



Isoniazid Derived Schiff Base Metal Complexes: Synthesis, Characterization, Thermal Stability, Antibacterial and Antioxidant Activity Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Transition metal complexes of Cu²⁺, Ni²⁺ and Co²⁺ with the Schiff base ligand, N-(2-methoxybenzylidene)isonicotinohydrazone, (L1) were synthesized by the conventional condensation approach. Ligand and its metal were characterized by FT-IR, UV-Vis, Magnetic moment measurements and Thermogravimetric (TGA) analysis. IR spectra revealed that the Schiff base ligand coordinated to the metal ion through nitrogen (N) of azomethine group and oxygen (O) of carbonyl group. IR data coupled with TGA analysis confirmed the presence of coordinated water molecules. Antibacterial activity for both ligand and its complexes were investigated against some pathogenic bacteria and the best activity was observed in the case of the CuL1 against E. coli when compared with standard drug, Kanamycin-30. The antioxidant activity of the CuL1 complex was the greatest among all the complexes when compared to that of BHT.

Keywords: Schiff base, transition metals; isoniazid; Kanamycin-30; antioxidant.

1. INTRODUCTION

The structure and coordination behavior of Schiff base (SB) metal complexes have drawn substantial attention [1-3]. SB metal complexes have notable chemical, optical, and magnetic characteristics when they are combined with a broad range of ligands. SB's metal complexes have piqued researchers' interest due to their structural characteristics and extraordinary stability. Structural analysis shows that the carbonyl group is replaced by imine or azomethine (>C=N) in an imine- or azomethine-derived Schiff base (usually termed as an "imine" or "azomethine") [4]. Assorted metal ions may easily couple with Schiff bases containing donor atoms of nitrogen, sulfur, or oxygen, making it possible to synthesize metal complexes [5]. Due to their wide range of biological actions, SB and their metal complexes have widened the scope of SB study [6]. The SB metal complexes have a broad variety of applications in the medical and pharmaceutical fields, comprising anticancer [7-8], antibacterial [9-10], antifungal, [11] and anti-inflammatory characteristics [12]. SB metal chemistry is emerging as a potential research area because of the ongoing quest for novel metal-based antibacterial medicines with improved mechanisms of action [13].

Isoniazid (INH) is a pro-drug with recognized therapeutic uses and has been used clinically as a first-line medicine for the prevention and treatment of TB [14-15] for over half a century. It is possible to produce Schiff base (SB) by condensing the free imine (-NH₂) group present in the INH moiety with a variety of carbonyl compounds, such as aldehydes and ketones [16]. Schiff bases derived from isoniazid have been shown to have antibacterial, antifungal, antitumoral, anticonvulsant, analgesic, and antiviral properties [17].

Many investigations have demonstrated that metal complexes of isoniazid, in which isoniazid acts as a mono-, bi-, or poly-dentate ligand, not only have antibacterial activities but also have fascinating biological features. Similarly, these compounds are more effective and less harmful to the liver than isoniazid [18-19]. Multiple studies have highlighted the significance of creating new isoniazid hydrazones as possible anti-tuberculous drugs.

In continuation of our research on the isoniazid-derived Schiff bases and their metal complexes, the present study describes the synthesis,

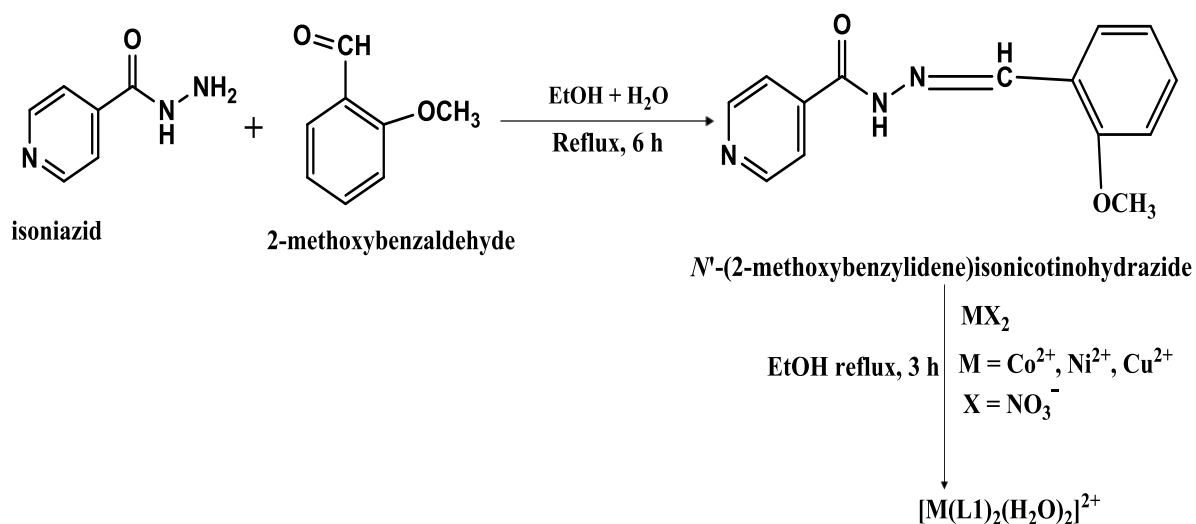
characterization, thermal stability of transition metal complexes of N-(2-methoxybenzylidene)isonicotinohydrazone (L1) and investigation of their antibacterial and antioxidant activities.

2. EXPERIMENTAL METHODS

All required chemicals with 99.9% purity were purchased from Merck and Loba chemicals. A METTLER PM 200 electronic balance was used to complete the weighing process. All produced metal complexes' melting or decomposition temperatures were measured using an electrothermal melting point equipment type o.AZ6512. The IR spectra of the produced compounds were acquired using a KBr disc on an FTIR-8400, SHIMADZU, Japan. The complexes' conductivities were measured in DMSO using a Horiba conductivity meter B173 with a set cell constant. The Uv-Vis spectra of the ligand and its complexes were measured using a THERMOELECTRON NICOLET evolution 300 UV-Visible spectrophotometer in DMSO solution (1 X 10⁻⁵ M). Sherwood Scientific Magnetic Susceptibility Balance was used in order to determine the values of all complexes' magnetic moments. The Perkin Elmer Simultaneous Thermal Analyzer, STA-8000, conducted the thermogravimetric analysis (TGA). Thin Layer Chromatography (TLC) was used to assess the ligand's purity and its metal complexes.

