

Synthesis, Characterization, Thermal Analysis and Antibacterial Activity of Cu (II) and Ni(II) Complexes with Thiosemicarbazone Derived from Thiophene-2-aldehyde

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Authors' contributions

This work was carried out in collaboration among all authors. Author DS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MFH, MKZ, MMH and RZ managed the analyses of the study. Author MAA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Metal complexes have been synthesized by the reaction of thiophene-2- aldehyde thiosemicarbazone with Cu(OAc)₂ and Ni(OAc)₂. The thiosemicarbazone coordinates to metal ions through the thionic sulfur and the azomethine nitrogen. The thiosemicarbazone is obtained by the reaction of thiosemicarbazide with thiophene-2- aldehyde. The identities of these compounds have been elucidated by IR and ESI-MS spectroscopic methods and elemental analyses. Thermogravimetric analysis data indicates that the metal complexes are thermally stable. The antibacterial activity of the synthesized compounds are tested by the disc diffusion assay against Gram-positive and Gram-negative bacteria. The antibacterial screening activity revealed that complexes showed moderate activity against tested bacterial strains and slightly higher compared to the ligand, L.

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Keywords: Thiosemicarbazone; complexation; thermal analysis; antibacterial activity.

1. INTRODUCTION

The chemistry of coordination metal complex with nitrogen-sulphur donor ligands has fascinated research attention currently, most of it driven on transition metal complexes with Schiff base ligands. This is because of the presence of both nitrogen and sulphur donor atoms in the backbones of these ligands [1,2]. Schiff bases are beneficial due to their ability to stabilize metal ions of different oxidation states, participation in numerous catalytic and industrial applications and broad spectrum biological activities [2-6]. The construction of stable metal complexes is due to nitrogen's lone pair of electrons of azomethine (-C=N-) group bonding in their structure [7,8]. Study of the transition metal complexes with several types of ligands has been intensified by the current advances in the fields of bioinorganic chemistry and medicine [9]. Over the years, Schiff bases have played an important role as chelating ligands in main group and transition metal coordination chemistry, due to their stability under a diversity of oxidative and reductive conditions, and to the fact that imine ligands are marginal between hard and soft Lewis bases [10-12]. A large number of Schiff bases and their metal complexes have been studied for their interesting and significant properties, e.g. their ability to reversibly bind oxygen, [13,14] catalytic activity in hydrogenation of olefins, [15] photochromic properties [16] and complexing ability towards some toxic metals [17]. Metal complexes also play an important role in the biological field, as exemplified by the many ways in which enzymes are known to be activated by metal ions [18]. Schiff bases derived from various compounds have attracted an increased interest in the bioinorganic chemistry field [19-24].

Thiosemicarbazones (TSCs) are organic compounds with the structure $R^1R^2C=N-NH-(C=S)-NR^3R^4$, which have been used as potential antituberculosis agents since 1950s [25]. Afterwards, and due to their prospective therapeutic properties, these multidentate ligands have constituted a significant class of compounds whose properties serve in a wide range of applications [26,27]. Thiosemicarbazones also have potent activity against corona virus diseases (COVID) [28,29]. The electronic properties of the NNS donor ligands and the diversity of the chemical species that the system can yield are the reasons why TSC ligands act as good chelating agents. These

ligands can simply coordinate with a great variety of transition metal ions, forming complexes that can change the biological activity of precursor ligands [30]. TSCs and their transition metal complexes, due to their chemical versatility, have a wide spectrum of pharmacological properties, such as antibacterial, antifungal, antiparasitic, and antiviral [31-35].

The cytotoxic activities of these ligands have improved upon coordination with Cu and Ni ion and also can improve their lipophilicity within the cell [36]. Considering the pharmacological potential of Cu(II) and Ni(II) thiosemicarbazone derivatives, we mainly synthesized Cu and Ni TSCs complexes expecting better antibacterial activity.

This paper describes the synthesis and characterization of Cu(II) and Ni(II) complexes with thiophene-2- aldehyde thiosemicarbazone ligand. We also report herein thermal and antibacterial properties of synthesized compounds.

