Synthesis, Characterization, Thermal Study of Some Transition Metal Complexes of N-(4-hydroxybenzylidene) isonicotinohydrazone and Investigation of Their Antibacterial and Antioxidant Properties.

Abstract

Cr^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} ions complexes of the Schiff base ligand, N-(4-hydroxybenzylidene)isonicotinohydrazone (L1), were synthesized and characterized by analytical and physicochemical techniques such as conductivity, magnetic susceptibility measurements, IR-spectra, and UV-Visible spectra and thermogravimetric analysis (TGA). FT-IR , TGA, Magnetic moment and UV-Vis spectra data confirmed the octahedral geometry for Cr^{3+}, Co^{2+}, and Cu^{2+} ion complexes, square planar geometry for Ni^{2+} complex and tetrahedral structure for Zn^{2+} ion complex. The metal complexes of L1 were tested against *P. aeruginosa* and *E. coli.* All produced complexes demonstrated strong antibacterial efficacy against P. aeruginosa when compared to standard Kanamycin-30, and the Ni^{2+} complex had the greatest activity. On the other hand, when compared to all compounds, the Zn^{2+} complex demonstrated strong antibacterial efficacy against E. coli. Furthermore, synthesized metal complexes exhibited moderate antioxidant activity than the L1. The Cu^{2+} complex was shown to have the highest antioxidant activity, whereas the Zn^{2+} complex exhibited the least activity out of all of the produced complexes.

Key words: Schiff base, Transition metals, Isoniazid, Kanamycin-30, Antioxidant

1. Introduction

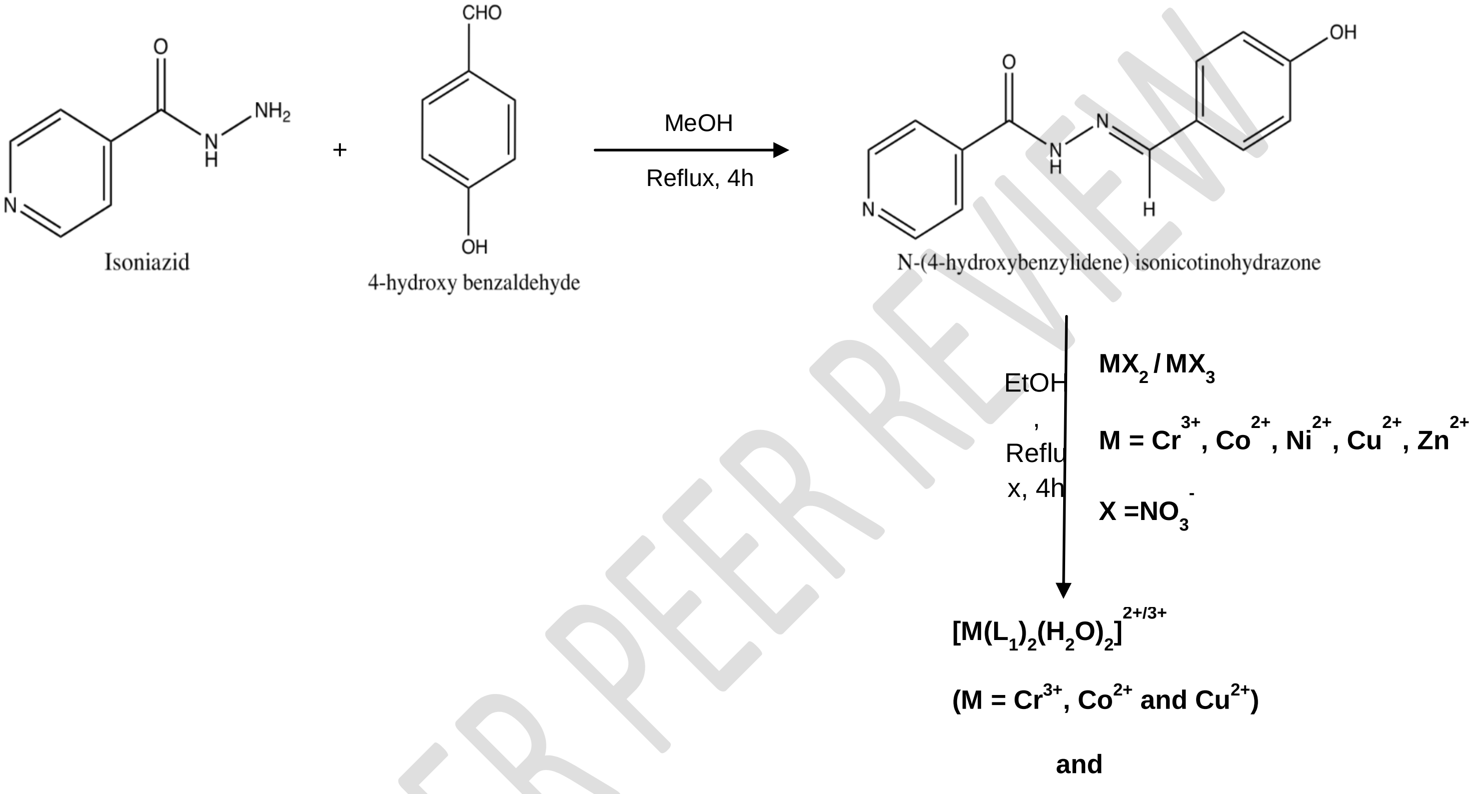
Compounds with the azomethine group (-C=N-) are referred to as Schiff bases; they are generated from the condensation reaction between primary amines and carbonyl compounds having aldehydes or ketones [1-2]. In the last decade, Schiff base ligands have gained more attention mainly by reason of their wide uses in the field of catalysis, biomimetic modeling as well as designing molecular magnet molecules and because of their antimicrobial and antifungal activity [3-4]. Another noteworthy feature is that they form stable complexes with the majority of transition metal ions, which has made them an important family of ligands in coordination chemistry [5-7] as well as inorganic chemistry [8]. Furthermore, they have various applications in biological, clinical, analytical, electrochemistry, medicinal, and industrial studies in addition to they are used as liquid crystals in the field of analytical, medicinal, and polymer chemistry [9-11]. Aside from that, Schiff bases and their complexes have biological actions that include antibiotic, antifungal, antibacterial, anti-inflammatory, anti-tumor, anti-oxidative, anti-HIV, and anti-cancer properties. [12-15]. Isoniazid is a very effective medicine that is used as the first-line therapy for TB (tuberculosis). It is a suggested therapeutic material for Mycobacterium TB due to its high level of antibacterial activity. It forms metal chelate complexes with several physiologically important bivalent ions [16–19]. We disclosed here the synthesis and characterization of Schiff base, N-(4-hydroxybenzylidene)isonicotinohydrazone obtained from the condensation reaction of p-hydroxybenzaldehyde and isoniazid and its metal complexes of Cr^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}. Some bioactivity test findings, such as antibacterial and antioxidant properties for ligands and their metal complexes were also mentioned.

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-(4-hydroxybenzylidene) isonicotinohydrazone Schiff base Ligand (L1)

N-(4-hydroxybenzylidene)isonicotinohydrazone, Schiff base Ligand, L1 was obtained (Scheme 1) by the conventional condensation reaction of p-hydroxybenzaldehyde with isoniazid (INH) in an equimolar ratio (i.e., 1:1). A methanolic solution of INH(1.37 g, 10.00 mmol) was taken in a round bottom flask, and then a methanolic solution of 4-hydroxybenzaldehyde (1.22 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 4 hours. TLC monitored the purity of the obtained product throughout the whole reaction. A light-yellow precipitate of the ligand was produced, which was then filtered and washed several times with cold CH_3OH solution before being dried in a desiccator over anhydrous $CaCl_2$.



