Synthesis Characterization and Study the Antibacterial Activity of Some Transition Metal Complexes of New Thiosemicarbazide Ligand

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Abstract
N-(2-carbamothioylhydrazine-1-carbonothioyl)-4-methoxybenzamide (L), a new thiosimecarbazide ligand, was prepared and characterised as part of the study. Three coordination were separated from the combination of the title ligand and the metal ions cobalt (II), nickel (II), and copper (II). Using EtOH as the medium, a 1:1 mole ratio of metal to ligand was used to carry out the reaction. The isolated coordination compounds have the following general chemical formula; [LMCl2.H2O)] M(II)= (Co, Ni and Cu). The structural identity of the predicted ligand and its metal complexes have been exhaustively established using various analytical and physico-chemical approaches. These consist of melting point, electronic spectra, FTIR Spectroscopy, and also (1H and 13C) Nuclear Magnetic Resonance spectra. Based on the analytical and spectroscopic data collected, it was found that the synthesized complexes (Co), (Ni) and (Cu) adopted a six-coordinate configuration with a characteristic distorted octahedral environment around the metal center. G+ and G- species antibacterial activity was investigated.

Keywords: Thiosemicarbazide ligand, metal complexes, structural characterization, antibacterial activity.

1. Introduction

The potential biological actions of heteroleptic complexes have led to an increase in interest in their coordination chemistry. Due to their significance in the domains of bioinorganic and medicinal chemistry, the synthesis of coordination molecules based on semicarbazone derivatives has increased dramatically [1]. Chalcogen-based organic species are an important class of materials that incorporate the *hard*/*hard* (N,O) or *hard*/*soft* (N,X) donor atoms where X= S, Se or Te [??????]. They have contributed significantly to the development of coordination and inorganic chemistry [???]. These organic species have been used as chelating agents and a range of semicarbazides, thiosemicarbazides, semicarbazone and thiosemicarbazone derivatives are reported [????]. More, these species indicated a range of biological activities [???] and their coordination compounds alter lipophilicity, which controls the rate of cell entrance [2,3].

Among the most common ligands that consist of nitrogen/oxygen donor atoms are semicarbazides. These compounds offer a diversity of binding mechanisms, a wide range of structural options, and biological uses [4-6]. The importance of these compounds is emphasised by using them as chelating agents that interact with a range of transition and non-transition elements [7]. Several parameters influenced the coordination modes of these species upon complexation. These include reaction conditions (pH, heat and medium), metal salts, counterions, and the kind of substituent on the backbone carbonyl molecule [8]. Semicarbazides are recognized for their diverse structural characteristics; in addition, their corresponding metal complexes frequently exhibit enhanced pharmacological and physiological activities compared to free ligands [9, 10]. Further, the condensation reaction of thiosemicarbazide with the appropriate aldehyde and/or ketone moiety resulted in the formation of a thiosemicarbazone compound. These species have a great complexation ability and the organic and coordination compounds have been extensively investigated, as a mimic, in the biological system and analytical applications [11]. This study describes the preparation and complete spectroscopic characterisation of the new ligand bearing the hard (O,N) and the soft sulphur atoms with its structure; N-(2-carbamothioylhydrazine-1-carbonothioyl)-4-methoxybenzamide (L) along with its metal complexes containing M(II) ions (Co), (Ni) and (Cu). Additionally, the ligand's and also its corresponding metal complexes' antibacterial evaluation is investigated

2. Experimental

2.1 Materials and methods

Aldrich-purchased reagents were used exactly as supplied. Before being used in the preparation, solvents were dried according to conventional procedures. The starting materials used were (4-methoxybenzoyl chloride (98% Sigma, $C_8H_7O_2Cl$, M.Wt. 170.59 g/mol), ammonium thiocyanate (98% Sigma, NH_4SCN, M.Wt. 76.12 g/mol), thiosemicarbazide (98% Sigma, CH_5N_3S, M.Wt. 91.14 g/mol), $CoCl_2 \cdot 6H2O$ (M.Wt. 237.93 g/mol, 99%, Sigma), $NiCl_2 \cdot 6H_2O$ (M.Wt. 237.69 g/mol, 99%, Sigma) and $CuCl_2 \cdot 2H_2O$ (M.Wt. 170.48 g/mol, 99%, Sigma) were used to prepare complexes. Absolute ethanol (C_2H_5OH, M.Wt. 46.068 g/mol, 99.9%, R&M) was used for the reaction.

2.2 Masurement techniques

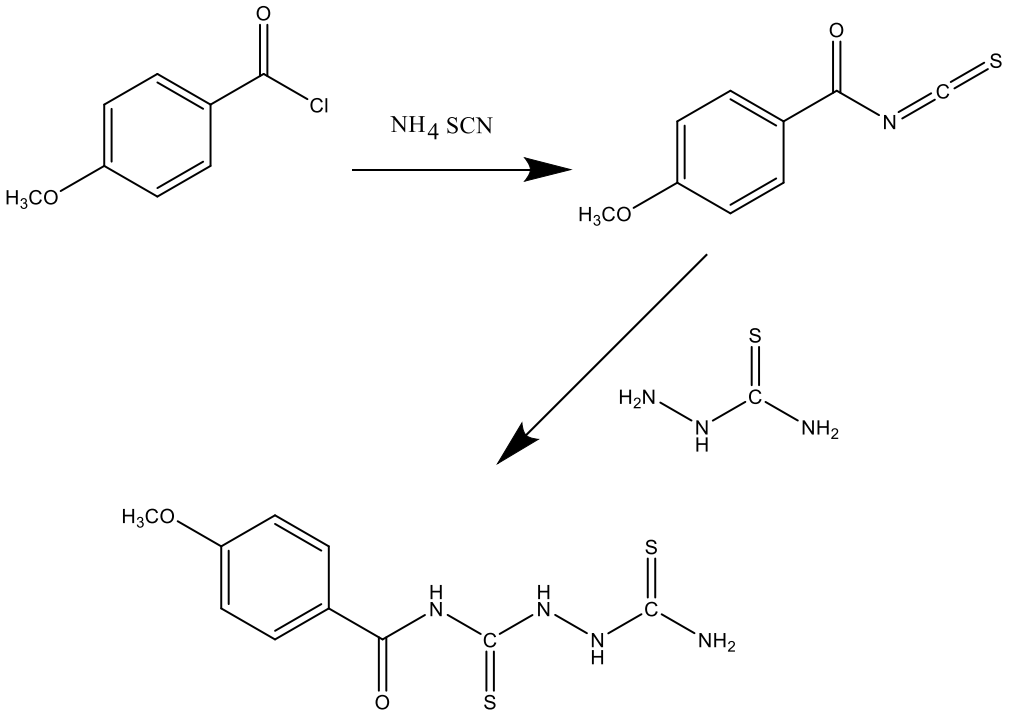
Perkin Elmer Spectrum GX spectrophotometer (Perkin Elmer, Waltham, Massachusetts, USA) was used to record the infrared (FTIR) spectra as KBr and CsI pellets. Tetramethylsilane (TMS) was used as an internal reference for 1H NMR spectra, which were obtained in DMSO-d6 solutions using a Bruker-400MHz for ^{1}H-NMR and 100.61MHz for ^{13}C-NMR. On an Electro-thermal Stuart (SMP40) capillary melting point, melting points were recorded without modifications. A Shimadzu 1800 spectrophotometer was utilised to assess samples' UV-Vis

spectra using a concentration of 10-3 M in room-temperature DMSO solutions between 200 and 1100 nm. The mass spectrum of the ligand was recorded using an positive ion mode of an electrospray ionisation mass spectrometer (ESI-MS).