2. EXPERIMENTAL

2.1 Reagents

Thiosemicarbazide (99%, Sigma-Aldrich) Thiophene-2-aldehyde (98%, Sigma-Aldrich), and copper and nickel acetate (98%, BDH Reagents & Chemicals) were of sufficiently high-grade to be used as it is. Methanol (GRP), Ethanol (95%), Dichloromethane (WINLAB GRG 98%), Diethyl ether and DMSO (BDH lab, England 99%) were used as solvents without further purification. Nutrient agar medium (Include-Peptone, Agar, sugar, marmite) was used to check anti-microbial activity.

2.2 Instrumentation

A digital melting point apparatus (METTLER TOLEDO) was used to identify the melting points of synthesized compounds. Elemental analyses for CHN were performed using a Vario EL cube [Germany elements (Elemental) analysis system]. FT-IR spectra were recorded on a FT-IR spectrophotometer [JASCO, FT-IR/4100 Japan], using KBr pellets as the standard reference. ESI-MS spectra were done with an Agilent Technologies MSD SL Trap mass spectrometer with ESI source coupled with an 1100 Series HPLC system. A Sherwood Scientific MX Gouy magnetic susceptibility apparatus was used to determine the magnetic properties of the metal complexes.

2.3 Synthesis of the Ligand, Thiophene-2-aldehyde Thiosemicarbazone (L)

Thiophene-2-aldehyde (0.93458 mL, 2.0 mmol) with absolute ethanol (15 mL) was boiled. Then, sufficient ethanol was added to give a homogeneous solution. Thiosemicarbazide (0.18228 g, 2.0 mmol) was then added drop-wise to the homogeneous solution of thiophene-2-aldehyde. Acetic acid (2-3 drops) were also added to the solution. The reaction mixture was refluxed for 4 hours and then allowed to cool slowly and to stand overnight. After then a white solid product was formed and it was filtered off and dried.

2.4 General Methodology for the Synthesis of Metal complexes with Thiophene-2-aldehyde Thiosemicarbazone

Ligand L (2 mmol) in ethanol was added to a solution (2 mmol) of metal acetate salts in ethanol. The mixture was refluxed for about 4 hours. Finally, the precipitates were formed and it was filtered and washed with ethanol and diethyl ether. Then, the products were dried in desiccator using anhydrous CaCl_2 .

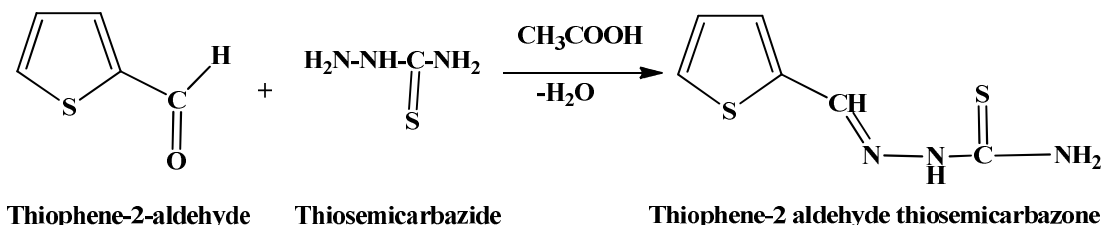
2.5 Metal Weight Determination

A known amount of metal complex was put into a conical flask whose weight was known. Then, concentrated H_2SO_4 (500 μL) was added. It was fumed until dry and the process was repeated.

Concentrated HNO_3 (500 μL) and HClO_4 (500 μL) were then added and the mixture was again fumed until dry. The process of adding acids and fuming was continued until there was no black material. 100 mL distilled water was added to dissolve the residue. Finally, the weight of the metal was estimated complexometrically and gravimetrically using EDTA (Ethylenediamine tetra acetic acid) and DMG (Dimethyl glyoxime) respectively.

2.6 Antimicrobial Study

The antibacterial activity of the synthesized compounds were tested against gram-negative *Enterobacter aerogenes* and gram-positive *Bacillus cereus* following Kirby Bauer's disc diffusion technique in the DMSO [37]. A uniform suspension of test organism was prepared in a test tube containing nutrient broth media. Sterile nutrient agar was then added to the Petri dishes. To ensure the uniform mixing of the microorganisms with the agar medium the Petri dishes was allowed to solidify. Sterile Whatmann filter paper discs were dipped in the solution of each compound and placed on the labelled plates. DMSO was used as a control of the solvent [38]. Streptomycin (*Bacillus cereus*) and Gentamicin (*Enterobacter aerogenes*) were used as standard microbes for comparison [39,40]. Plates were kept in the incubator for 24 hours at 37°C. The diameter of the zone of inhibition around each disc was measured by scale and results were recorded in mm.