2.1 Synthesis of N-(2-methoxybenzylidene)isonicotinohydrazone Schiff base Ligand (L1)

N-(2-methoxybenzylidene)isonicotinohydrazone, Schiff base Ligand, L1 was obtained (Scheme 1) by the conventional condensation reaction of 2-methoxyoxybenzaldehyde with isoniazid (INH) in an equimolar ratio (i.e., 1:1). An ethanolic solution of INH (1.37 g, 10.00 mmol) was taken in a round bottom flask, and then ethanolic solution of 2-methoxybenzaldehyde (1.36 g, 10.00 mmol) was added to it with continuous stirring. As a catalyst, little amount of glacial acetic acid (2-3 drops) was added dropwise to this mixture. The resultant mixture was allowed to reflux for about 6 hours. TLC monitored the purity of the obtained product throughout the whole reaction. A white precipitate of the ligand was produced, which was then filtered and washed several times with cold CH₃CH₂OH solution before being dried in a desiccator over anhydrous CaCl₂.



Scheme 1. Synthesis of the Schiff base ligand, L1 and its metal complexes

2.2 General Procedure for Synthesis of Metal Complexes

15 mL warm ethanolic solutions (1 mmol) of nitrate salts of metal (Co^{2+} , Ni^{2+} , and Cu^{2+}) were slowly added to the warm ethanolic solution (15 mL) of Schiff base ligand L1 (2 mmol) in a reflux set. The resulting mixture was refluxed for about 3 h. After cooling, the obtained precipitates were filtered and washed with cold $\text{C}_2\text{H}_5\text{OH}$ solution and dried under a vacuum on anhydrous CaCl_2 .

2.3 Antibacterial Studies

Antimicrobial activity of the L1 and its metal complexes with Cu^{2+} , Ni^{2+} , and Co^{2+} ions were performed against *S. aureus*, *P. aeruginosa* and *E. coli* in DMSO by disc diffusion approach [20-21]. All pathogenic bacteria under this study were collected from the Department of Pharmacy, University of Rajshahi, Rajshahi-6205, Bangladesh.

2.4 Antioxidant Studies

The DPPH free radical scavenging technique was used to calculate antioxidant activity. The inhibition percentage, which was associated with the compounds' radical scavenging activity, was calculated by using the following formula [22]:

$$\text{DPPH Scavenging Activity (\%)} = (A_0 - A_{\text{sample}}) / A_0 \times 100$$

Where A_0 is the absorbance of blank and A_{sample} is the absorbance of the tested sample.

Calculation of IC_{50} values: In order to get the IC_{50} value, a linear regression was performed between the percentage inhibition and log concentration. Higher antioxidant activity is indicated by a lower IC_{50} value [23].

3. RESULTS AND DISCUSSION

Each complex has a distinct color, is soluble in DMF and DMSO but insoluble in common polar solvents, and does not have a strong melting point but decomposes around 250°C . All produced complexes had conductivity values in the range of $119\text{-}127 \text{ ohm}^{-1}\text{cm}^2\text{mol}^{-1}$, demonstrating their 1:2 electrolytic character [24-25]. The physical properties of the L1 and its metal complexes have shown in Table 1. Magnetic moments for the high-spin octahedral Co^{2+} complexes range from 4.7 to 5.2 B.M. The Co^{2+} ion in an octahedral complex has a ground $^4\text{T}_{1g}$, contributing a significant orbital moment to magnetic moments. Therefore, the observed magnetic moment's value (4.87 B.M) of the CoL1 complex supported its octahedral structure rather than tetrahedral structure [26]. The μ_{eff} value for the NiL1 complex is 2.95 B.M which is consistent with the regular octahedral geometry. This observed value is somewhat higher than the spin-only value (2.83 B.M). The higher value may be owing to spin-orbit coupling and contributions from $^3\text{A}_{2g}$ and the next higher $^3\text{T}_{2g}$ [26]. For the CuL1 complex, the magnetic moment indicates its paramagnetic nature, and the observed value (1.85 B.M) corresponds to its octahedral geometry [27].

Table 1. Physical properties of the L1 and its metal complexes

Ligand/Complexes (Symbol)	Body Color	M.W	% Yield	M.P/(°C)	Molar Conductivity (ohm ⁻¹ cm ² mol ⁻¹)	μ _{eff} (B.M)
C ₁₄ H ₁₃ N ₃ O (L1)	Crystalline white	255.20	75 %	185	NA	NA
[Co(L1) ₂ (H ₂ O) ₂](NO ₃) ₂ (CoL1)	Red powder	729.40	70 %	230	125	4.87
[Ni(L1) ₂ (H ₂ O) ₂](NO ₃) ₂ (NiL1)	Yellowish green powder	729.00	65 %	254	119	2.95
[Cu(L1) ₂ (H ₂ O) ₂](NO ₃) ₂ (CuL1)	Green powder	733.90	73 %	269	127	1.85