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 (Cr^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{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 4 h. After cooling, the obtained precipitates were filtered and washed with cold C_2H_5OH solution and dried under vacuum on anhydrous $CaCl_2$. A reference complex, having composition $[Cu(L1)_2(H_2O)_2]Cl_2$ symbolized as CuCL1 has also prepared according to the above procedure for comparative antibacterial study.

2.3 Antibacterial Studies

Antimicrobial activity of the ligand and its complexes were performed against *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]:

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

Where A_o 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

All of the produced complexes were insoluble in polar solvents, although they were soluble in DMSO and DMF. At room temperature, the molar conductance values of all generated complexes (10^{-3} M) were tested in DMSO solution. The physical properties of the L1 and its metal complexes have shown in Table 1. The conductivity of the Cr^{3+} complex was determined to be 160 $ohm^{-1}cm^2mol^{-1}$, implying a 1:3 electrolyte, whereas other complexes were 1: 2 electrolytes [24-25]. The magnetic moments for Cr^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} complexes were 3.73 BM, 4.81 BM, 0.43 BM, 1.78 BM, and 0.62 BM, respectively. The magnetic moment's value of the Cr^{3+} complex indicated the octahedral geometry [26] having three unpaired electrons, slightly less than the spin-only value (3.88 BM). Complexes having three unpaired electrons might be tetrahedral or octahedral geometry. Magnetic moments for the high-spin octahedral Co^{2+} complexes range from 4.7 to 5.2 B.M. The Co^{2+} has a ground state of $^4T_{1g}$ in an octahedral complex, which contributes a large orbital moment to magnetic moments. Therefore, the observed magnetic moment's value of the Co^{2+} complex supported its octahedral structure rather than tetrahedral [27]. For tetrahedral Ni^{2+} complex, the magnetic moment value should be in the range of 3.4 to 4.2 BM. The possible reasons for the increasing magnetic moment compared to that of spin only value has already been disclosed by Nyholm et al.[27]. However, the magnetic moment of the Ni^{2+} complex was 0.43 BM, suggesting its diamagnetic nature and square planar geometry [28]. For the Cu^{2+} complex, the magnetic moment indicates its paramagnetic nature, and the mentioned value corresponds to octahedral geometry [29]. Similarly, the magnetic moment of the Zn^{2+} complex corresponds to its diamagnetic nature as well as its tetrahedral environment [30].

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

Ligand/Complexes (Symbol)	**Appearance and body color**	**M.W**	**% Yield**	**M.P (°C)**	**Molar Conductivity ($ohm^{-1}\,cm^2\,mol^{-1}$)**	**μ_{eff} (B.M)**
$C_{13}H_{11}N_3O_2$ (L_1)	Light yellow powder	241.2	75%	185		
$[Cr(L_1)_2(H_2O)_2]\,(NO_3)_3$ (CrL1)	Dark brown powder	756.4	71%	>300	160	3.73
$[Co(L_1)_2(H_2O)_2]\,(NO_3)_2$ (CoL1)	Brown powder	701.4	69%	>300	121	4.81
$[Ni(L_1)_2]\,(NO_3)_2$ **(NiL1)**	Crimson powder	665.1	72%	>300	115	0.43
$[Cu(L_1)_2(H_2O)_2]\,(NO_3)_2$ (CuL1)	Green powder	706.4	78%	>300	125	1.78
$[Zn(L_1)_2]\,(NO_3)_2$ (ZnL1)	White powder	671.8	71%	>300	119	Dia

3.1 IR Spectral Studies

The IR spectra of the ligand, L1 has presented in the **Figure 1**. The IR spectra of the ligand revealed a strong band at 1658 cm^{-1} owing to the ν (C=O) of the amide group. In all complexes (**Figures 2-6**), this intense band has moved and been significantly displaced, demonstrating coordination via the oxygen of carbonyl (C=O) group. The azomethine group ν (C=N) band positioned at 1598 cm^{-1} has shifted to lower frequencies in all complexes, showing that the azomethine nitrogen (N) is engaged in coordination [31]. Due to the combined mode of ν(O-H) and N-H stretching vibrations, a broad, strong band developed in the range of 3467-3434 cm^{-1}. The appearance of a new band at 1025 cm^{-1} owing to δH_2O supports the existence of coordinated water in complexes [32] except NiL1 and ZnL1 complexes. The existence of coordinated water was further confirmed by the TGA data summarized in the **Table 4**. Along with this, the complexes' IR spectra revealed additional non-ligand bands in the ranges between 588-560 and 494-464 cm^{-1}, which were designated as M-O (metal to oxygen) and M-N stretching vibrations, respectively [33-34]. Consequently, it may be concluded that the ligand (L1) interacts with the metal ions via the nitrogen (N) and oxygen (O) atoms in the azomethine and carbonyl groups of its structure. However, all observations with assignments have given in the **Table 2**.