Scheme 1. Synthesis of Schiff base ligand, L

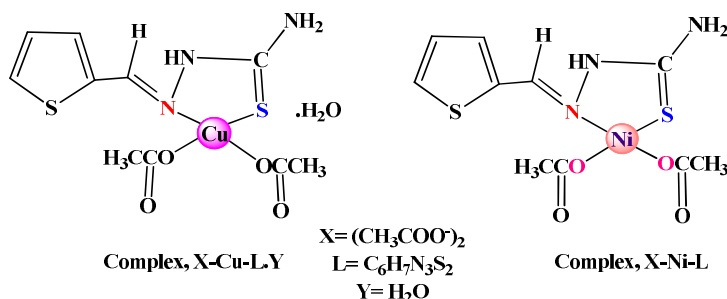


Fig. 1. Proposed structure of the synthesized complexes

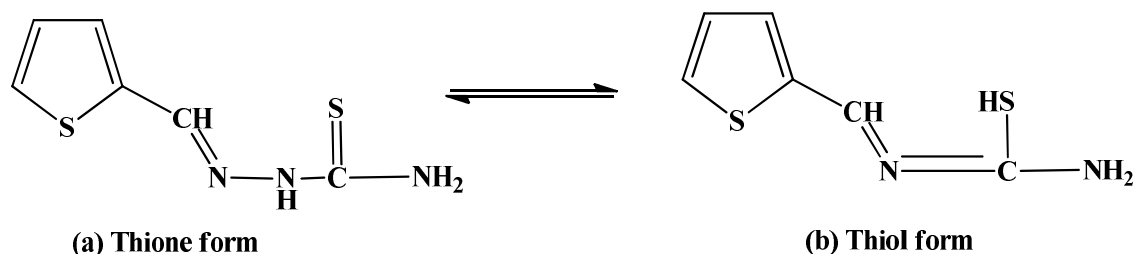


Fig. 2. Thione and Thiol form of the ligand, L

3. RESULTS AND DISCUSSION

The ligand, L (thiophene-2- aldehyde thiosemicarbazone) was prepared in good yield from the condensation reaction of thiophene-2- aldehyde and thiosemicarbazide in a 1:1 stoichiometric ratio. Reaction of the metal acetate salt with the ligand, L formed the complexes corresponding to 1:1 metal-ligand ratio.

Physical and analytical data of the synthesized compounds are presented in Tables 1 and 2.

3.1 Microanalysis

The elemental analysis data suggest that the complexes are mononuclear. The microanalysis data also revealed that metal-to-ligand ratio for the synthesized complexes was 1:1. The proposed structure of the ligand and complexes are consistent with these data.

3.2 Magnetic Measurements

Magnetic moment value of the synthesized copper complex is very consistent with the previously reported value [41]. The magnetic moment of four coordinated X-Ni-L compounds is quite low, compared to the reported values for the tetrahedral complexes, at 1.18 BM. Square planar nickel (II) complexes are diamagnetic and there are some reports on weakly paramagnetic nickel(II) complexes [42]. The low magnetic moments could be due to equilibrium in the solid state between the square planar and tetrahedral structures [43]. Splitting of the highest occupied molecular orbital in planar paramagnetic nickel(II) complex is small and the spin free configuration contributes to ground state and it could be another reason for the low magnetic moment value [44].

3.3 Molar Conductivity Measurements

The low molar conductance value (Table 2) indicates that the metal complexes were non-electrolyte in nature [45].

