

Synthesis, Characterization and Antibacterial Activity of some New Metal Complexes Containing Semicarbazide

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Abstract

The research includes the preparation and characterization of the new N-cyclohexyl-2-((dimethylcarbamoyl) carbamothioyl) hydrazine-1-carboxamide (L). Metal ions Co^{+2} , Ni^{+2} , and Cu^{+2} were combined with the ligand (L) to form three transition metal complexes. The chemical formulas are the following $[\text{LCoCl}_2 \cdot \text{H}_2\text{O}]$, $[\text{LNiCl}_2 \cdot \text{H}_2\text{O}]$, $[\text{LCuCl}_2 \cdot \text{H}_2\text{O}]$. The reaction was performed by mixing metal ligand in a [1:1] mole ratio using (MeOH) acting as a solvent. The entity of the expected structure of the ligand and its metal complexes were illustrated through a range of physicochemical techniques. These include: FT-IR, electronic spectra, (^1H and ^{13}C -NMR) spectra, elemental analysis (CHNS), chloride content, metal content, melting point, molar conductivity, and magnetic susceptibility of three-coordinate complexes with deformed octahedral geometry around the center atom was determined by the spectral and analytical for the Co^{+2} , Ni^{+2} and Cu^{+2} atoms. The biological activity (antibacterial) (G^+) and (G^-) bacterial was explored

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1. INTRODUCTION

coordination chemistry, an academic field, focuses on metal complexes, which are groups of ions or particles that coexist but prefer to be linked in a specific configuration. Critical to current inorganic research is the proof of the compounds' heterogeneity, reactivity, analytical uses, and catalytic effects. [1] The intriguing biological actions of heteroleptic complexes have recently heightened interest in their coordination chemistry. Using semicarbazone derivatives for metal coordination has become more important for pharmaceutical and bioinorganic chemists [2]. Semicarbazone-derived ligands demonstrate many bioactivities, such as antiviral effects [3], antioxidant properties, antifungal and antibacterial activities [4], and even antiparasitic effects [5]. Condensation of semicarbazides with appropriate aldehydes or ketones yields significant chemicals such as semicarbazones and thiosemicarbazones. A sulfur-containing derivative of semicarbazone, thiosemicarbazone is an alternative to semicarbazone that contains oxygen. Typically, semicarbazones and thiosemicarbazones act as chelating ligands and combine with the cations of metals to form complexes. Important pharmacological features make the production of transition metal complexes with thiosemicarbazone and semicarbazone ligands an important topic of research [6].

The probable biological properties of these species have prompted extensive research on them and their metal complexes [7]. Semicarbazides are commonly used nitrogen or oxygen compounds that have several biological applications, various structural choices, and a variety of binding processes.[8-10] interacting with transitory elements as chelating agents, these chemicals become even more important. [11] The ion coordination modes seen by semicarbazides are sensitive to a variety of factors, including reaction circumstances, carbonyl substituent type, presence of metal salts, and counter-ion nature.[12] It is believed that semicarbazides possess a diverse array of structural characteristics and that the physiological activity of their metal complexes surpasses that of free ligands.[13, 14] Semicarbazone transition metal complexes' coordination and analytical uses have prompted substantial research into these compounds [15]. This work represents the synthesis and spectral characterization of a new ligand namely, the N-cyclohexyl-2-((dimethylcarbamoyl)carbamothioyl) hydrazine-1-carboxamide (L) reaction with M^{+2} ions (Co^{+2} , Ni^{+2} , and Cu^{+2}). The antibacterial properties of the ligand and its metal complexes are also investigated.

