaks are observed in the DTA curve, one broad exothermic peak centered at about 490°C, another at 820°C, and the third one at 930°C. The complex **5** was thermally stable up to 100°C after that there was decomposition up to 180°C. This loss in weight of the molecule corresponds to two water molecules. This process is accompanied by endo-effect observed on the DTA curve with maximum at 120°C. The second decomposition occurred at 320–360°C, and the third decomposition occurred at 540–680°C. Four small endothermic peaks are observed at the temperature 360, 530, 550, and 620°C in the DTA.

TABLE 2
In vitro antibacterial activity of ligand **1** and its complexes **2–5**

Compounds	Bacteria tested	Diameter (mm) of compounds at concentrations (μg mL^{-1}) 200	100	50
1	*S.aureus*	10	6	—
	E. coli	7	4	—
2	*S.aureus*	17	9	5
	E. coli	14	7	3
3	*S.aureus*	14	7	4
	E. coli	11	5	2
4	*S.aureus*	15	8	5
	E. coli	13	7	2
5	*S.aureus*	12	5	4
	E. coli	9	4	2
Pencillin (standard)	*S.aureus*	18	10	7
	E. coli	20	12	8

Biological Activity

The invitro antimicrobial properties of the heterocyclic ligand **1** and its metal complexes **2–5** were evaluated against gram-positive and gram-negative bacteria and fungi, and the results at different loading volume are presented in Table 2 and Table 3. All of the tested compounds showed a remarkable biological activity at higher concentration (200 μg) against microorganisms. The ligand **1** exhibit a moderate activity against both bacteria

TABLE 3
In vitro antifungal activity of ligand **1** and its complexes **2–5**

Compounds	Fungus	Fungal inhibition (%) at concentrations (μg mL^{-1}) 200	100	50
1	*R. bataticola*	54.22	32.0	16.0
	A. alternata	34.12	23.22	14.2
2	*R. bataticola*	84.21	71.11	42.10
	A. alternata	90.12	74.01	43.22
3	*R. bataticola*	76.34	69.23	38.09
	A. alternata	80.12	72.22	40.03
4	*R. bataticola*	67.32	56.32	34.02
	A. alternata	72.33	58.11	36.33
5	*R. bataticola*	70.22	65.01	36.11
	A. alternata	67.23	68.11	37.22
Chlorothalonil (standard)	*R. bataticola*	85.5	73.9	45.0
	A. alternata	94.8	76.0	44.0

and fungi. A significant inhibition activity, higher than that of the corresponding ligand, is displayed by metal complexes. Copper complex showed good inhibition against all bacteria at 200 μg mL^{-1} concentration when compared to those of cobalt, nickel, and zinc complexes, which showed moderate activity. The high antimicrobial activity of the metal complexes than the free ligand can be understood in terms of chelation theory, which states that upon complexation, the polarity of the metal complexes facilitate them to cross the cell membrane easily.[32] Chelation reduces the polarity of the metal ion in the complexes considerably, mainly due to the partial sharing of its positive charge with the donor group. The possible electron delocalization over the chelate ring system in turn increases the hydrophobic character of the metal chelate thus favoring its permeation through lipoid layer of microorganism.

Structure-activity relationship evidences that the complexation with copper enhances the antimicrobial activity of the ligand against some of the tested microorganisms. Copper complexes exhibited enhanced antimicrobial activity, in comparison to their analogous containing Co(II), Ni(II), and Zn(II) ions,[32] the metal seems to play a relevant role in the activity of these compounds. The increased effectiveness of the copper complexes to inhibit microbial growth was formerly disclosed in many comparative studies on the antibacterial and antifungal activities of metal complexes.[33]

CONCLUSION

The present article describes the synthesis, characterization, and antimicrobial activity of transition metal complexes of 5-(2-phenylpyridin-4-yl)-1,3,4-oxadiazole-2(3H)-thione. The antimicrobial activity of the complexes has been found to be enhanced as compared to the ligand; Maximum activity is achieved in case of copper complex. Such a study will be helpful in designing novel antimicrobial metal-based drugs.

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