2.3 Synthesis of N-(2-carbamothioylhydrazine-1-carbonothioyl)-4-methoxybenzamide (L)

The ligand has been produced using the procedure described in [16] and as follows;

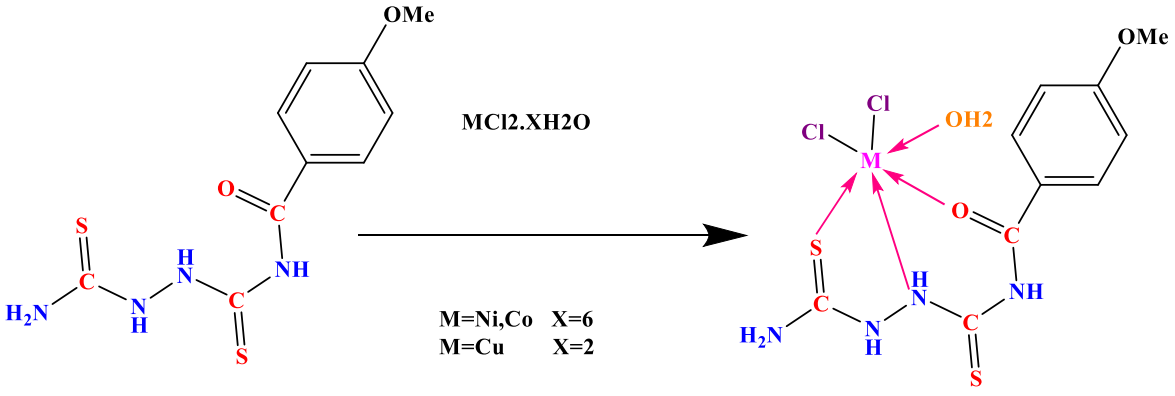
A mixture of 4-Methoxybenzoyl chloride (1.7g, 10mmol) and ammonium thiocyanate (0.76 g, 10mmol) in ethanol (20mL) had been heated for one hour at reflux. The mixture of reaction was allowed to cool to room temperature and then filtrated off. To the filtrate, thiosemicarbazide (0.91g,10 mmol), (20) mL of EtOH had been added dropwise, and also the mixture was refluxed for two hours. Upon cooling, the title compound was obtained by filtering off the white solid, washing it with 10 mL of ethanol, and drying it in a desiccator over anhydrous silica gel, Scheme 1.



Scheme 1: Route of synthesis of L.

2.4 General synthetic procedure of complexes

In a 100mL round-bottomed flask charged with N-(2-carbamothioylhydrazine-1-carbonothioyl)-4-methoxybenzamide (L) (0.568g 2mmole) dissolved in 10 mL of ethanol, and the title metal ions $MCl_2.nH_2O$ (2 mmol) ($M^{(II)}$=Co, Ni, n=6 and Cu, n=2) were added dropwise to a 10 mL ethanolic solution. After the coloured solution was refluxed for four hours and allowed to cool to room temperature, a coloured solid began to form. Filtration was used to gather the solid metal complex, which was then allowed to air dry (Scheme 2).



Scheme 2: General Route of synthesis of complexes.

Table (1) The physical properties of the prepared compounds

No	Compound	M.p	Molecular Formula	Molecular Weight	Color	Yield %
1	L	165-167	$C_{10}H_{12}N_4O_2S_2$	284.04	White	88
2	$[CoCl_2(H_2O)(L^1)]$ C_1	215-217	$C_{10}H_{14}Cl_2CoN_4O_3S_2$	432.77	purple	86
3	$[NiCl_2(H_2O)(L^1)]$ C_2	222-224	$C_{10}H_{14}Cl_2NiN_4O_3S_2$	432.17	green	88
4	$[CuCl_2(H_2O)(L^1)]$ C_3	196-198	$C_{10}H_{14}Cl_2CuN_4O_3S_2$	436.58	Brown	81

3. Results and discussion

3.1 the spectrum of FT-IR for L

The synthesised ligand's solid-state infrared (Figure 1) was measured between 4000 and 370 cm^{-1}. Table 2 displays the ligand's important FTIR bands. The spectrum showed the main bands of the functional groups around 3430-3182 and 1662 cm^{-1} associated with ν(N-H) and ν(C=O) carbamoyl while the bands of ν(C=S) thiocyanate and ν(C=S) semicarbazide was shown at 783 and 732 cm^{-1}, respectively [12-14]. The bands found at 1192 and 1138 cm^{-1} were identified as ν(C–N) and also ν(N–N) stretching modes, respectively [15].

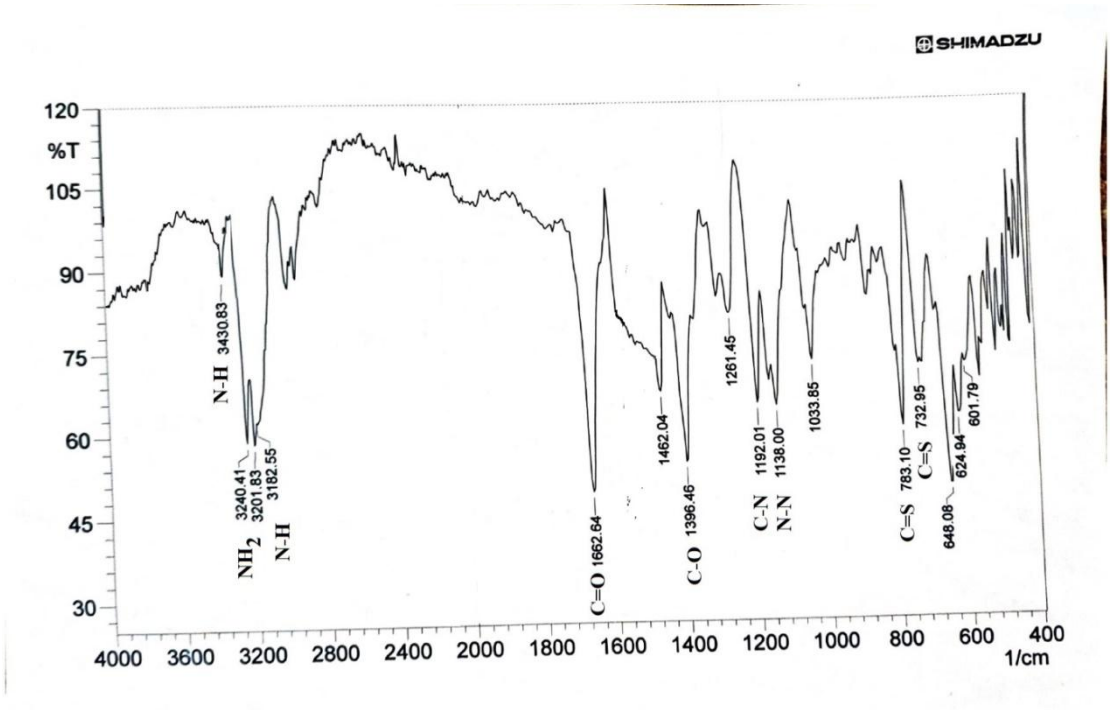


Figure 1. FTIR spectrum of N-(2-carbamothioylhydrazine-1-carbonothioyl)-4-methoxybenzamide *(L).*

3.2 Ligand's UV-Vis Spectrum

The Ligand's UV-Vis Spectrum, Figure 2, showed a high-intensity absorption peak at 206nm and 299 which is associated to the (L) field ($\pi \rightarrow \pi^*$) and also ($n \rightarrow \pi^*$) transitions [16, 17].