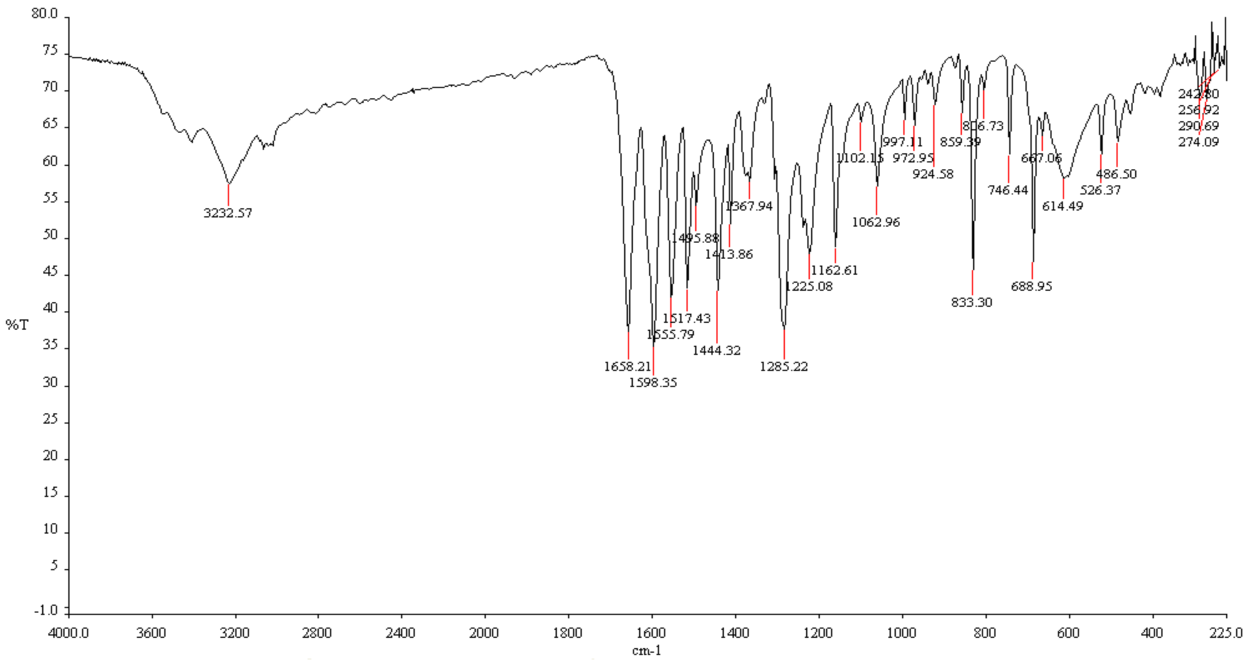


Figure 1: IR spectrum of L1

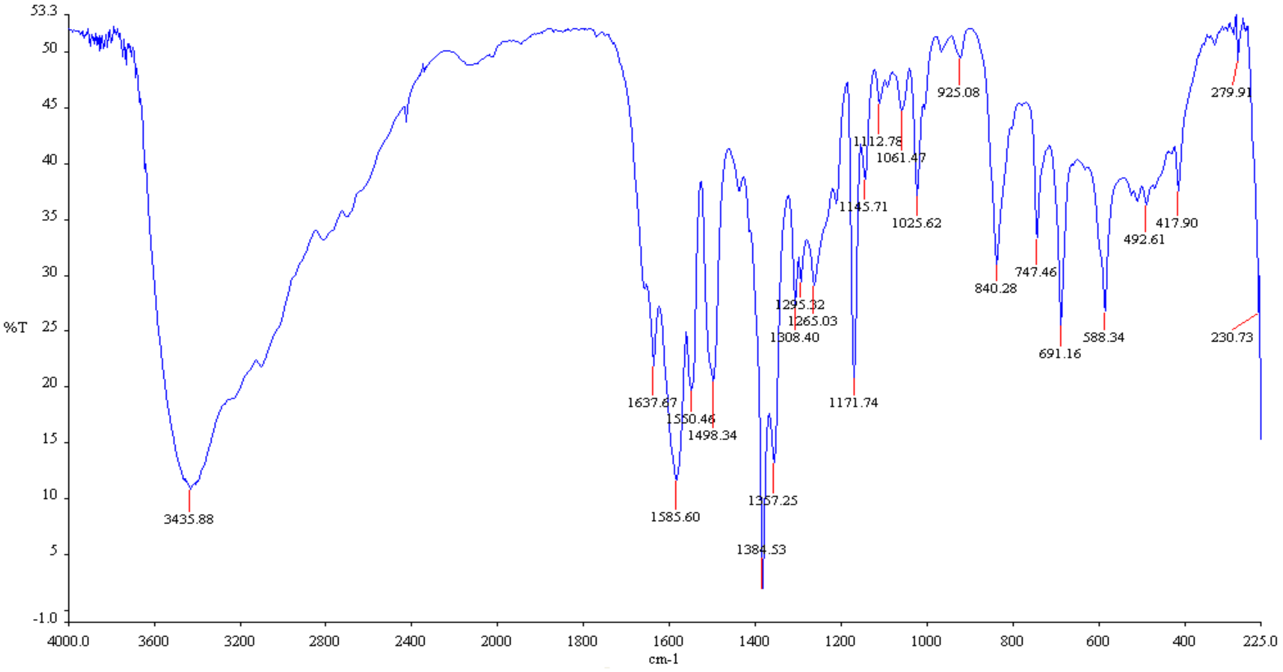


Figure 2: IR spectrum of CrL1

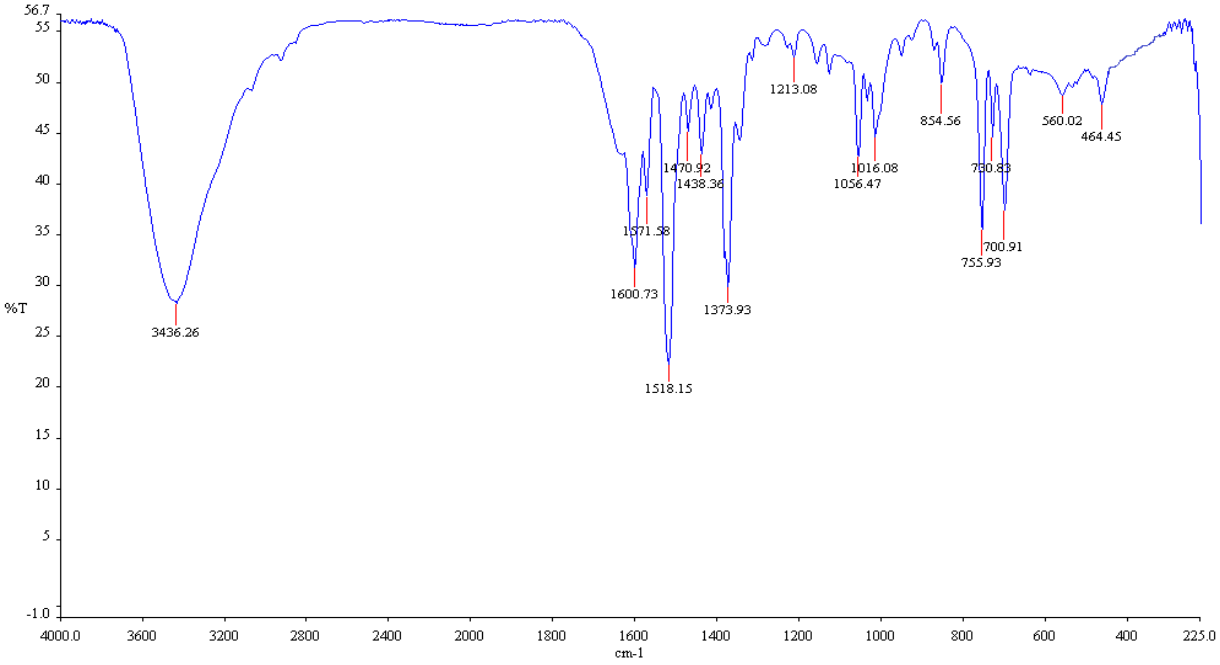


Figure 3: IR spectrum of CoL1

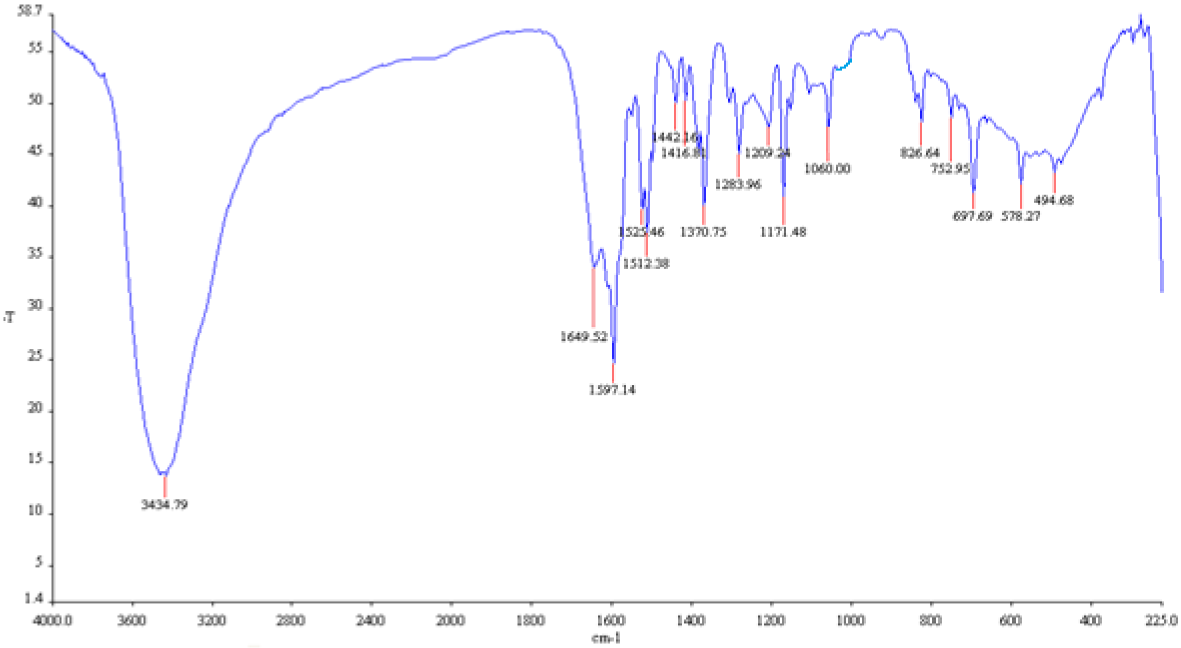


Figure 4: IR spectrum of NiL1

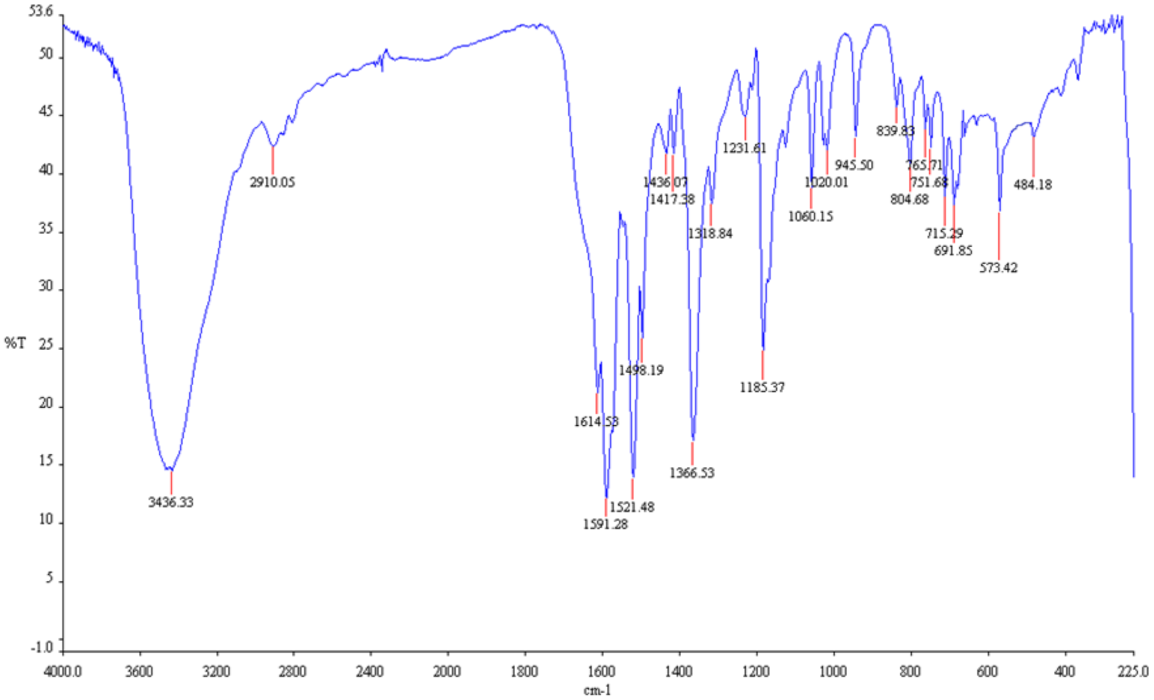


Figure 5: IR spectrum of CuL1

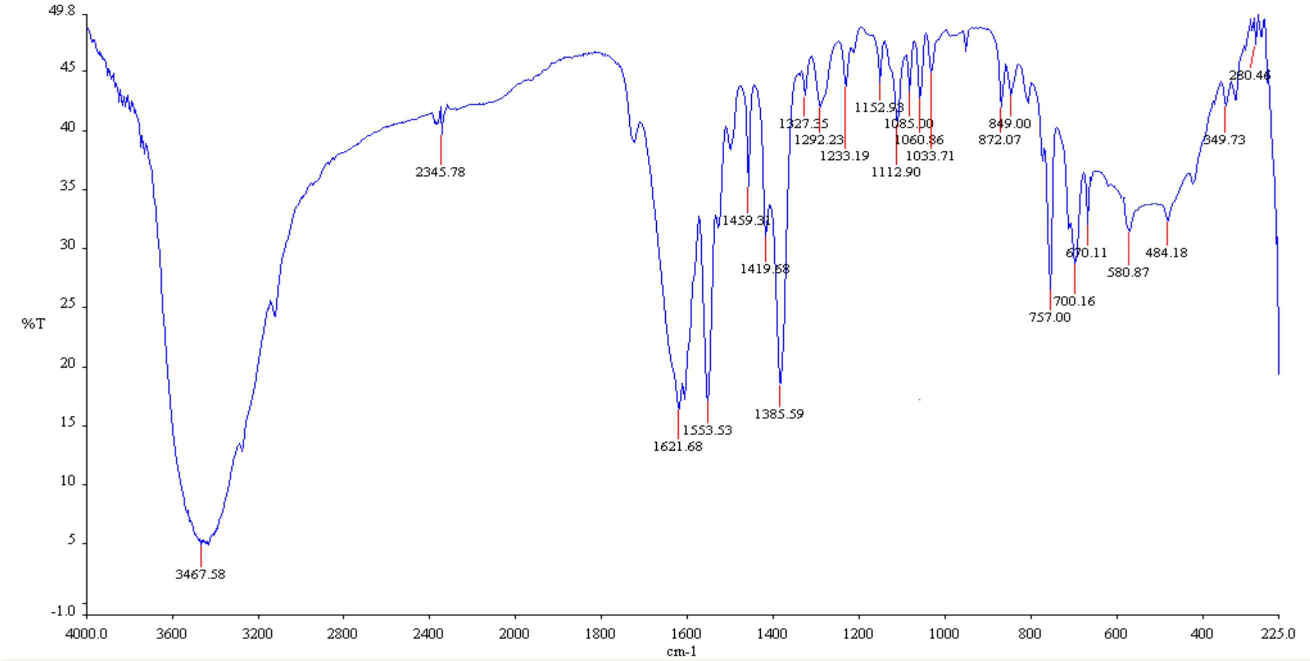


Figure 6: IR spectrum of ZnL1

Table 2: Key Infrared bands (cm^{-1}) of ligand L1 and its metal complexes

Ligand/ Complexes	$\nu_{(OH)} + \nu_{(NH)}$	$\nu_{(C=O)}$	$\nu_{(C=N)}$	$\nu_{(M-O)}$	$\nu_{(M-N)}$
L1	**3232**	**1658**	**1598**	**--**	**--**
CrL1	**3435**	**1637**	**1585**	**588**	**492**
CoL1	**3436**	**1600**	**1571**	**560**	**464**
NiL1	**3434**	**1649**	**1597**	**578**	**494**
CuL1	**3436**	**1614**	**1591**	**573**	**484**
ZnL1	**3467**	**1621**	**1553**	**580**	**484**

3.2 Electronic Spectra

L1 showed two distinct bands at 271 and 324 nm, which were for π-π* and n-π* transitions, respectively (**Figure** 7). For the CrL1 complex, three bands were identified at 282, 351, and