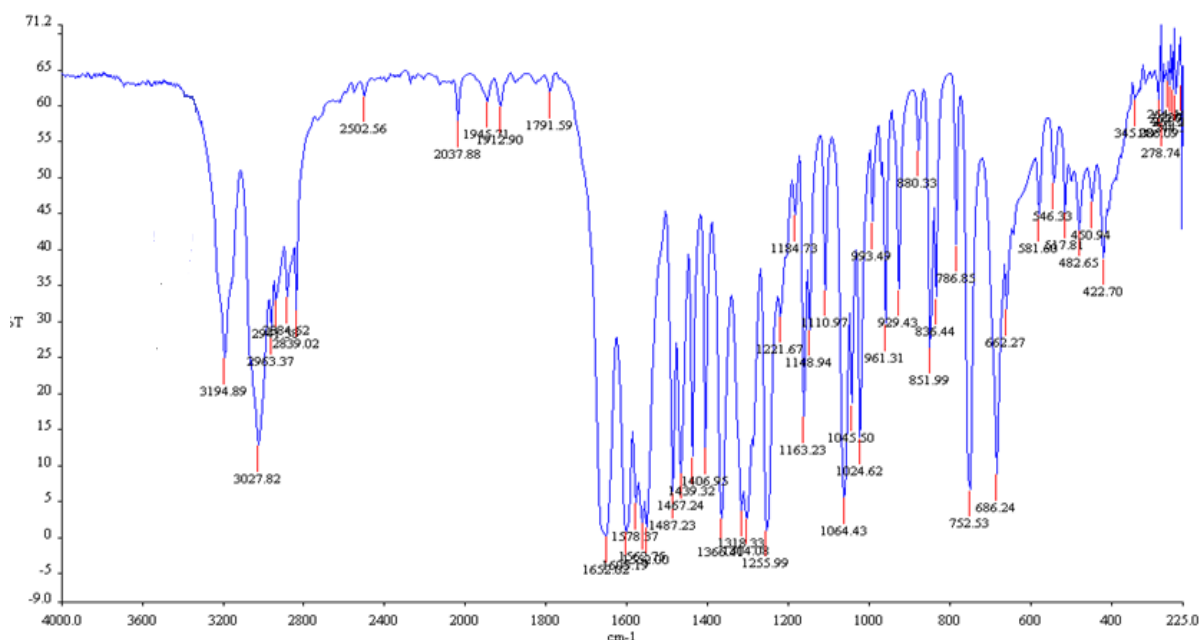


Fig. 1. IR spectrum of L1

3.1 IR Spectral Studies

Table 2 displays the IR spectral bands of L1 (Fig. 1) and its metal complexes. Complexes CoL1, NiL1, and CuL1 show (CO) bands around 1635--

1638 cm⁻¹ (Figs. 2-4), which is lower than the free ligand value [(C=O) at 1652 cm⁻¹]. The appearance of bands, which are generated by M–O stretching vibrations at 584–587 cm⁻¹ in the IR spectra of these complexes, provides further

support for this notion [28]. This definitely indicates that the carbonyl oxygen is coordinated to the metal ions. In the spectra of all of the examined complexes, the azomethine band, which was previously found at a frequency of 1605 cm^{-1} , has been moved to lower frequencies that range from $1597\text{--}1599\text{ cm}^{-1}$. This suggests that the nitrogen atom of the azomethine group is actively participating in the coordination of the metal ions [29]. The new bands that arise in the $475\text{--}485\text{ cm}^{-1}$ region of the IR spectra of these

complexes are attributed to the $\nu(\text{M-N})$ vibration [30]. A wide, strong band develops at 3435 cm^{-1} due to the combined mode of $\nu(\text{O-H})$ and $\nu(\text{N-H})$ stretching vibrations. The development of a new band for all complexes at the range of $1013\text{--}1016\text{ cm}^{-1}$ due to $\delta(\text{H}_2\text{O})$ indicates the presence of coordinated water in complexes [31]. TGA results reported in Table 4 also verified the presence of coordinated water.