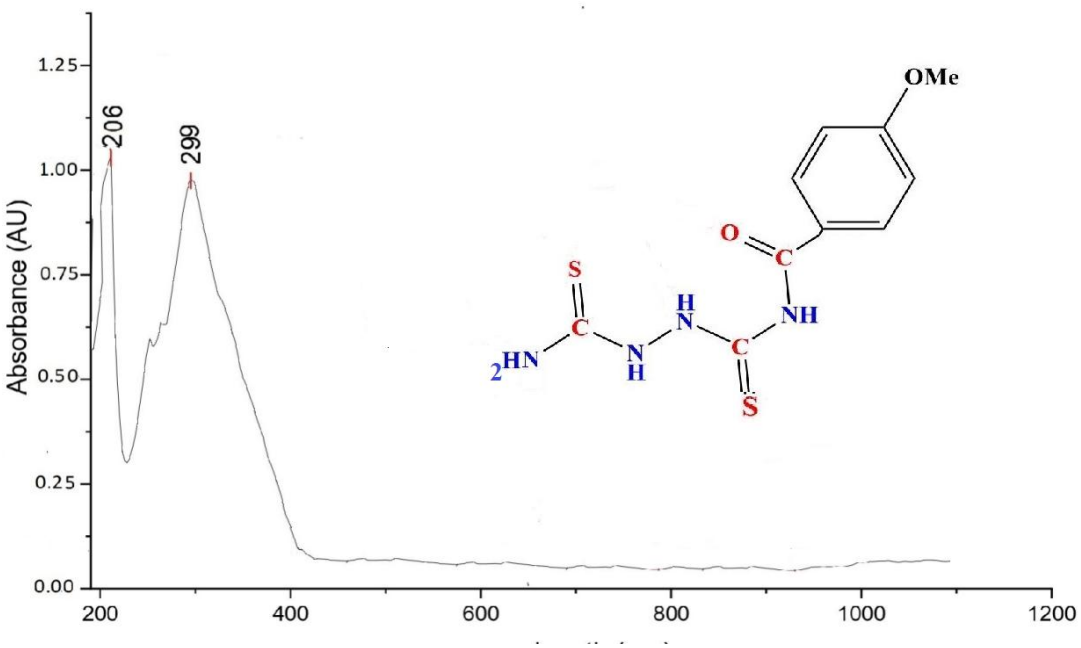


Figure-2. The UV-Vis Spectrum of L in DMSO solvent.

3.3 Nuclear Magnetic Resonance (NMR) spectra of Ligand

The 1H-Nuclear Magnetic Resonance spectrum of N-(2-carbamothioylhydrazine-1-carbonothioyl)-4-methoxybenzamide in DMSO-d6 solvent is presented in Figure 3. One proton corresponding to the singlet peak at (11.5 ppm) is related to (1H, s, N(1)-H). At 8.25 ppm, which is equivalent to one proton, the signal refers to (1H, s, N(3)-H), which is observed as a distinct singular peak. [18]. At (10.77 ppm) which is equivalent to two proton is related (2H, s, N(4)-H) observed as a distinct singlet peak. At (10.05 ppm) equal to two protons are associated with (2H, s, N(2,3)-H) observed as a distinct singlet peak [19]. The dublet chemical shifts at (7.76,7.72 ppm) is due to (2H, C(4,6)-H). aromatic, and the dublet chemical shifts at (7.31,7.27 ppm) that is equal to two protons given for [2H, C(3,7)-H] [20]. The chemical shift that is detected as a singlet at (2.07 ppm) is due to methoxy group (3H, s, C(1)-H).

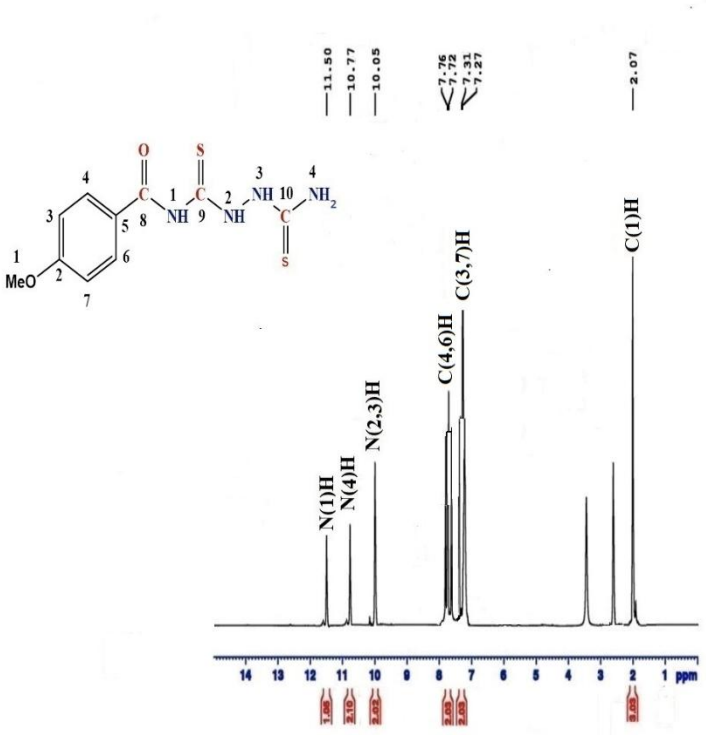


Figure 3. ^{1}H NMR of N-(2-carbamothioylhydrazine-1-carbonothioyl)-4-methoxybenzamide

Figure 4 displays the ligand's ^{13}C Nuclear Magnetic Resonance spectrum in DMSO-d_6. The spectrum of L showed downfield shifts at 185 and 180 ppm corresponding to (C=S) of thiocyanate and thiosemicarbazide respectively1. Variations in the chemical shift values of these peaks are presumably attributed to the distinct electronic environments surrounding the C=S groups. The spectrum shows two chemical shifts at 165 and 160 ppm

corresponding to groups of (C=O) and also (C-O), respectively. The spectra revealed a resonance at 130,125 and 115 ppm are appeared as expected in the aromatic region rang. At 60 ppm, the methoxy group resonances appeared in the aliphatic area as expected. The ligand's ^{13}C-NMR chemical shift positions are all consistent with values published for other thiosemicarbazide ligands [21].

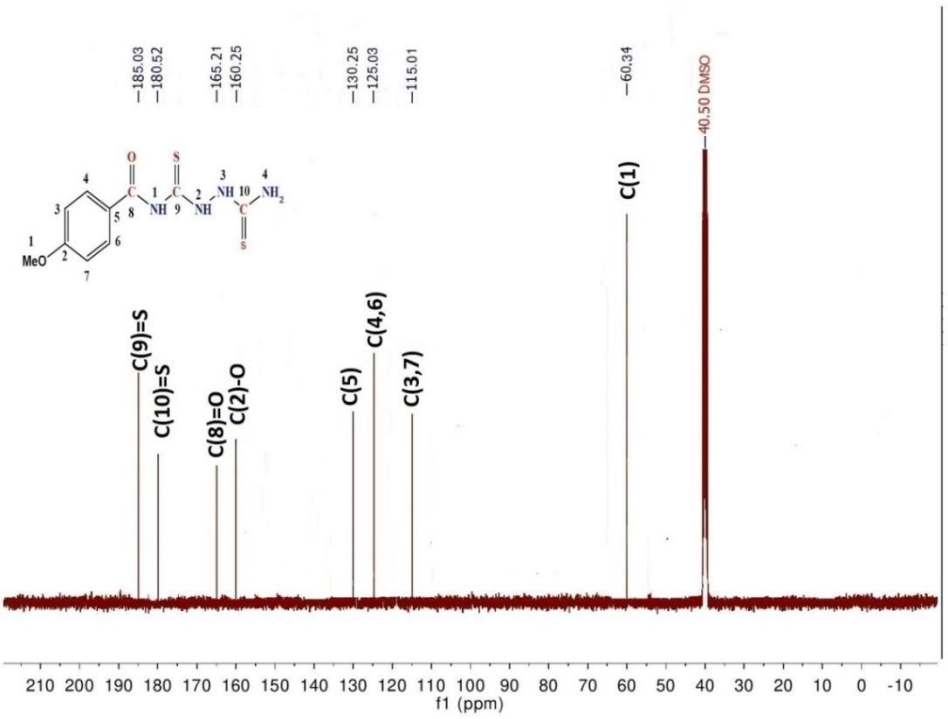


Figure 4. ^{13}C NMR spectrum of N-(2-carbamothioylhydrazine-1-carbonothioyl)-4-methoxybenzamide (L).