440 nm. The band at 282 nm owing to the π-π* transition is marginally altered by chelation in comparison to the free ligand. In contrast, the band at 351 nm, which corresponds to azomethine, broadened and shifted to a longer wavelength, showing the involvement of ligand to metal through the azomethine molecule. However, the band positioned at 440 nm is due to the d-d transition [26]. There were four bands at 271, 336, 380, and 460 nm for the CoL1 complex. The absorption band centered at 380 nm may be related to the ligand to metal charge transfer (LMCT) transition. The band at 460 nm corresponds to the $^4T_{1g}$ (F)→ $^4T_{1g}$ (P) transition, which is indicative of octahedral geometry [35]. The NiL1 complex, like the other complexes, exhibited the transitions stated above. In the case of square planar Ni^{2+} complex, there should have a d-d transition above 500 nm, but this band does not observe in our research work. The CuL1 complex also showed three bands at 270, 360 and 532 nm, respectively. The band centered at 532 nm, is a d-d absorption band, which is attributed to ^2E_g → $^2T_{2g}$ transition suggesting the octahedral geometry of this complex [36]. The ZnL1 complex also showed three bands positioned at 270, 339 and 354 nm. The ZnL1 complex with a d^{10} electronic configuration displayed a band at 354 nm due to the LMCT transition, which corresponds well with the tetrahedral geometry [37]. All observations have presented in the tabulated form in **Table 3**.