3.4 IR Spectral Studies

All the featured IR data are presented in Table 3. Assignments of selected characteristic IR peak positions provide important indication for the formation of thiosemicarbazone and its metal complexes. The thiosemicarbazone can exist in thione and thiol tautomeric forms shown in Fig. 2. However, the presence of a strong peak in the region 1097 cm^{-1} due to $\nu(\text{C}=\text{S})$ stretch, absence of any peak in the region $2267\text{--}2799\text{ cm}^{-1}$ due to $\nu(\text{C}-\text{SH})$ stretch, and the existence of $\nu(\text{N}-\text{H})$ stretch at 2866 cm^{-1} in the spectra of the ligand, L suggest that the thiosemicarbazone remain in their thione form in the solid state (Fig.3.). The downward shift of $\nu(\text{C}=\text{S})$ peak by 5 cm^{-1} and 38 cm^{-1} in the complexes [Cu(II)-complex: 1092 cm^{-1} ; Ni(II)-complex: 1059 cm^{-1}] suggested the coordination of sulfur in thionic form. A strong band at 1630 cm^{-1} was assigned to $\nu(\text{C}=\text{N})$ stretch of azomethine linkage in the spectra of free thiosemicarbazone. In the complexes this band shifted to lower frequency by 38 cm^{-1} and 120 cm^{-1} [Cu(II)-complex: 1592 cm^{-1} ; Ni(II)-complex: 1510 cm^{-1}] and this lowering was ascribed to the coordination of azomethine nitrogen with metal ions and formation of M-N band (Figs. 4 and 5.) [46]. On the other hand, new peaks observed in the infrared spectrum of the complexes at 1317 and 1097 cm^{-1} for copper complex and at 1251 and 1148 cm^{-1} for nickel complex are ascribed to $-\text{C}-\text{C}-\text{O}$ and $\text{O}-\text{C}-\text{C}$ stretching confirming the coordination of acetate group to the metal ions [47].

3.5 ESI-Mass Spectra

The obtained m/z values are similar to the formula weight of the studied compounds shown in Table 1. This similarity supports the proposed structure of the synthesized compounds.

Table 1. Physical data of the ligand, L and its metal complexes

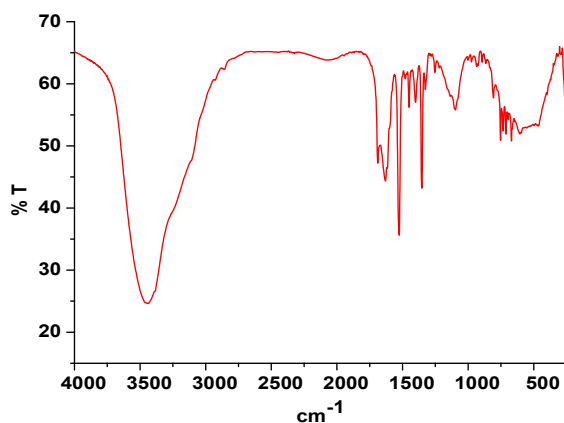
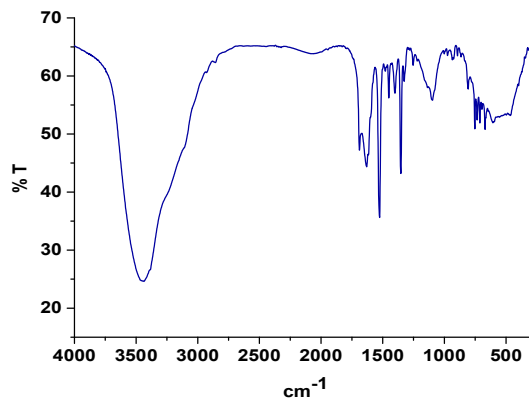
Compound	Empirical Formula	F.W. (g/mol)	Colour (%yield)	m.p. (°C)
L	C ₆ H ₇ N ₃ S ₂	185.27	White (88%)	178
X-Cu-L.Y	C ₁₀ H ₁₅ CuN ₃ O ₅ S ₂	384.92	Yellowish Brown (72%)	270
X-Ni-L	C ₁₀ H ₁₃ N ₃ NiO ₄ S ₂	362.05	Dark Brown (73%)	265

Table 2. Analytical data of the compounds

Compound	Found (Calculated) (%)				μ_{eff} (BM)	Conductivity (μScm^{-1})
	Cu	C	H	N		
L	-	37.80(38.90)	3.75(3.81)	22.50(22.68)	-	-
X-Cu-L.Y	16.45(16.51)	30.50(31.20)	3.85 (3.93)	10.52(10.92)	1.69	7
X-Ni-L	16.15(16.21)	32.85(33.17)	3.45(3.62)	11.50(11.61)	0.30	8