3.4 The Mass Spectrum of L

The parent molecule of L at m/z = 284.7 amu (33%) (L+) obtained for ($C_{10}H_{12}N_4O_2S_2$) require = 284.35 was displayed in the electrospray ionization (+) mass spectrum of L, Fig. (5).

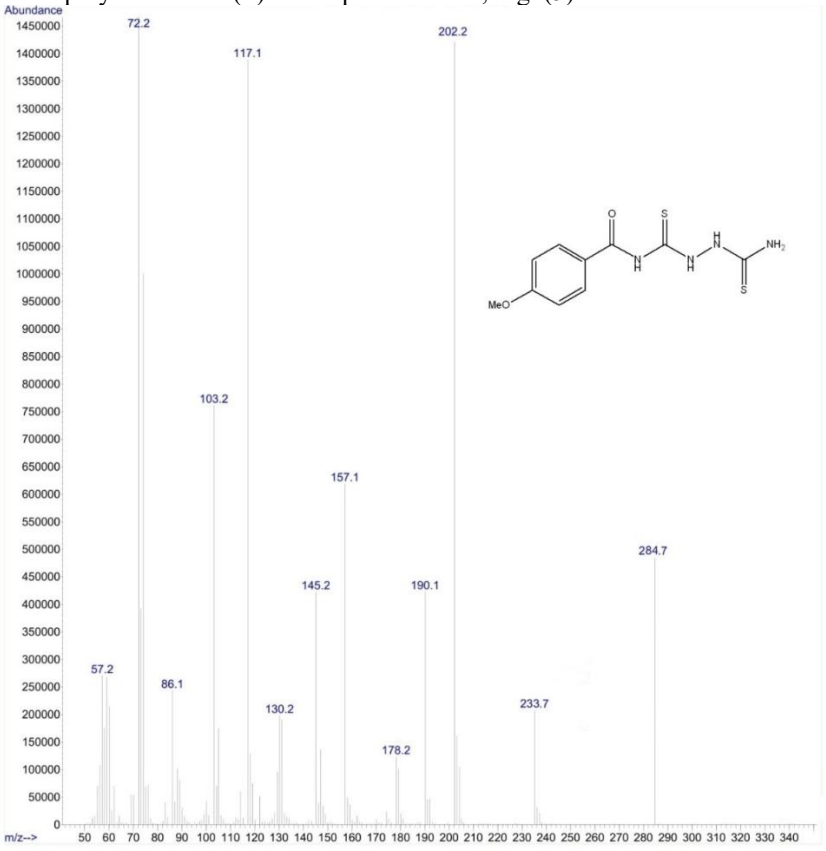


Figure 5. ESI-MS spectrum of the ligand.

4. Spectroscopic analyses of complexes

4.1 The FT-IR spectra for the complexes prepared

The Fourier Transform Infrared spectrum for complexes 1, 2, and also 3 are displayed in Figures 6-8, and Table 2 shows the distinct bands. cobalt $^{(II)}$, nickel $^{(II)}$, and copper $^{(II)}$ FTIR spectra revealed peaks associated with *v*(O-H) stretches at 3525, 3525, and 3520 cm^{-1}, respectively. These peaks were attributed to the aqua molecule's [22-24]. The spectra revealed bands in the range 3448-3132cm^{-1} that were associated to the *v*(N-H). These bands have been shifted to an increasingly high wavenumber, compared to that observed in the 3430-3182cm^{-1} range in the free ligand spectrum [25], Table 1. FT- Infrared spectra of cobalt (II), nickel (II) and copper (II) complexes revealed bands between 1639 and 1600 cm^{-1} corresponding to the group *v*(C=O). The displacement of these bands towards a lower wavenumber region, compared to those seen in the ligan infrared spectrum at 1662 cm^{-1}, indicating that this moiety is involved in the coordination with the metal center [25-29]. The band of thiosemicarbazide *v*(C=S) detected at 732 cm^{-1} in the free ligand, figure 1, was shifted to a higher wavenumber during complexation and appeared in the range (840-810 cm^{-1}). The participation of these fragments in coordination with the metal center is linked to the displacement of the thiosemicarbazide band (C=S). The spectrum of the metal complexes discover additional peaks between 600 and 200 cm^{-1} that were not presented in the L spectrum. Peaks correlated with v(Co-O), v(Ni-O) and v(Cu-O) were observed at 685, 633 and 631 cm^{-1}, respectively[30, 31]. At 533, 485 and 553 cm^{-1} the band detected are related to v(Co-N), v(Ni-N) and v(Cu-N) respectively. Bands seen at 435, 434 and 494 cm^{-1} attributed to *v*(Co-S), *v*(Ni-S) and *v*(Cu-S), respectively. The peaks found at (255,225), (252, 220) and (234, 219) cm-1 were corresponding with v(Co-Cl), v(Ni-Cl) and v(Cu-Cl) respectively [31-33].

Table2. Characteristic infrared vibration frequencies (cm^{-1}) of the L and its corresponding complexes.

N O	v(O-H)	v(N-H)	v (C=O) carbamoyl	v (C-O)	v (C-N)	v (N-N)	v(c=s)	v(c=s) thiosemicarbazid	v(O-H)	v (M-O)	v (M-N)	v (M -S)	v(M-Cl)
L	------	**3430-3182**	**1662**	**1396**	**1192**	**1138**	**783**	**732**	**-**	**-**	**-**	**-**	**-**
C_1	**3525**	**3448-3170**	**1600**	**1311**	**1192**	**1126**	**783**	**810**	**972**	**685**	**533**	**435**	**255, 225**
C_2	**3525**	**3348-3132**	**1639**	**1346**	**1238**	**1157**	**783**	**840**	**979**	**633**	**485**	**434**	**252, 220**
C_3	**3520**	**3440-3170**	**1624**	**1315**	**1195**	**1125**	**783**	**810**	**972**	**631**	**553**	**494**	**234, 219**