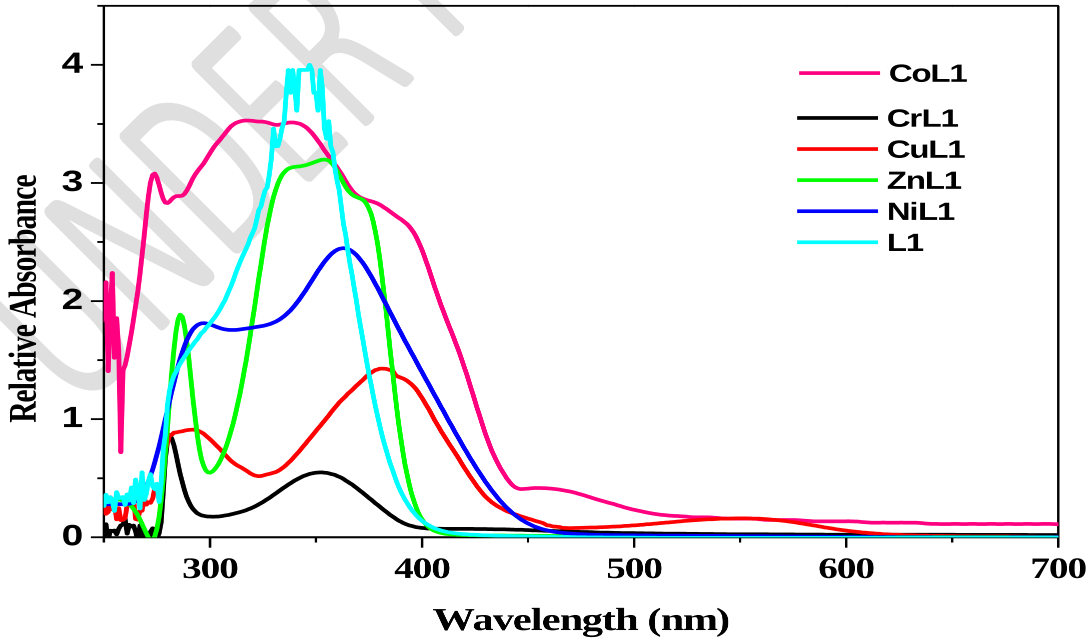


Figure 7: Uv-Vis spectra of L1 and its metal complexes

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

Ligand/ Complexes	Band Positions (nm)	Assignment	Geometry
L1	**271** **324**	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$	
CrL1	**282** **351** **440**	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ $^4A_{2g}$ (F) → $^4T_{1g}$ (P)	**Octahedral**
CoL1	**271** **336** **380** **460**	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ **CT** $^4T_{1g}$ (F) → $^4T_{1g}$ (P)	**Octahedral**
NiL1	**274** **341**	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$	**Square planar**
CuL1	**270** **360** **532**	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ $^2E_g \rightarrow {}^2T_{2g}$	**Octahedral**
ZnL1	**270** **339** **354**	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ **CT**	**Tetrahedral**

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 ^oC. The thermogram of complexes exhibits multi-stage weight loss [**Figures 8-10**]. For the CrL1 complex, the first step occurred at around 250°C due to the elimination of two coordinated H_2O molecules (calcd. 4.76%, found 4.74%) [38]. In the temperature range of 250-380 ^oC, 35.70% weight loss was found (calcd. 35.72%), which was due to the removal of $2C_6H_5N_3O$ (part of the ligand). Third weight loss (calcd. 49.46%, found 49.31 %) due to the removal of another part of ligand ($2C_7H_6O$) along with some gases (i.e., NO_2 and O_2) was observed in the temperature range of 380-680 ^oC. Above 680 ^oC, no weight loss was observed in the TGA curve of the CrL1 complex. This may be due to the formation of metallic oxide (Cr_2O_3) [39]. For CoL1 complex, first weight loss (calcd. 5.14 %, found 5.13 %) was observed around 200 ^{o}C suggesting the removal of two molecules of coordinating water. The second step of decomposition was observed with a mass loss of 83.84 % (calcd. 84.18 %) within the range of 200-650 ^{o}C of indicating the dissociation of ligands together with some gases leaving CoO as residue. In the case of the CuL1 complex, the TGA curve showed three steps of decomposition up to 680 ^{o}C. The first stage (like other complexes) at around 235 ^{o}C with a weight loss of 5.13 % (calcd. 5.10 %) confirmed the presence of two coordinated water molecules. The second step with a mass loss of 30.08 % (calcd. 30.05) at 235-375 ^{o}C, corresponds to the loss of $2C_6H_4NO$ (part of ligand). The penultimate step in the range of 375-680 ^{o}C, having a mass loss of 53.75 % (calcd. 53.56 %) supports the elimination of the residual ligand ($2C_7H_7N_2O$) as well as some gases. The final residue with a constant weight represents CuO [40].