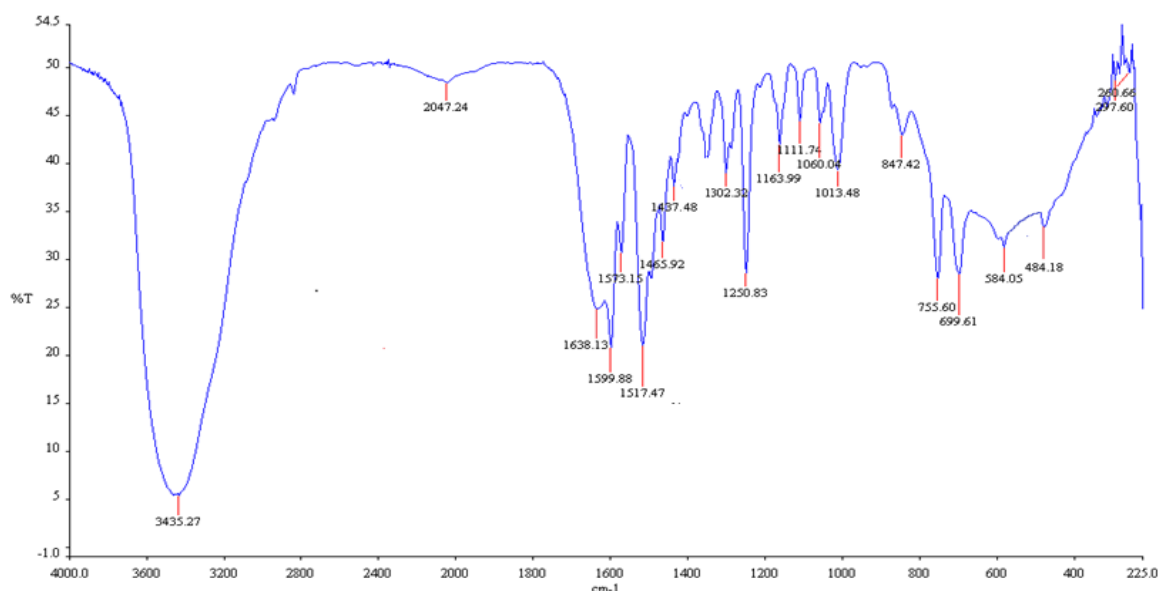


Fig. 2. IR spectrum of CoL1

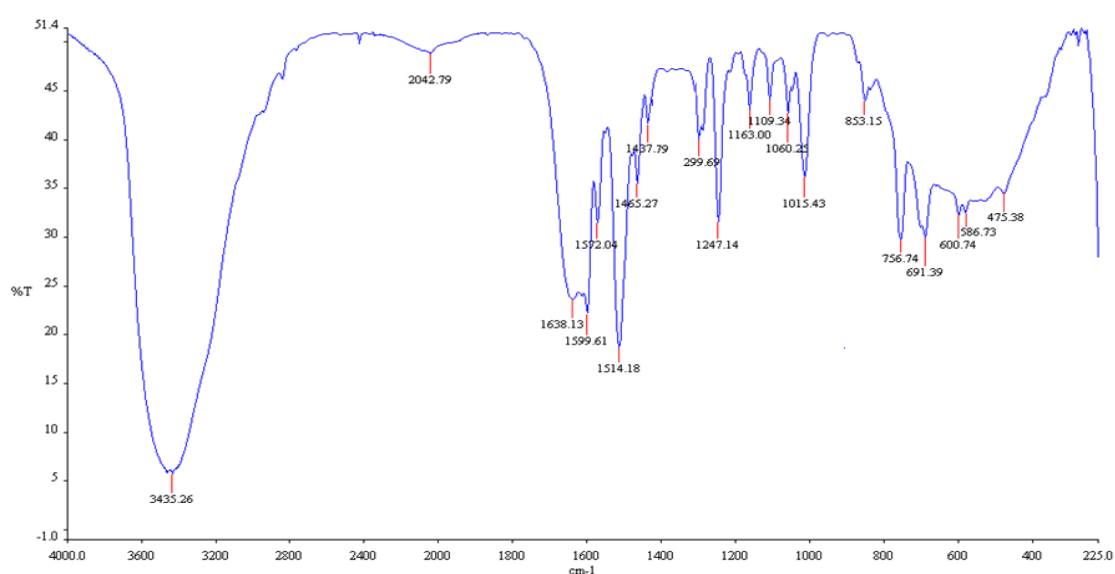
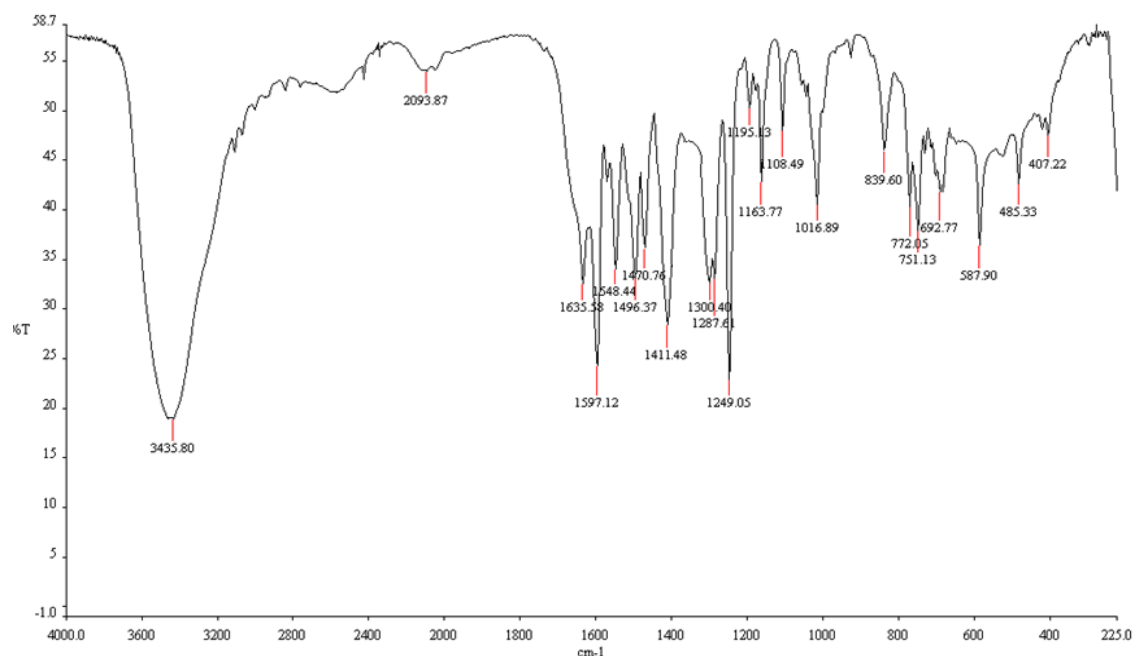


Fig. 3. IR spectrum of NiL1

Table 2. Key Infrared bands (cm⁻¹) of ligand L1 and its metal complexes

Ligand/ Complexes	$\nu(\text{OH}) + \nu(\text{NH})$	$\nu(\text{NH})$	$\nu(\text{C=O})$	$\nu(\text{C=N})$	$\nu(\text{M-O})$	$\nu(\text{M-N})$
L1	-----	3194	1652	1605	--	--
CoL1	3435		1638	1599	584	484
NiL1	3435		1638	1599	586	475
CuL1	3435		1635	1597	587	485

**Fig. 4. IR spectrum of CuL1**

3.2 Electronic Spectra

The L1 showed two distinct bands at 285 and 328 nm, which were for $\pi-\pi^*$ and $n-\pi^*$ transitions, respectively (Fig. 5). Like L1, all complexes showed these two transitions. In addition, the CoL1 complex showed an absorption band at 504 nm due to ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transition, which is indicative of octahedral geometry [32]. On the other hand, the CuL1 complex also showed three bands at 285, 342, and 584 nm, respectively. The band centered at 584 nm, is a d-d absorption band, which is attributed to ${}^2E_g \rightarrow {}^2T_{2g}$ transition suggesting the octahedral geometry of this complex [33]. The shift of spectral peak takes place mainly in metal coordination with ligand imine. In the case of NiL1, the d-d transition does not appear due to very low intensity. A band positioned at 375 nm

could be assigned as a CT band. All bands with proper assignments have presented in Table 3.

3.3 Thermogravimetric Analysis (TGA)

TGA studies were carried out on complexes in a nitrogen (N_2) gas atmosphere in the temperature range of 25-800°C. The thermogram of complexes exhibits multi-stage weight loss [Figs. 6-8]. In the 1st step, all metal complexes of L1 ligand shows weight loss above 200°C, which suggests the existence of coordinated H_2O molecules [34] and the obtained weight loss (for CoL1) is 4.74% (calcd. 4.94%) indicates the removal of two coordinated H_2O molecules. The final residue with a constant weight represents metallic oxide [35]. The weight loss due to change of temperature (from 25-800°C) with possible assignments have presented in Table 4.