Table 3. Key Infrared Bands (cm^{-1}) of the Ligand (L) and its Metal Complexes

Compound	$\nu(\text{C}=\text{S})$	$\nu(\text{C}=\text{N})$	$\nu(\text{M}-\text{N})$	$\nu(\text{C}-\text{C}-\text{O})$	$\nu(\text{O}-\text{C}-\text{C})$
L	1097	1630	-	-	-
X-Cu-L.Y	1092	1592	710.50	1317	1261
X-Ni-L	1059	1510	631.56	1251	1148

**Fig. 3. IR Spectrum of the ligand, L****Fig. 4. IR Spectrum of complex, X-Cu-L.Y**

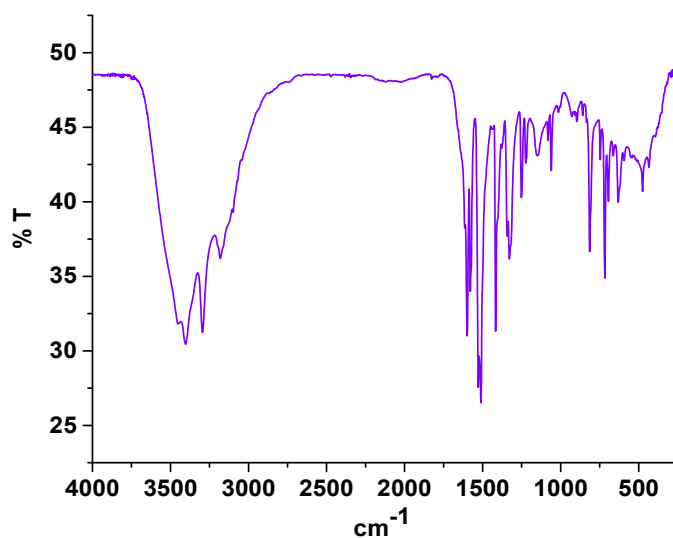


Fig. 5. IR Spectrum of complex, X-Ni-L

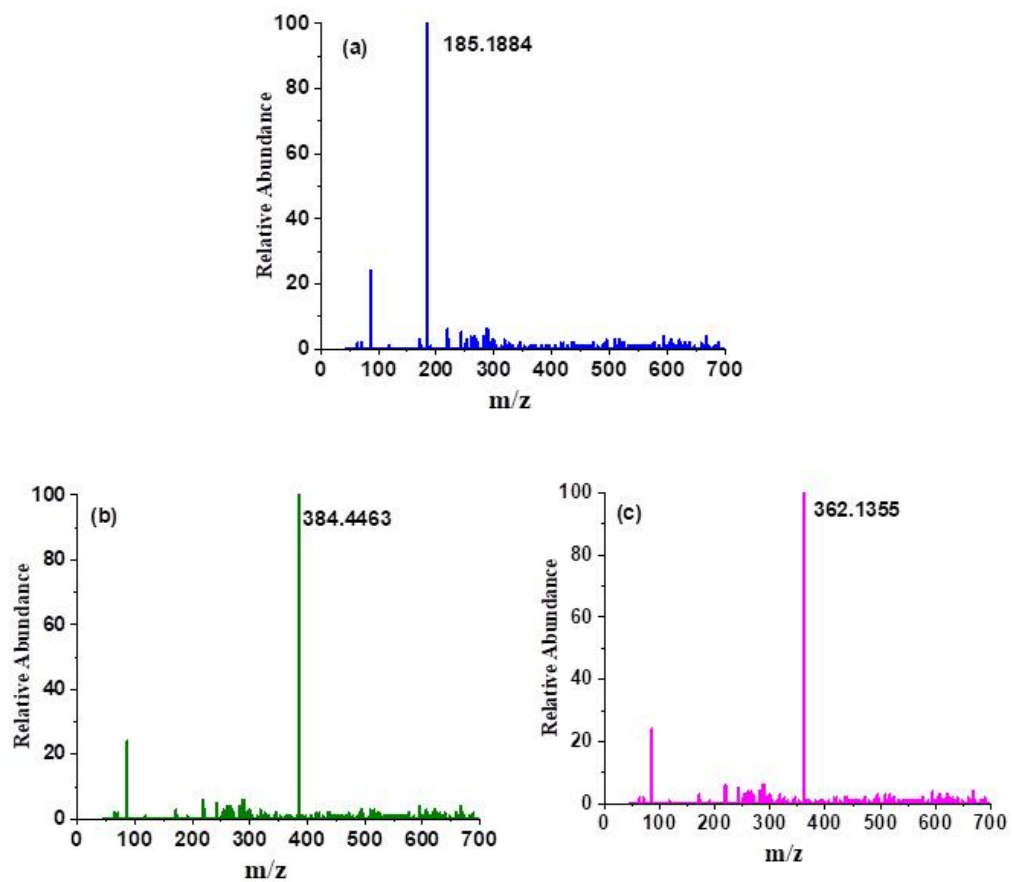


Fig. 6. ESI-Mass Spectra for (a) Ligand L (b) X-Cu-L.Y and (c) X-Ni-L

3.6 Thermo-gravimetric Analysis (TGA)

The simultaneous TGA analysis of the metal complexes are studied where the heating rates was appropriately controlled at $20^{\circ}\text{C min}^{-1}$ under nitrogen atmosphere and the weight loss is measured from ambient temperature upto 700°C . The TGA data for the Cu(II) complex are summarized in Table 4 and the representative thermogram is given in Fig. 7.

TGA of Cu(II) complex shows four steps weight loss which is shown in Fig. 7. At the first step, 5.00% (calc. 4.67%) weight loss in the temperature range $125\text{--}183^{\circ}\text{C}$ indicates that there was hydrated water molecule in the crystalline solid. The second stage occurs at $183\text{--}320^{\circ}\text{C}$, with a mass loss of 29.31%, corresponding to the loss of $\text{C}_5\text{H}_5\text{NS}$ (calc.