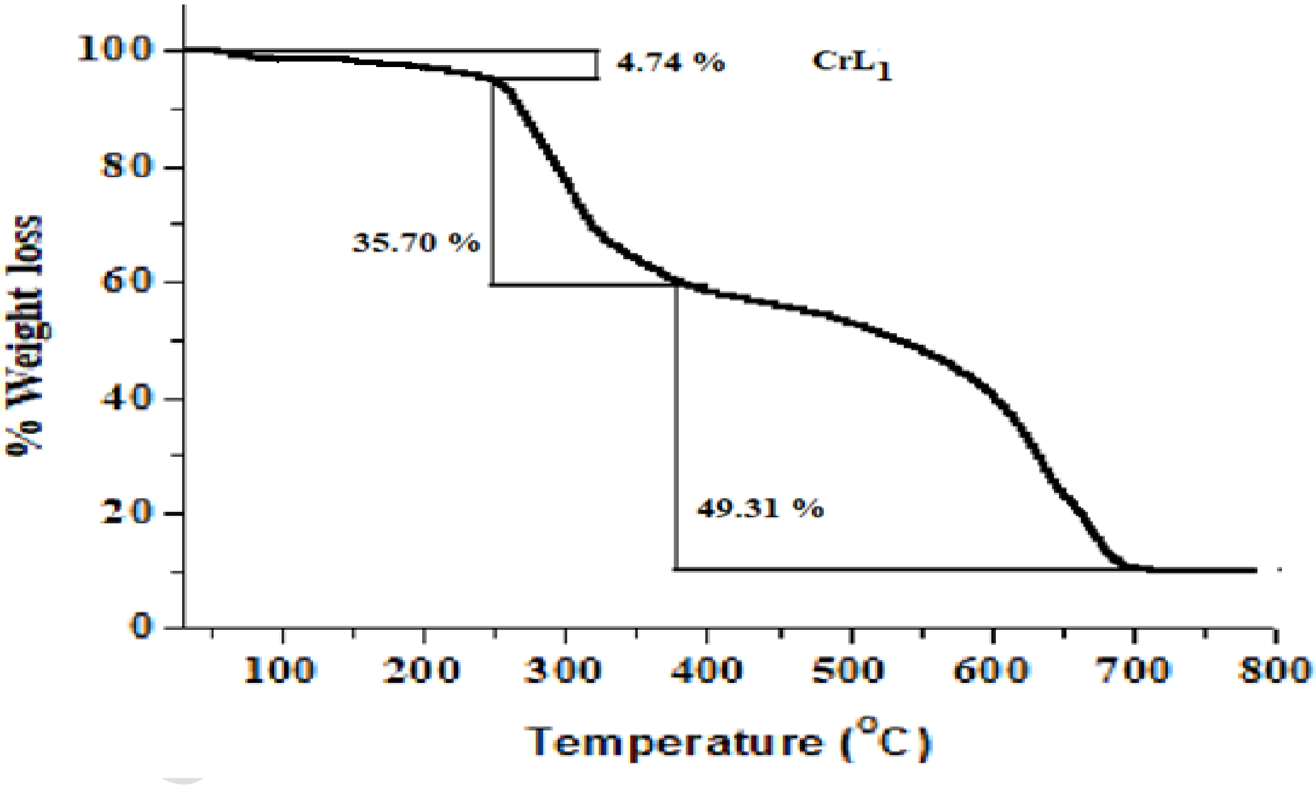


Figure 8: TGA curve of CrL1 complex

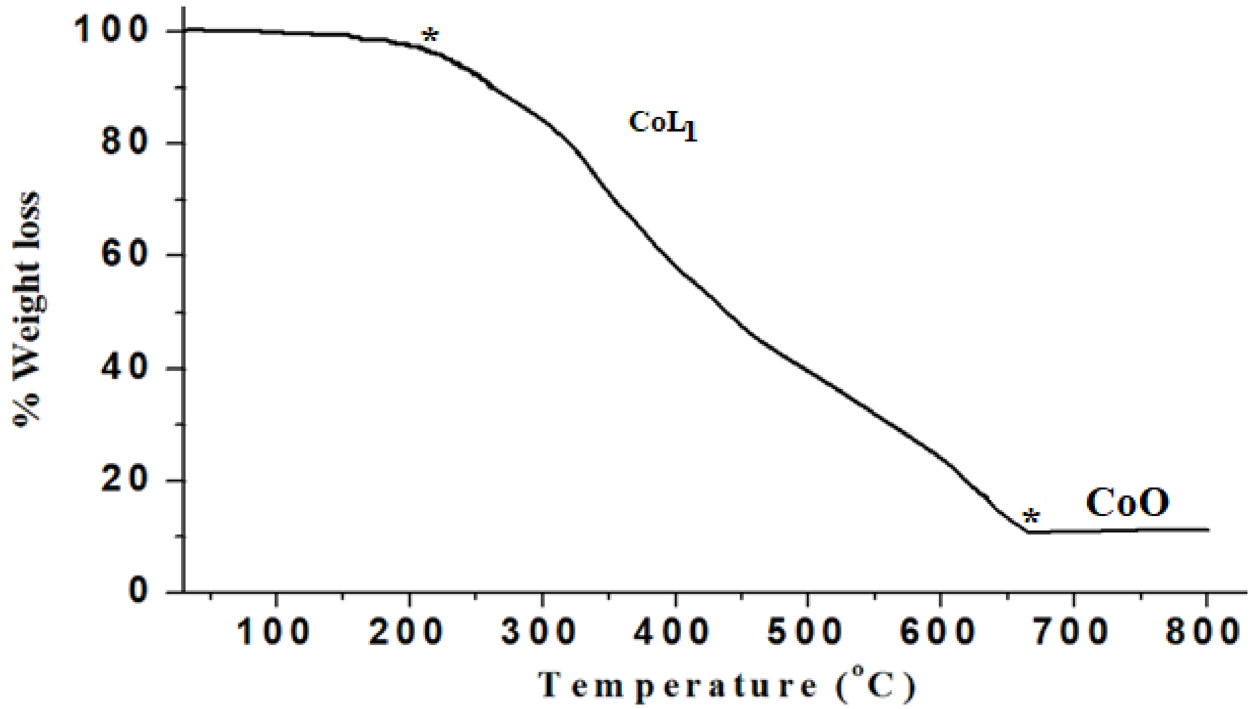


Figure 9: The TGA curve of CoL1 complex

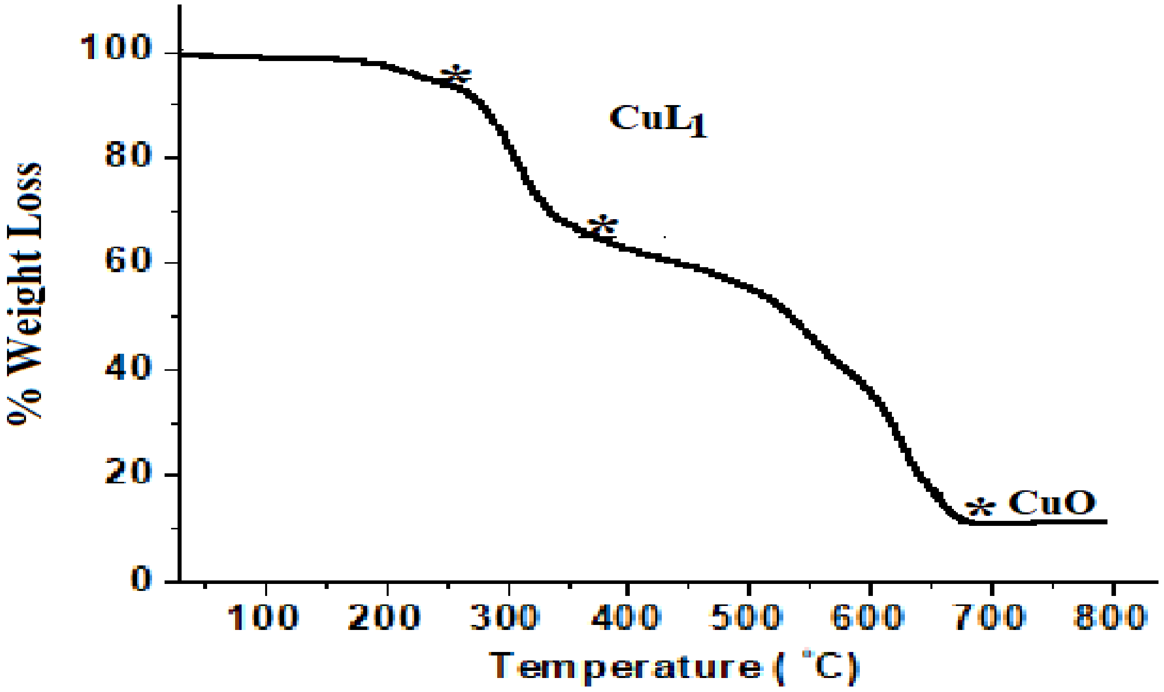
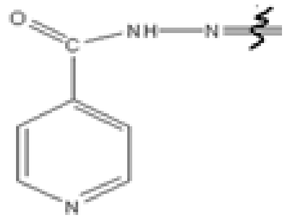


Figure 10: The TGA curve of CuL1 complex

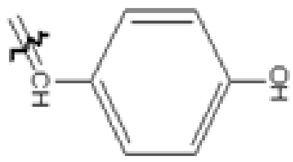
Table 4: Thermoanalytical data of CrL1, CoL1 and CuL1 complexes

Complex	Temperature Range (°C)	Weight loss (%)		Assignments
		Found	Calculated	
CrL1	**30 – 250**	**4.74**	**4.76**	**Loss of two coordinated H_2O molecules**
	250-380	**35.70**	**35.72**	**$2C_6H_5N_3O$**
	380-680	**49.31**	**49.46**	**$2C_7H_6O + 3NO_2 + 0.75\ O_2$**
	> 680	**10.25**	**10.05**	**$0.5\ Cr_2O_3$**
CoL1	**30 – 200**	**5.13**	**5.14**	**Loss of two coordinated H_2O molecules**
	200-650	**83.84**	**84.18**	**2 L1 + $2NO_2 + 0.5\ O_2$**
	> 650	**11.03**	**10.68**	**CoO**
CuL1	**30 – 235**	**5.13**	**5.10**	**Loss of two coordinated H_2O molecules**
	235-375	**30.08**	**30.05**	**$2C_6H_4NO$**
	375-680	**53.75**	**53.56**	**$2C_7H_7N_2O + 2NO_2 + 0.5\ O_2$**
	> 680	**11.04**	**11.26**	**CuO**