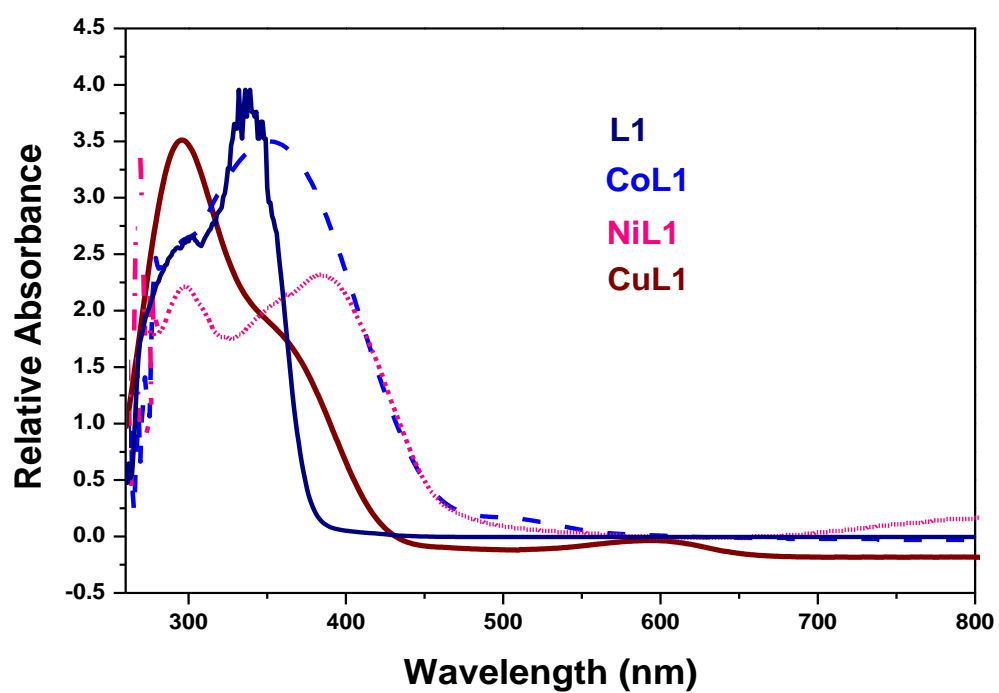


Fig. 5. UV-Vis spectra of L1 and its metal complexes

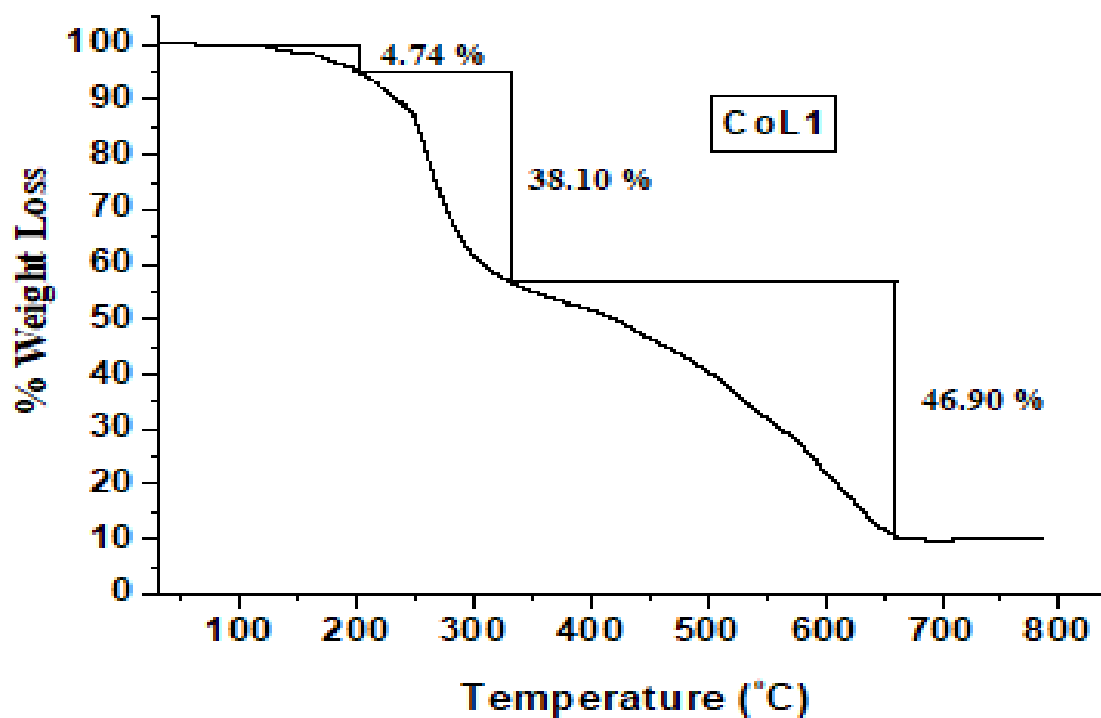


Fig. 6. TGA curve of CoL1 complex

Table 3. Key UV bands (nm) of ligand L1 and its metal complexes

Ligand/ Complexes	Band Position (nm)	Assignment	μ_{eff} (B.M)	Geometry
L1	285 328	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$		---
CoL1	285 345 504	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ ${}^4T_{1g}(\text{F}) \rightarrow {}^4T_{1g}(\text{P})$	4.87	Octahedral
NiL1	286 350 375	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$ CT	2.95	Octahedral
CuL1	285 342 584	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$ ${}^2E_g \rightarrow {}^2T_{2g}$	1.85	Octahedral