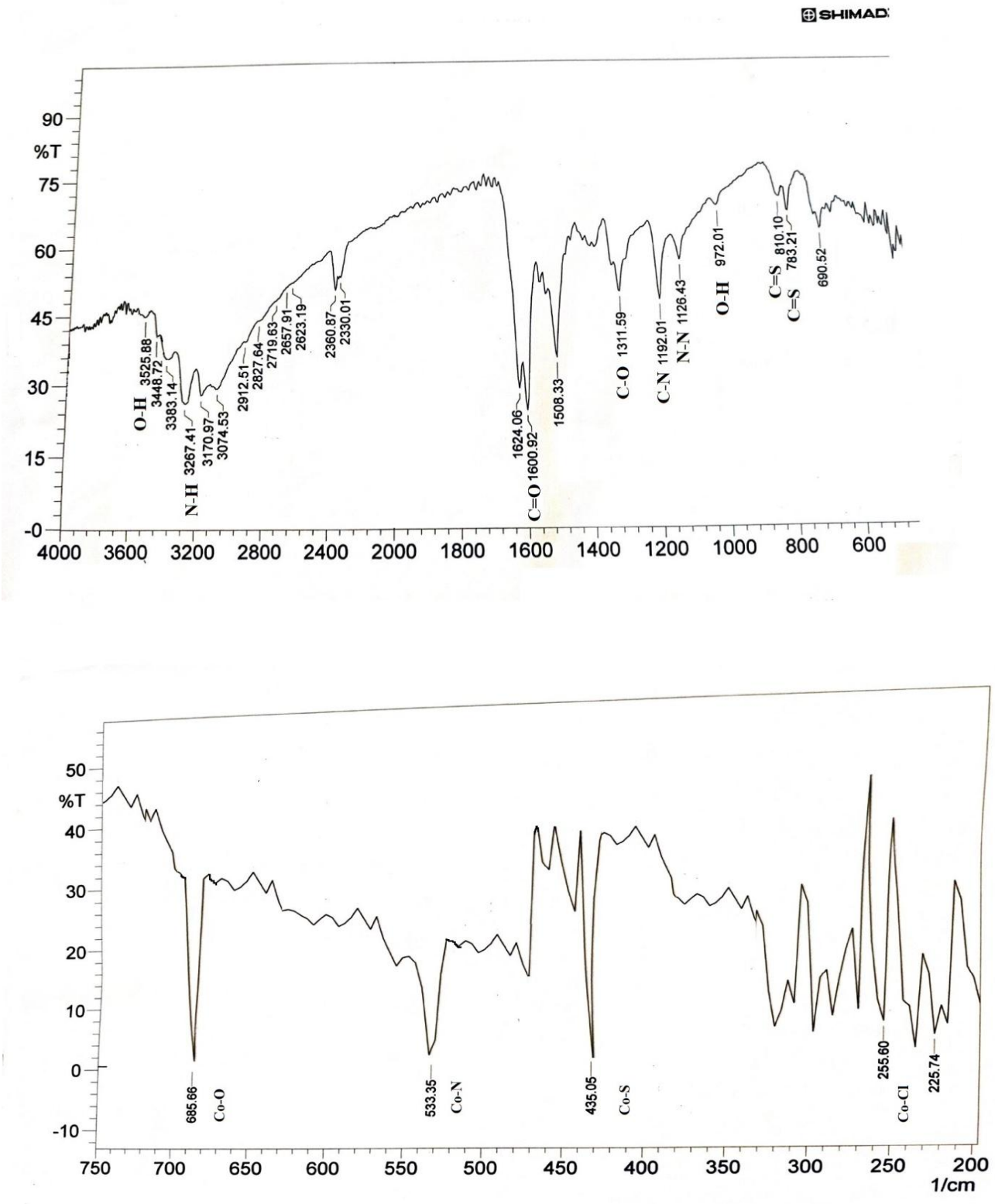


Figure 6. The IR spectrum of [$LCoCl_2H_2O$].

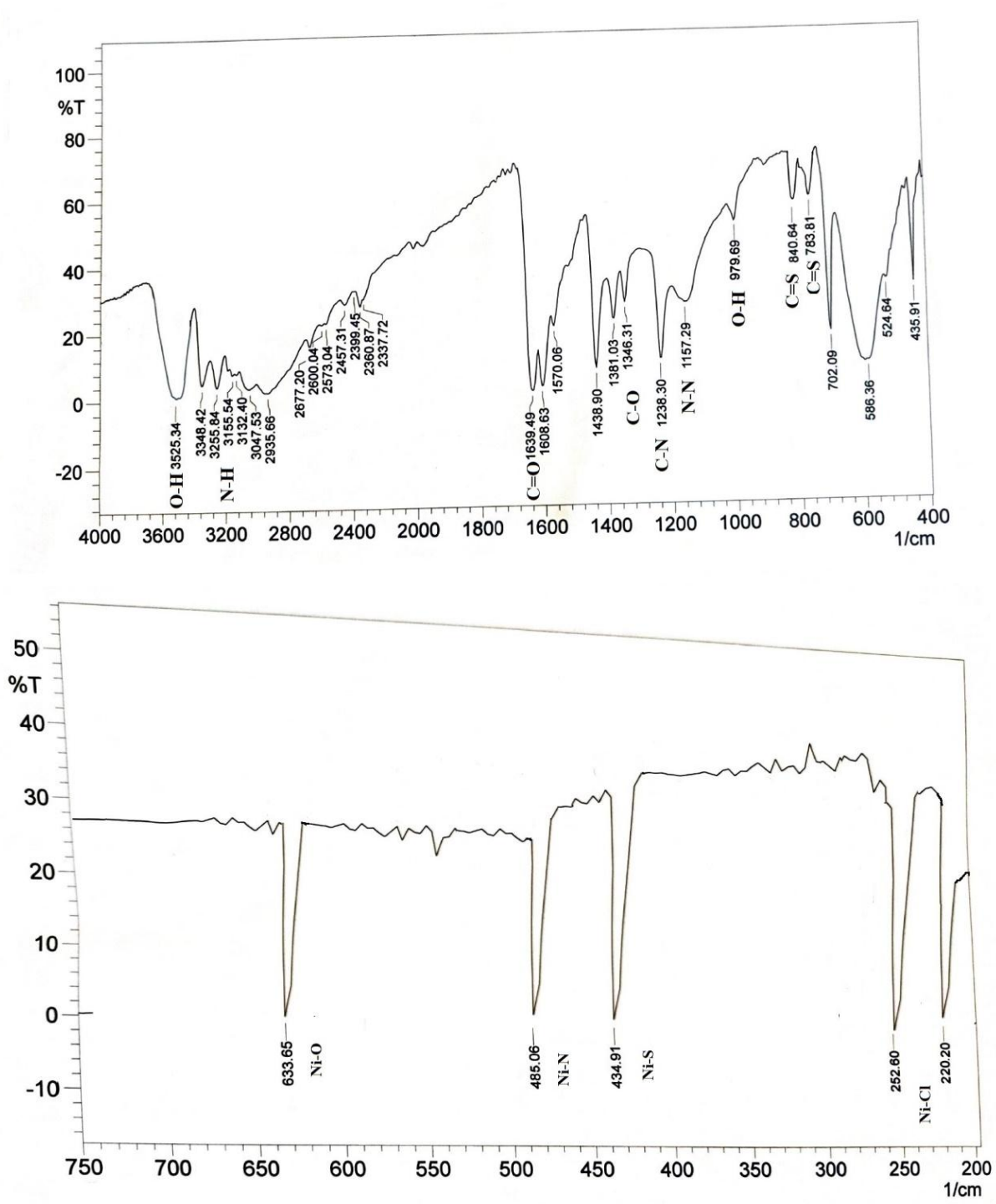


Figure 7. The IR spectrum of [$LNiCl_2H_2O$].