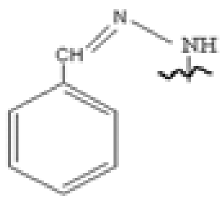


$C_6H_5N_3O$

C_6H_4NO

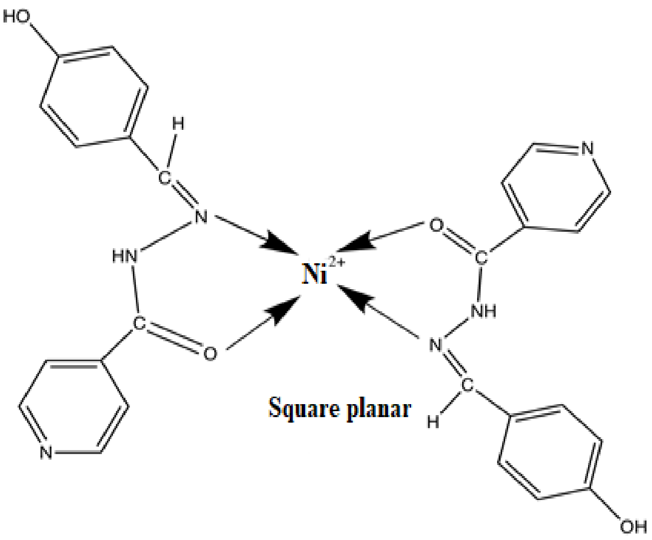


C_7H_6O

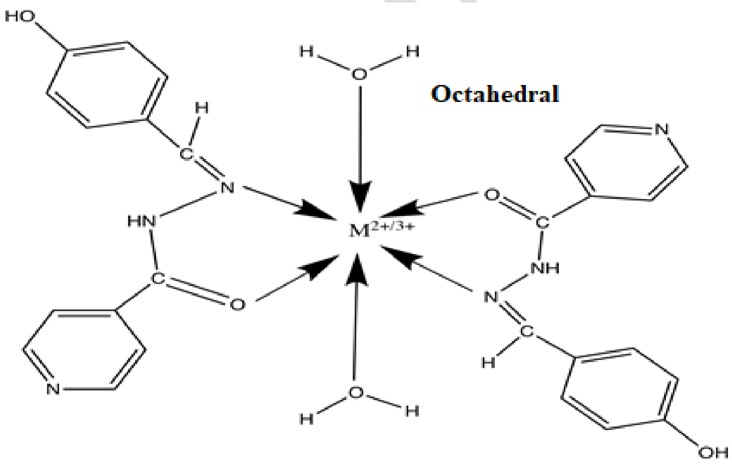


$C_7H_7N_2O$

Proposed Structure: On the basis of above characterizations, the following structures can be proposed for the obtained metal complexes.

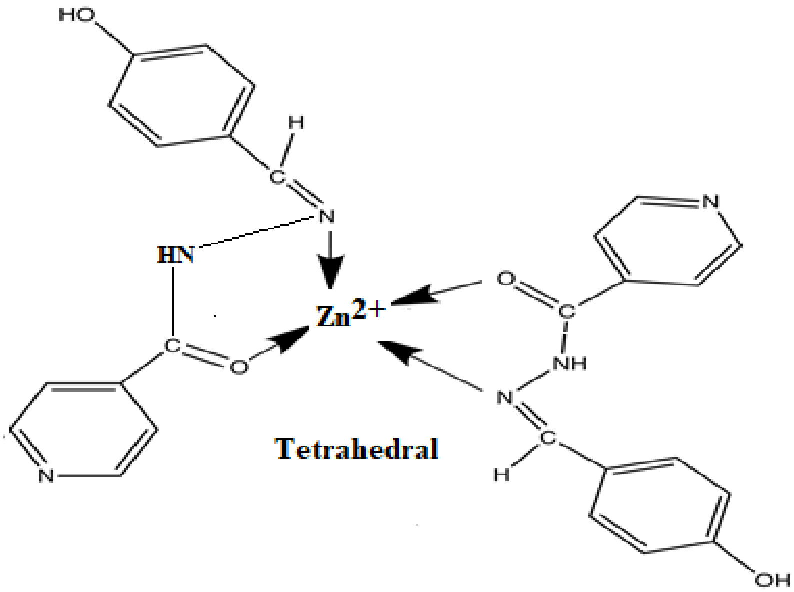


Square planar



Octahedral

M = Cr^{3+}, Co^{2+} and Cu^{2+}



Tetrahedral

3.3. Antibacterial Activity

The antibacterial activity of Schiff base ligands and its metal complexes against *Escherichia coli* and *Pseudomonas aeruginosa* was studied at a concentration of 100 µg/ 10 µL in DMSO. 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 two pathogenic bacteria. Among all synthesized complexes, the Ni^{2+} complex showed good antibacterial activity against *Pseudomonas aeruginosa* and the following trend is observed: NiL1> CuL1> CrL1> CoL1> CuCL1(Ref.) > ZnL1 = Kanamycin-30> L (**Figure 11**). On the other hand, the Zn^{2+} complex showed good activity against E. coli when compared with all synthesized compounds. In this case the order of the antibacterial activity follows the following trend: Kanamycin-30 > ZnL1> CuL1> CoL1 > CrL1= NiL1 > CuCL1(Ref.) > L1. Some factors such as the lipophilic nature of metal complexes, solubility, coordinating sites, complex geometry, steric hindrance, concentration, and hydrophobicity have a significant impact on antibacterial potency [41-43]. However, 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 [41].

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

Diameter of Zone of Inhibition (mm) of tested compounds (100µg/disc)		
Compounds	Gram Negative	
	Escherichia coli	*Pseudomonas* aeruginosa
Kanamycin (30 µg/disc)	30	15
Ligand (L1)	07	10
CrL1	20	21
CoL1	21	18
NiL1	20	25
CuL1	23	23
CuCL1 (Ref.)	15	17
ZnL1	25	15