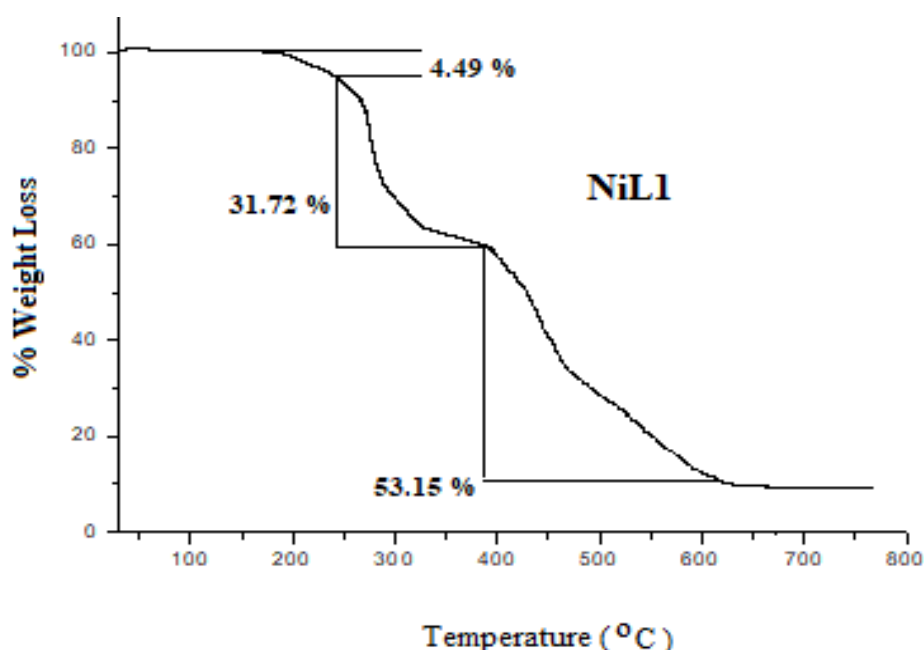


Fig. 7. The TGA curve of NiL1 complex

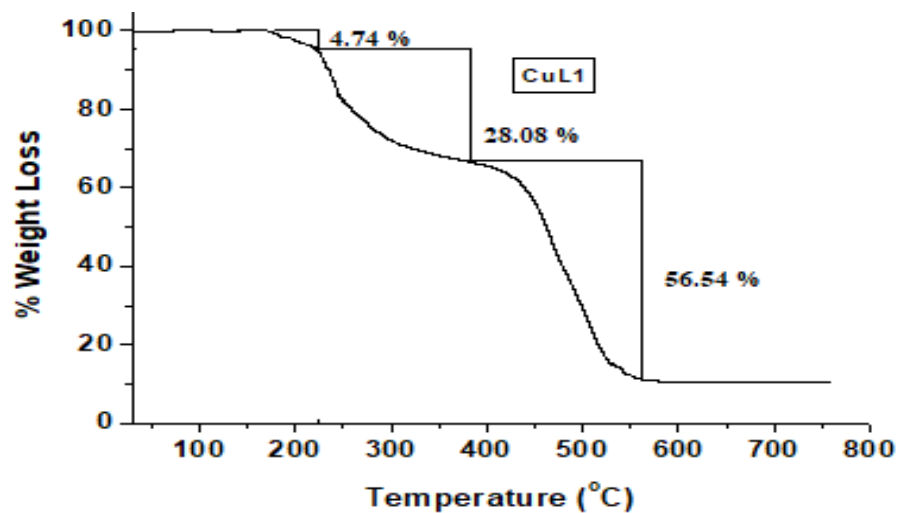
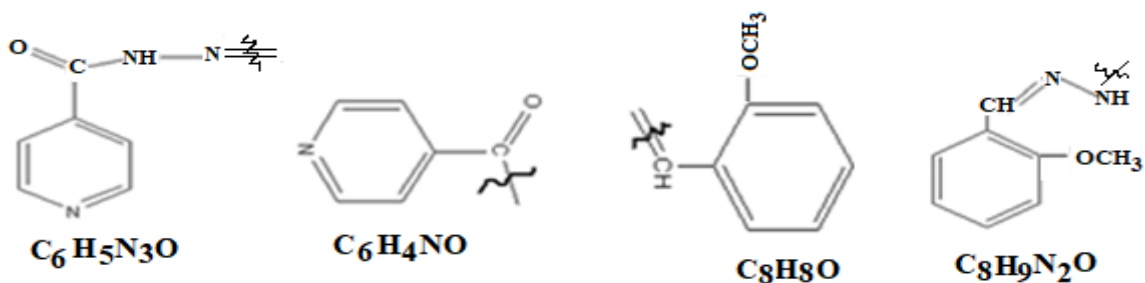