30.72%). In the third step from 320°C to 541°C , 16.12% weight loss occurs corresponding to the loss of CH_2NS (calc. 15.58%). The decompositions of the copper complex ended with formation of CuO and gaseous products [48]. The thermogravimetric analysis data for the copper (II) complex are presented in Table 4.

The TG of Ni(II) complex (Fig. 8.) shows three steps decomposition. Upto 263°C , no weight loss is observed indicating that there was no hydrated water molecule in the solid complex. At the initial stage at $263\text{--}282^{\circ}\text{C}$, 16.29% weight loss occurs corresponding to the loss of $\text{C}_2\text{H}_3\text{O}_2$ (calc. 16.30%). From 282°C to 507°C , 27.18% weight loss indicates the loss of $\text{C}_3\text{HN}_2\text{S}$ (calc. 30.66%). At the final step, the nickel complex decomposes to NiO . All the data for the TGA of Ni(II) complex are shown in Table 5.

Table 4. TGA data for the copper (II) complex

Compound	Step	Temperature Range ($^{\circ}\text{C}$)	TG Weight Loss (%) Calc. (Found)	Evolved Product	Final Product
X-Cu-L.Y ($\text{C}_{10}\text{H}_{15}\text{CuN}_3\text{O}_5\text{S}_2$)	1 st	125–183	4.67(5.00)	H_2O	CuO
	2 nd	183–320	30.72(29.31)	$\text{C}_5\text{H}_5\text{NS}$	+
	3 rd	320–541	15.58(16.12)	CH_2NS	Gaseous
	4 th	541–694	25.46 (24.12)	$\text{C}_4\text{H}_4\text{NO}_2$	product