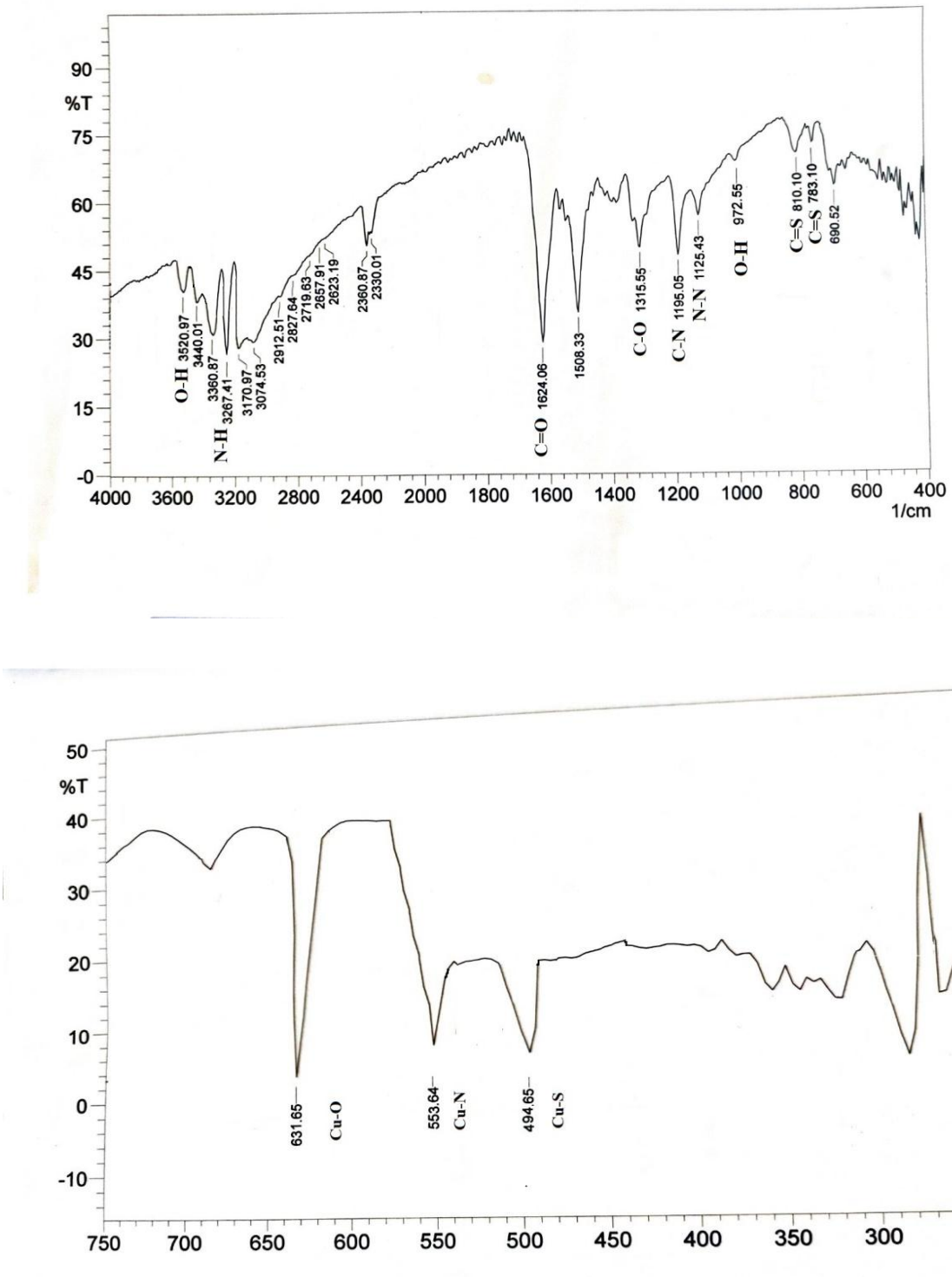


Figure 8. The IR spectrum of [LCuCl$_2$H$_2$O].

4.2 The electron absorption spectra of the complexes

The complexes' electron absorption spectra were measured in DMSO solutions (con. = 1x 10-3 M). The UV-visible spectra of cobalt $^{(II)}$, nickel $^{(II)}$, and copper $^{(II)}$ are presented in Figures 9, 10 and 11 respectively. The spectra indicated peaks, see Table 3, in the range (211-225) nm related to $\pi \rightarrow \pi^*$ (ligand field transitions) [34, 35]. In the d-d region for the cobalt (II) complex, At 612 nm the band recorded was attributed to $^4T_1g \rightarrow {}^4A_2g$ suggesting the adoption of a deformed distorted octahedral shape around the central metal ion [36, 37]. In the $Ni^{(II)}$ complex, the peaks observed at 521 nm are attributed to $^3A_2g \rightarrow {}^3T_1g$. indicating a distorted octahedral shape around the metal centre [38]. At 513 nm in the spectrum of the $Cu^{(II)}$ complex this peak may refer to $^2B_{2g} \rightarrow {}^2A_1g$ transition and which definitively establishes a deformed octahedral coordination sphere around the metal center [38-40].

Table 3. The UV-visible data of ligand and its corresponding metal complexes in DMSO solutions

Complex	nmλ	$cm^{-1}\lambda$	ΣMax (dm^3 mo^{-1} cm^{-1})	Assignment	Suggested geometry
L	206 299	48543 33444	1281 950	π→π* n→π*	
C_1	212 612	47169 16339	875 15	π →π* $^4T_{1g}\rightarrow{}^4A_{2g}$	Distorted Octahedral
C_2	211 521	47393 19193	11125 97	π→π* $^3A_{2g}\rightarrow{}^3T_{1g}$	Distorted Octahedral
C_3	225 513	44444 19493	1189 27	π→π* $^2B_{2g}\rightarrow{}^2A_{1g}$	Distorted Octahedral

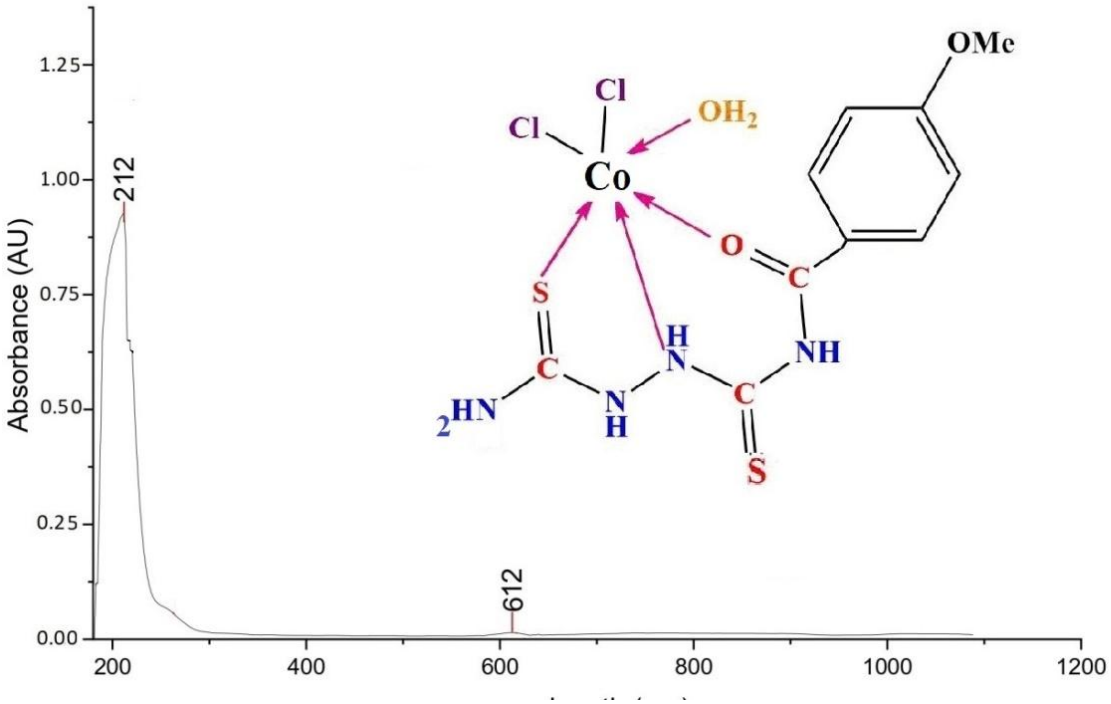


Figure 9. Electronic spectrum of [(L)$CoCl_2H_2O$].