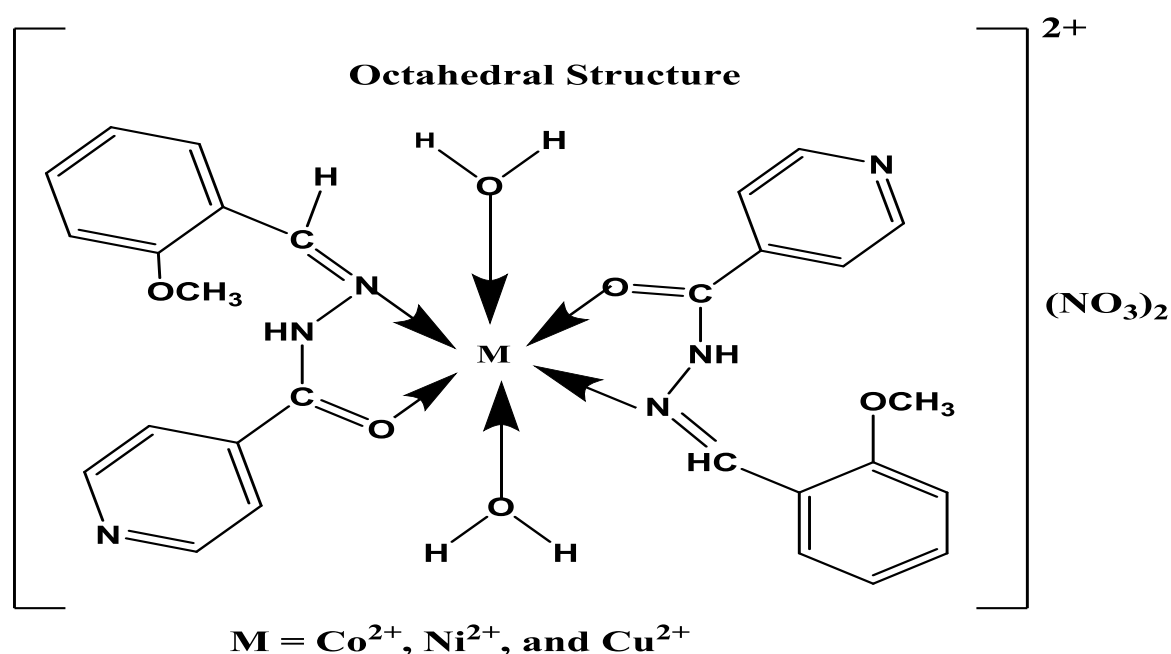
Fig. 8. The TGA curve of CuL1 complex

Table 4. Thermoanalytical data of CoL1, NiL1 and CuL1 complexes

Complex	Temperature Range (°C)	Weight loss (%)		Assignments
		Found	Calculated	
CoL1	30 – 210	4.74	4.94	Loss of two coordinated H ₂ O molecules
	210-330	38.10	37.03	2C ₆ H ₅ N ₃ O
	330-660	46.90	47.75	2C ₈ H ₈ O + 2NO ₂ + 0.5 O ₂
	> 660	10.26	10.27	CoO
NiL1	30 – 260	4.49	4.94	Loss of two coordinated H ₂ O molecules
	260-330	31.72	32.95	2C ₈ H ₈ O
	330-625	53.15	51.85	2C ₆ H ₅ N ₃ O + 2NO ₂ + 0.5 O ₂
	> 625	10.64	10.24	NiO
CuL1	30 – 220	4.74	4.90	Loss of two coordinated H ₂ O molecules
	220-380	28.08	28.91	2C ₆ H ₄ NO
	380-530	56.54	55.35	2C ₈ H ₉ N ₂ O + 2NO ₂ + 0.5 O ₂
	> 530	10.64	10.83	CuO



Proposed Structure: On the basis of above characterizations, the octahedral structure can be proposed for the CoL1, NiL1 and CuL1 obtained metal complexes.



3.3 Antibacterial Activity

The antibacterial activity of L1 and its metal complexes against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* was investigated. The diameter of the inhibitory zone was measured in millimeters, and the results of their antibacterial activity have presented in Table 5. The metal complexes showed more antibacterial activity than free ligand against *E. coli*. Among all synthesized complexes, the CuL1 complex showed good antibacterial activity against *E. coli* and the following trend is observed: CuL1 > Kanamycin-30 > NiL1 > CoL1 > L1 (Fig. 9). On the other hand, the L1 and its metal complexes did not show any activity against *P. aeruginosa*. Same result was observed in case of *S. aureus* except CuL1. The increased antibacterial activity of

metal complexes compared to the free ligand can be well understood by Overtone's idea and Tweedy's chelation hypothesis [36]. Chelation of metal ion with the ligand diminishes its polarity due to partial sharing of its positive charge with donor groups (i.e., O, N, S, etc. depending on the structure of the ligand) of the ligand and the possibility of π -electron delocalization inside the chelate ring. During chelation with ligands, the lipophilicity of the central metal ion is considerably enhanced, which facilitates its passage through the lipid layers of the cell membrane and the blockage of metal-binding sites on microbial enzymes. The impermeability of the microorganisms' cell or changes in the ribosomes of microbial cells determine the efficiency of various compounds against different species.

Table 5. Antibacterial activities of ligand L1 and its metal complexes

Diameter of Zone of Inhibition (mm) of tested compounds (100 μ g/disc)			
Compounds	Gram Negative		Gram Positive
	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>
Kanamycin (30 μ g/disc)	12	30	30
Ligand (L1)	04	-ve	-ve
CoL1	08	-ve	-ve
NiL1	10	-ve	-ve
CuL1	17	-ve	05

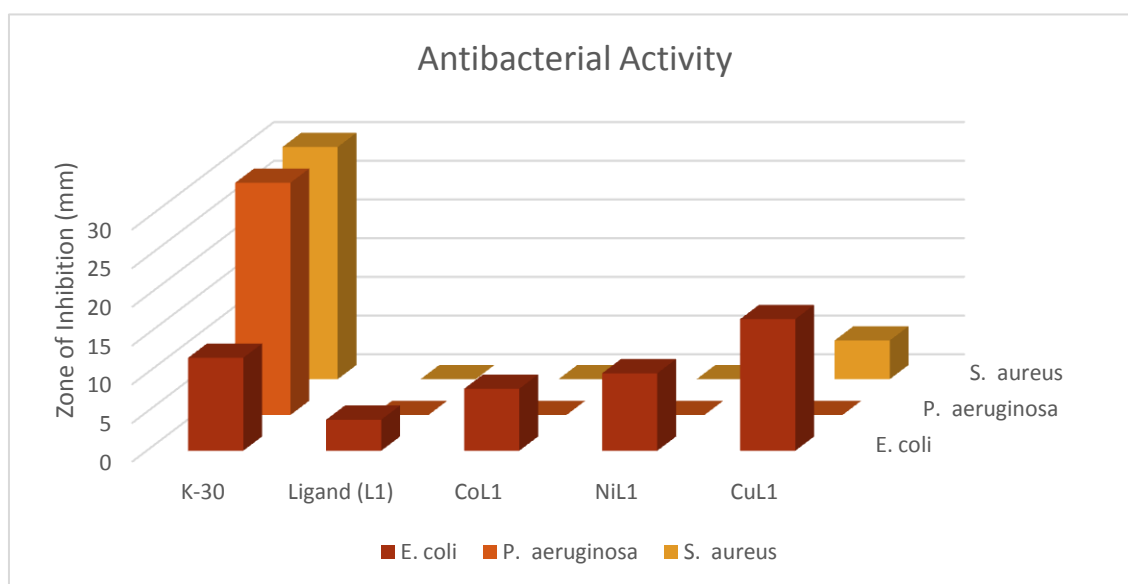


Fig. 9. Graphical representation of antibacterial activity of ligand L1 and its metal complexes against mentioned bacteria with standard Kanamycin-30 (K-30)