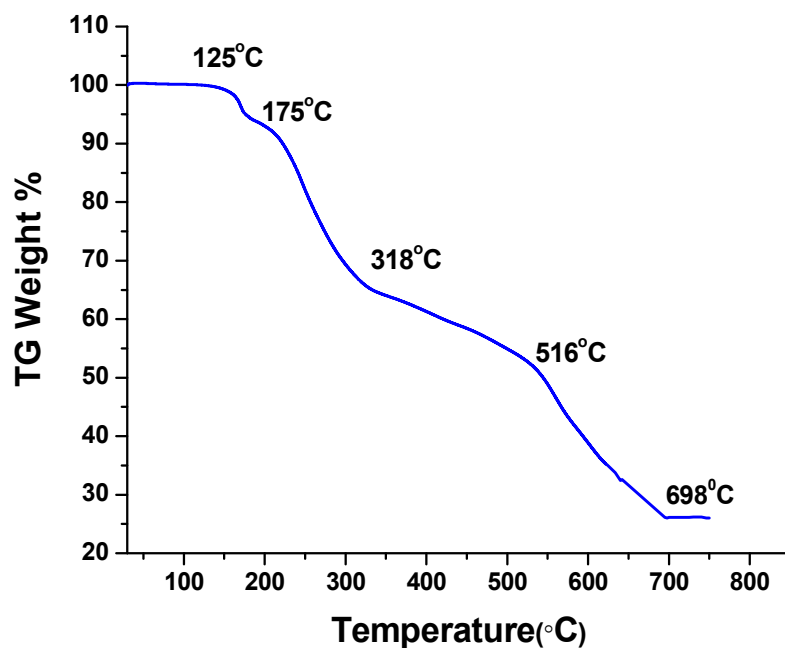


Fig. 7. TGA curve of the copper complex, X-Cu-L.Y

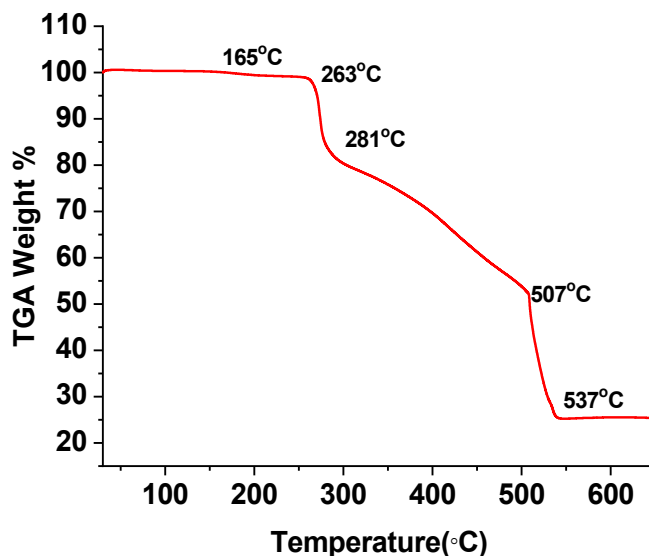


Fig. 8. TGA curve for the complex, X-Ni-L

Table 5. Thermogravimetric analysis data for the Ni (II) complex

Compound	Step	Temperature Range (°C)	TG Weight Loss (%) Calc. (Found)	Evolved Product	Final Product
X-Ni-L (C ₁₀ H ₁₃ N ₃ NiO ₄ S ₂)	1 st	263-282	16.30 (16.29)	C ₂ H ₃ O ₂	NiO +
	2 nd	282-507	30.66 (30.39)	C ₅ H ₅ NS	Gaseous
	3 rd	507-540	27.10 (27.18)	C ₃ HN ₂ S	product

Table 6. Antibacterial screening results of ligand L and its complexes

Compounds	Antibacterial zone of inhibition (mm)	
	Gram-negative	Gram-positive
	<i>Enterobacter aerogenes</i>	<i>Bacillus cereus</i>
L	7	6
X-Cu-L.Y	10	12
X-Ni-L	11	13

3.7 Antimicrobial Screening Result

Antibacterial activity of the ligand L and complexes against *Enterobacter aerogenes* (Gram-negative) and *Bacillus cereus* (Gram-positive) is measured in millimeters, in terms of inhibition zone. The ligand L and its Cu(II) and Ni(II) complexes show good to moderate antibacterial activity (Table 6).

Metal complexes exhibit more inhibitory effects than the parent ligands against bacterial strains. This enhanced antibacterial activity may be due to electron delocalization over the whole chelate ring upon complexation. Such chelation

increases the lipophilicity and enhances the permeation through the lipid layer of the cell membrane (chelation theory) [49,50]

4. CONCLUSION

On the basis of above analytical and spectral data, the Schiff base is coordinated to metal ion Cu(II) and Ni(II) as bidentate ligand *via* imine nitrogen and thione sulphur. Elemental analysis and ESI-MS data supports the proposed structure of synthesized compounds. On the basis of thermal analysis data, the complexes have been found to be thermally stable. All complexes exhibit moderate antibacterial activity

against both gram positive and gram negative bacteria.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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