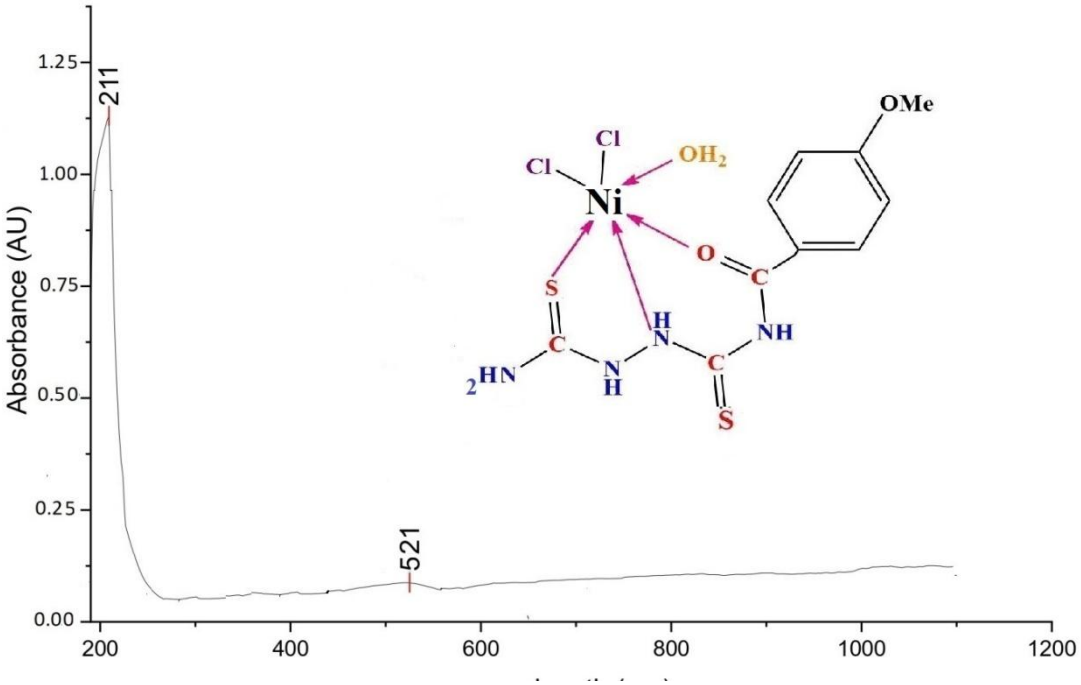
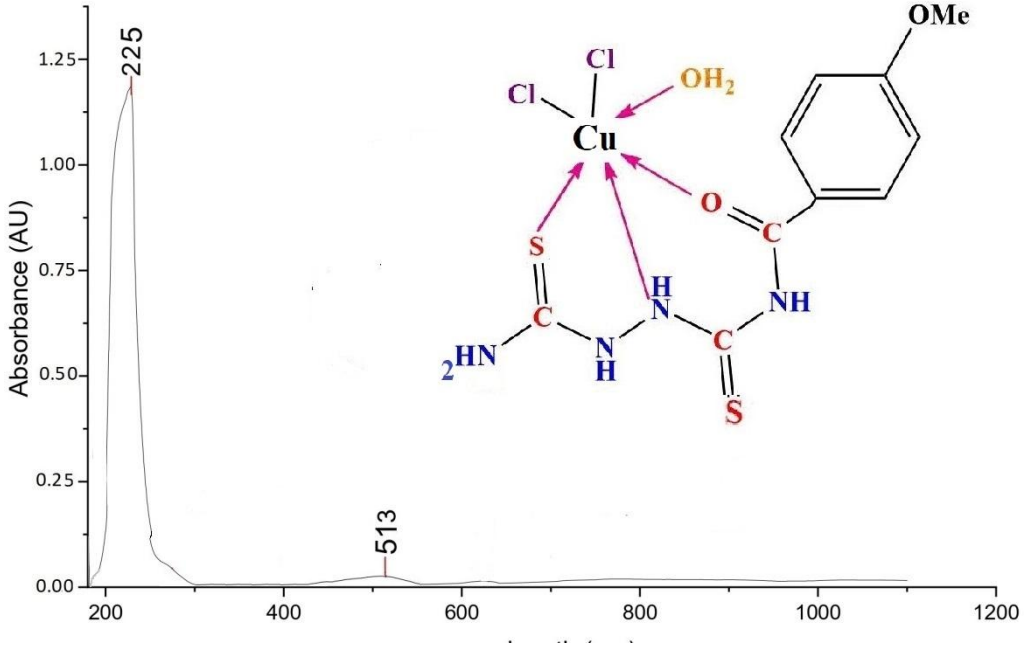


Figure 10. Electronic spectrum of [(L)NiCl₂H₂O].



Figur11 ..Electronic spectrum of [(L)CuCl₂H₂O].

5. Biological Activity

The microbiological activity of the ligand and its corresponding metal complexes against a type of isolate of *G-* bacteria (*Klebsiella pneumoniae*) and *G+* bacteria (*Staphylococcus aureus*) was investigated in table (4). The disc diffusion method had been used to check the antibacterial activity. The *in vitro* antibacterial experiments were carried out against pathogenic bacterial strains at doses of 50 mg/ml, 25 mg/ml, 12.5 mg/ml, 6.25 mg/ml, and 3.125 mg/ml. Cefotaxime (CTX 10 µ g) served as the negative control, while Penicillin (10 µ g/disc) served as the positive control. The assay medium was prepared by aseptically pouring the molten nutrient agar into sterilized Petri dishes and allowing it to solidify. Standard bacterial were prepared by culturing the strains in a nutrient broth at 37°C for 24 h; these bacterial suspensions were then spread uniformly on the surface of the solidified agar. Whatman No. 1 filter paper discs with a diameter of 5 mm were cut out and autoclaved under aseptic conditions for 15 minutes at 15 psi. The chemical will diffuse from the filter paper into the agar when a disc of filter paper is impregnated with it. The chemical will only be present in the agar around the disc due to diffusion. The solubility and molecular size of the chemical will determine the size of the chemical infiltration area surrounding the disc if it is susceptible to it. The inhibition zone is the region where there is no growth. To create a homogenous suspension, a loopful of an overnight slant culture of the test organism was added to 5µL of 140 sterile physiological salines. Using a sterile cotton swab, this suspension culture was surface spread throughout a nutrient

agar plate to produce a uniform grass culture. Using sterile forceps, the discs containing the test samples created as previously described were positioned on the swabbed surfaces of the plates (five discs per plate). After a 24-hour incubation period at 37°C, Zones of inhibition around the discs were examined for on the plates. In terms of *Klebsiella pneumoniae* complexes of (C_2)and (C_3), the initial concentration (50 µL) demonstrated a higher level of biological activity. Nevertheless, L showed no efficacy against the pathogenic under investigation. The complexes (C_2) and (C_3) at the first concentration 50 demonstrated a strong effect against Staphylococcus aureus, however the free ligand demonstrated no activity against this type of bacterium, according to the biological activity of the studied compounds.

Table 4. values of some produced compounds' biological activity against harmful bacterial isolates.