3.4 Antioxidant Activity

The antioxidant properties of L1 and its metal ion complexes were evaluated using the free radical molecule 1, 1-Diphenyl-1-picryl hydrazyl (DPPH). Table 6 displays the percentage of DPPH radical scavenging activity of L1, metal complexes, as well as BHT (butylated hydroxytoluene) as a reference. According to the findings, all of the metal complexes showed moderate DPPH radical scavenging activity (Fig. 10). The order can be expressed as BHT > CuL1 > NiL1 > CoL1 > L1. The CuL1 complex has higher

antioxidant activity than other synthesized complexes. The increased antioxidant activity of this complex is owing to the acquisition of more superoxide dismutating centers (SOD), which increases the molecule's capacity to stabilize unpaired electrons and hence scavenge the free radical [37]. Further investigation is required to recommend CuL1 complex as a potential drug for the ailment of various types of diseases caused by the free radical propagation in human body. The IC₅₀ value of all stated compounds in combination with standard BHT has been calculated and shown in Fig. 11.

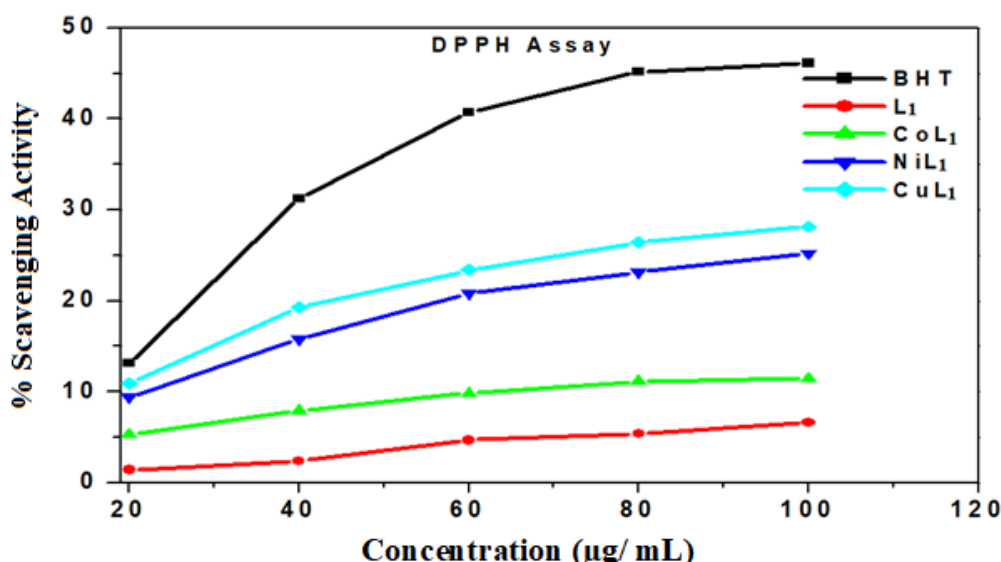


Fig. 10. DPPH radical scavenging activity of the L1 and its metal ions complexes at different concentrations (20, 40, 60, 80, and 100 µg/mL) with standard BHT

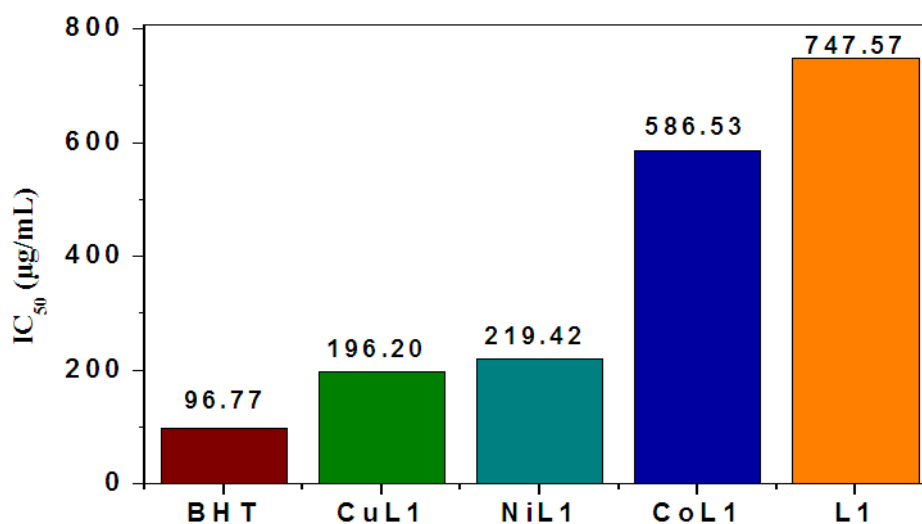


Fig. 11. IC₅₀ value of the metal complexes of ligand L1 at various concentrations (20, 40, 60, 80, and 100 µg/mL) with standard BHT

Table 6. % of scavenging activity of BHT, ligand L1, and its metal complexes

Conc. (µg/mL)	% BHT	% L1	% CoL1	% NiL1	% CuL1
20	13.11	1.39	5.31	9.38	10.89
40	31.26	2.37	7.93	15.76	19.31
60	40.69	4.66	9.85	20.82	23.36
80	45.17	5.35	11.14	23.13	26.43
100	46.17	6.58	11.46	25.22	28.16

4. CONCLUSION

The reaction of bidentate Schiff base ligand (L1), with transition metals Cu^{2+} , Ni^{2+} and Co^{2+} ions yielded new series of mononuclear. Successfully synthesized compounds were characterized by Melting point, Conductivity, Magnetic moments, FT-IR, UV-Vis spectroscopy and thermogravimetry (TGA) analysis. The coordination modes of ligand with divalent metal ions were also elucidated. The coordination environment for all metal complexes is octahedral structure. In addition, the antibacterial and antioxidant properties for both L1 and its metal complexes were investigated and the best activity was observed in the CuL1 complex, which may be due to the smallest cationic size of the Cu^{2+} ion and its strong chelation with the L1 ligand compared to other complexes. However, The CuL1 complex after further investigations should be considered as a promising drug for the treatment of diseases caused by E. coli bacteria.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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