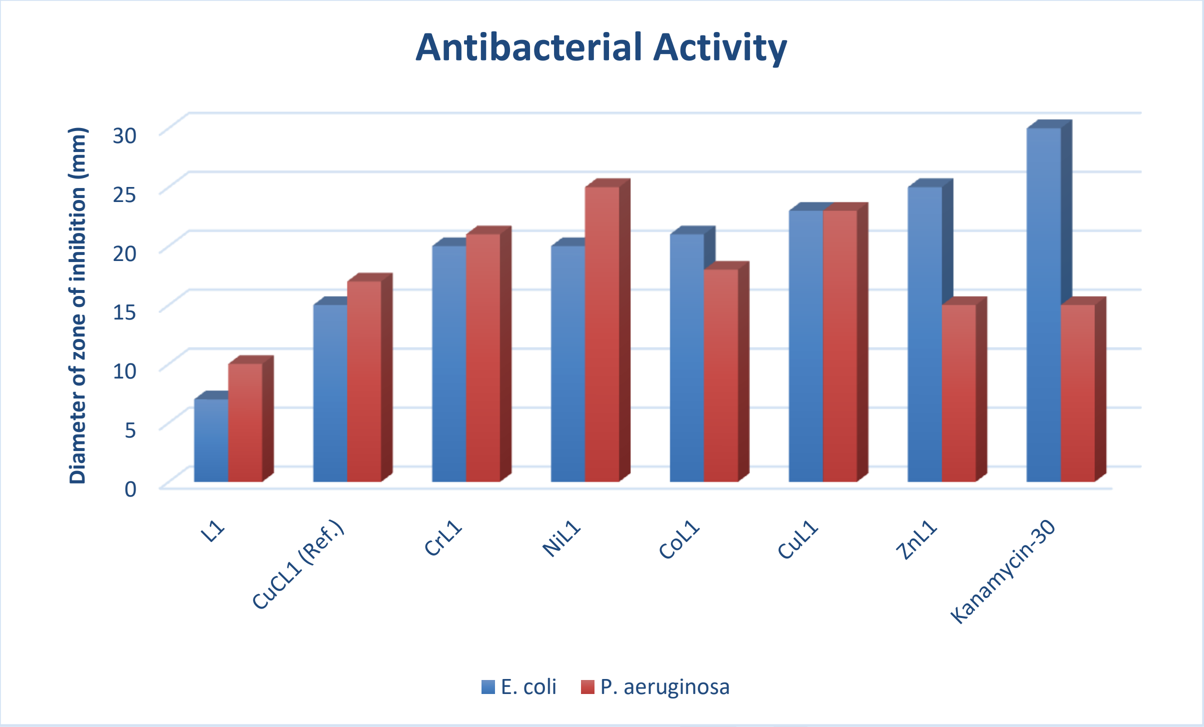


Figure 11: Graphical representation of antibacterial activity of ligand L1 and its metal complexes against *Escherichia coli* and *Pseudomonas* sp. with standard Kanamycin-30 and ref.

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 (**Figure 12**). The order can be given as BHT> CuL1> CrL1> NiL1> CoL1> ZnL1 >L1. The redox characteristics and coordination environment of the Schiff base metal complexes may explain the variance in antioxidant activity. Several variables impact the redox characteristics of metal complexes, including chelate ring size, chelate ring unsaturation and axial ligation. [42, 43]. Since the Zn^{2+} ion is not a transition metal and therefore cannot participate in electron-transfer processes, its activity is reduced [44]. On the other hand, the Cu^{2+} complex has higher antioxidant activity than other synthesized complexes may be due to its reducing ability and proton donation characteristic, which allows Cu^{2+} to serve as a superoxide scavenging center [44]. As a consequence, the findings of this research suggest that the CuL1 complex might be used to treat pathological disorders caused by oxidative stress. The IC_{50} value of all stated compounds in combination with standard BHT has been calculated and shown in **Figure 13**.

Table 6: % of Scavenging activity of BHT, ligand L1, and its metal complexes

Conc. (µg/mL)	% BHT	% L1	% CrL1	% CoL1	% NiL1	% CuL1	% ZnL1
20	12.41	1.38	5.34	3.75	2.69	10.7	2.34
40	27	2.87	15.25	10.97	3.54	24.13	5.61
60	36.98	4.11	17.83	12.88	5.09	29.56	6.72
80	41.2	6.02	19.62	14.65	7.50	31.77	8.24
100	45.78	6.99	22	15.27	9.34	32.28	8.91

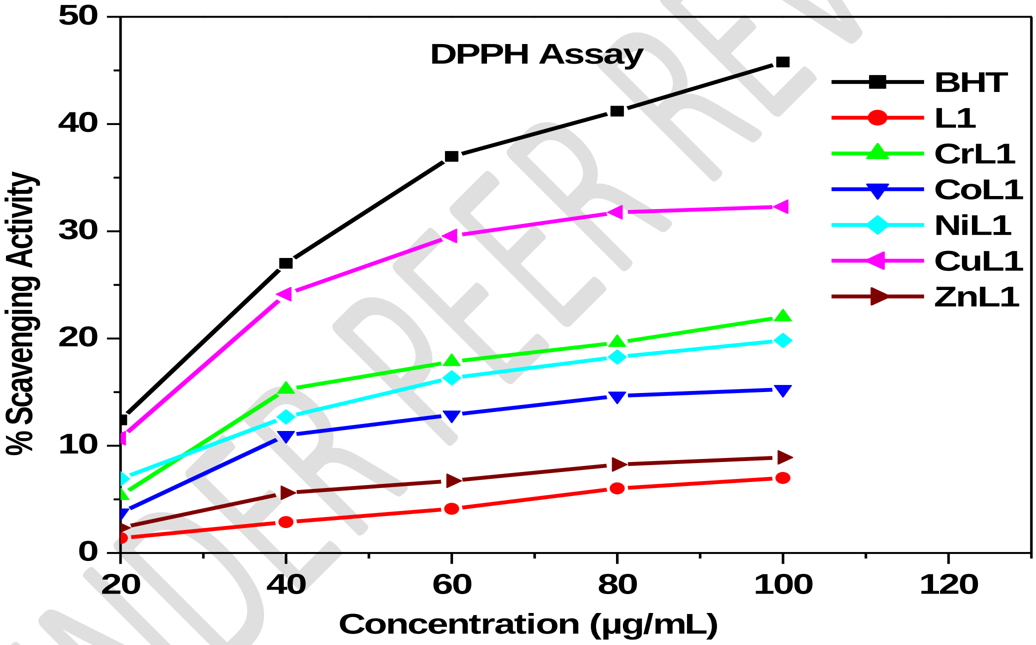


Figure. 12: DPPH radical scavenging activity of the L1 and its metal ions complexes at different concentrations (20, 40, 60, 80, and 100 µg/mL) with standard BHT.

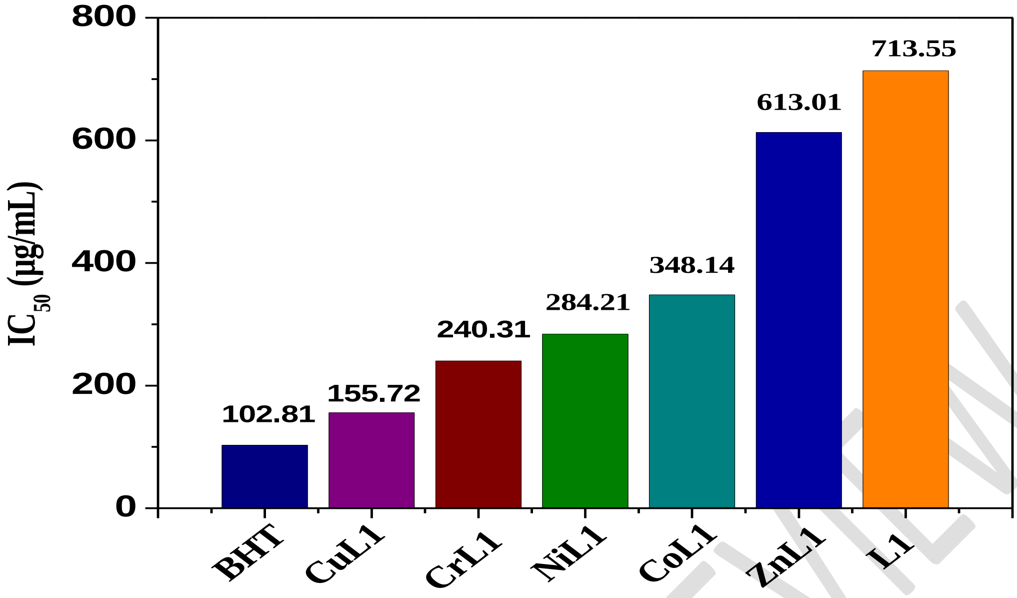


Figure. 13: IC_{50} value of the metal complexes of ligand L1 at various concentrations (20, 40, 60, 80, and 100 µg/mL) with standard BHT.

4. Conclusion

Condensation of 4-hydroxybenzaldehyde with isoniazid results in the formation of a novel bidentate Schiff base ligand. When compared to the Kanamycin-30, all produced complexes were determined to be the most active against *P. aeruginosa*. The antibacterial activity of the CuL1 complex against two different pathogenic bacteria is particularly remarkable. The antioxidant activity of the CuL1 complex was the greatest among all the complexes when compared to that of BHT. Further research is needed before CuL1 can be used as a possible medication to treat oxidative stress.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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