Compound	C. (µg/ml)	Staphylococcus aureus (G+)	*Klebsiella pneumoniae* (G-)
L	**50**	**0**	**0**
	25	**0**	**0**
	12.5	**0**	**0**
	6.25	**0**	**0**
	3.125	**0**	**0**
C_1[LCo]	**50**	**12**	**0**
	25	**11**	**0**
	12.5	**0**	**0**
	6.25	**0**	**0**
	3.125	**0**	**0**
C_2[LNi]	**50**	**19 17**	**20**
	25	**15 14**	**19**
	12.5	**0**	**17**
	6.25		**14**
	3.125		**10**
C_3[LCu]	**50**	**16**	**16**
	25	**15**	**14**
	12.5	**13**	**12**
	6.25	**12**	**10**
	3.125	**0**	**0**

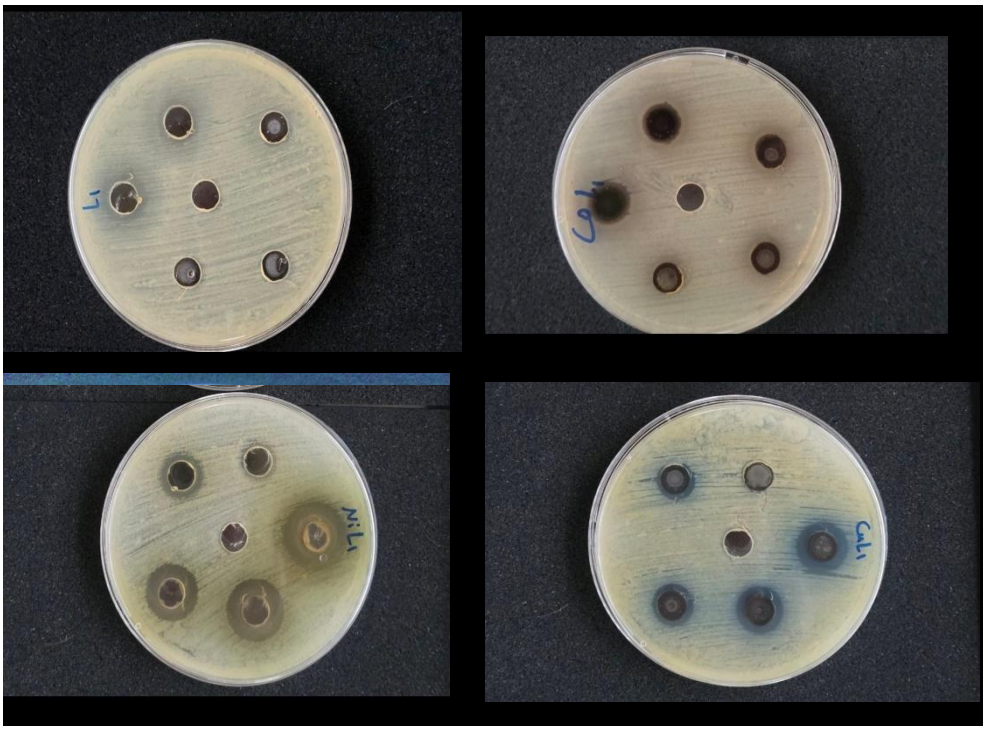
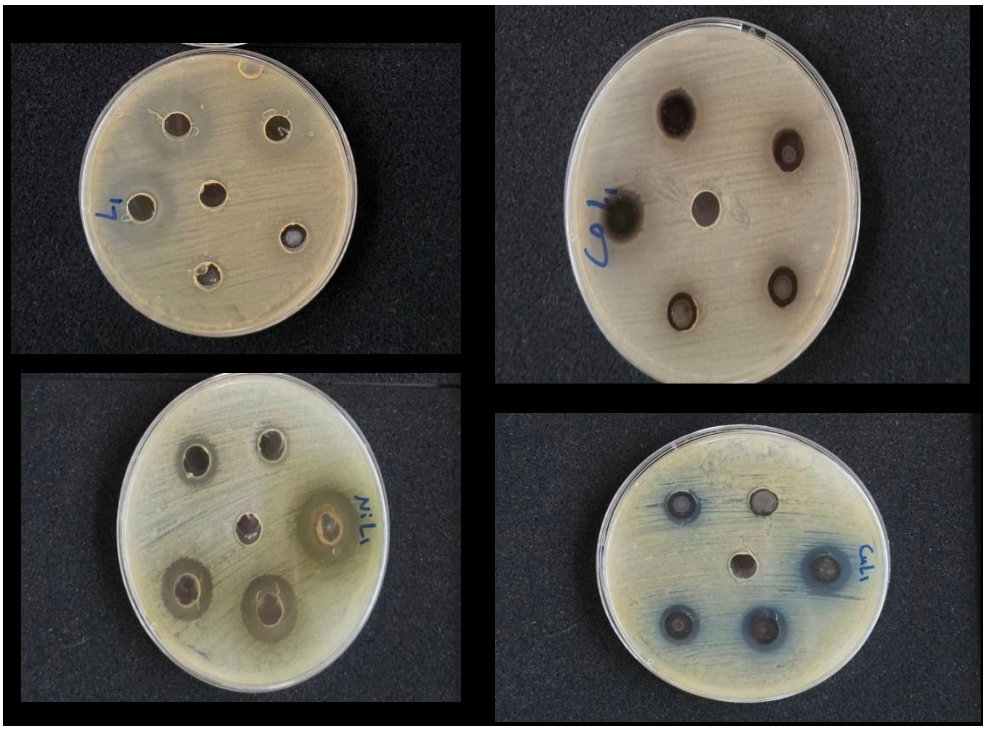


Figure 12. Antibacterial activity of the compounds against Staphylococcus aureus of L and its complexes [C_1, C_2, C_3]



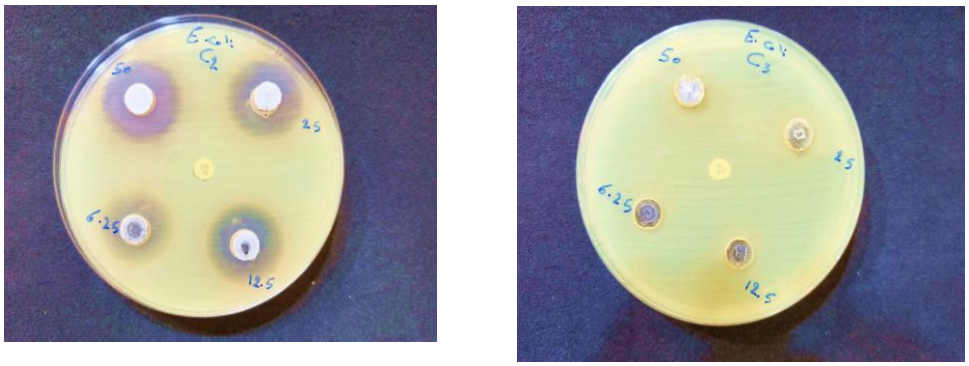


Figure 13. Antibacterial activity of the compounds against Klebsiella pneumoniae of L and its complexes [C_1, C_2, C_3]

6. Conclusions

The synthesis and characterisation of N-(2-carbamothioylhydrazine-1-carbonothioyl)-4-methoxybenzamide (L) and its new metal complexes with cobalt $^{(II)}$, nickel $^{(II)}$, and copper $^{(II)}$ ions are reported. The synthesis of the ligand was accomplished via two preparation steps. This is included the preparation of 4-methoxybenzoyl isothiocyanate, which then reacted with thiosemicarbazide to give the title ligand. The monomeric complexes were obtained from the preparation of the ligand with the title metal chloride salts of cobalt $^{(II)}$, nickel $^{(II)}$, and copper $^{(II)}$ ions in a one:one (ligand: metal) mole ratio. The chemical structures of the compounds and the general bonding behaviour of the complexes were verified using physicochemical techniques. Six-coordinate monomeric complexes with the general formula [$LMCl_2H_2O$] ($M^{(II)}$= Co, Ni, and Cu) were isolated, according to the characterisation data. The antibacterial activity of L and also its complexes against (*G*+ and *G*-) bacteria was explored. The data reveraled no resistant against ligang. However, C_2 and C_3 have shown good antibactrial activiy.

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