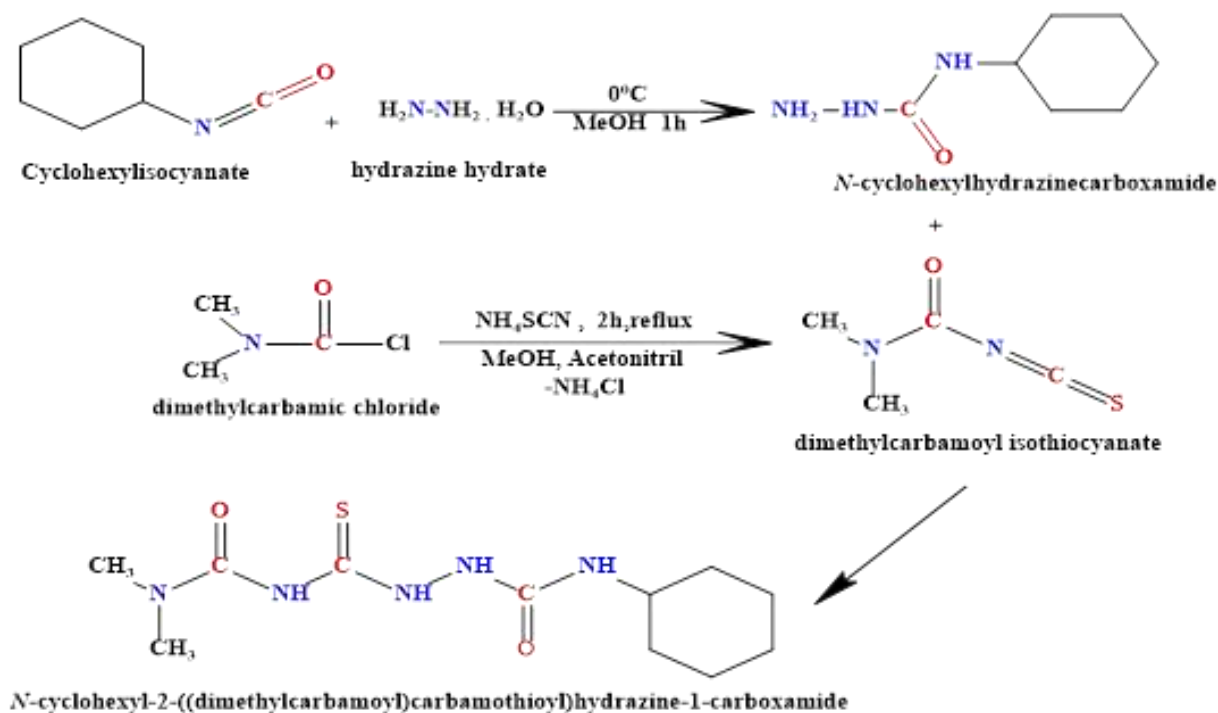
Materials and methods

Reagents that were purchased from Aldrich were used as received. Solvents were dried using standard protocols before their use in the preparation.

2. METHOD

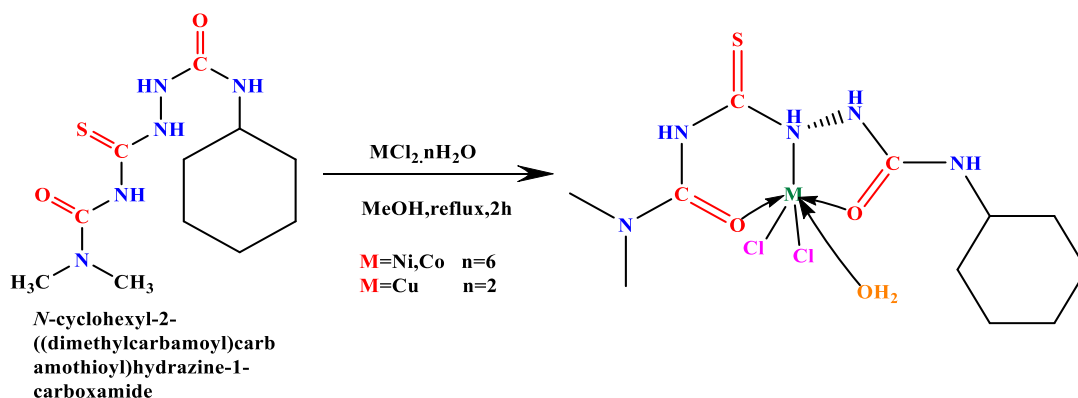
Synthesis of the N-cyclohexyl-2-((dimethylcarbamoyl) carbamothioyl) hydrazine-1-carboxamide (L)

The ligand was prepared according to the method reported in [16] and it was synthesized in two steps. The first step included the preparation of N-cyclohexylhydrazinecarboxamide, which was achieved from the reaction of cyclohexyl isocyanate 0.625g, 5mmol, and 0.250 g, 5 mmol of hydrazine hydrate using methanol. Below the freezing point, the reaction occurred. In the second step, a solution containing (1.35g, 5 mmol) of dimethyl carbamoyl chloride and (0.76g, 5mmol) of ammonium thiocyanate in 40 mL of acetonitrile and methanol was heated under reflux for 1 hour. To filter off the reaction mixture, it was cooled to room temperature. N-cyclohexylhydrazinecarboxamide (1.02g, 5 mmol) in acetonitrile 10 mL was added to the filtrate, and the mixture was refluxed for 2 hours. A white solid appeared upon cooling. it was collected via filtration, washed with 10 mL of acetonitrile, and desiccated over anhydrous silica gel in a desiccator. to give the title compound, Scheme 1:



Synthesis of complexes

In 100 mL of a round-bottomed flask was mixed N-cyclohexyl-2-((dimethylcarbamoyl) carbamothioyl) hydrazine-1-carboxamide (L) (0.5g, 2mmole). The resulting mixture was refluxed for 1hours and then a methanolic solution (10mL) of metal ions $[MCl_2 \cdot nH_2O]$ (2 mmol) ($M^{+2} = Co, Ni$ or Cu) was added dropwise. The resulting colored solution was allowed to reflux for 2h and then cooled to room temperature. The metal complexes were collected by filtration and air-drying (Scheme 2).



Scheme 2. Synthetic route of complexes

3. RESULTS AND DISCUSSION

3.1. FT-IR spectrum of (L)

Solid state infrared of the prepared ligand Figure (1) was recorded in the range of $4000-400\text{ cm}^{-1}$. The main FTIR bands of the ligand are presented in Table 1. The FTIR spectra of ligand (L) show bands around $(3302-3039), 1666, 1558\text{ cm}^{-1}$ assigned to ν (N-H), ν (C=O)_{carbamoyl} and ν (C=O)_{semicarbazide}, respectively. Bands detect at (1149) and (1080) were attributed to ν (C-N) and ν (N-N), respectively. the ν (C=S) of the appeared at 763 cm^{-1} [17].

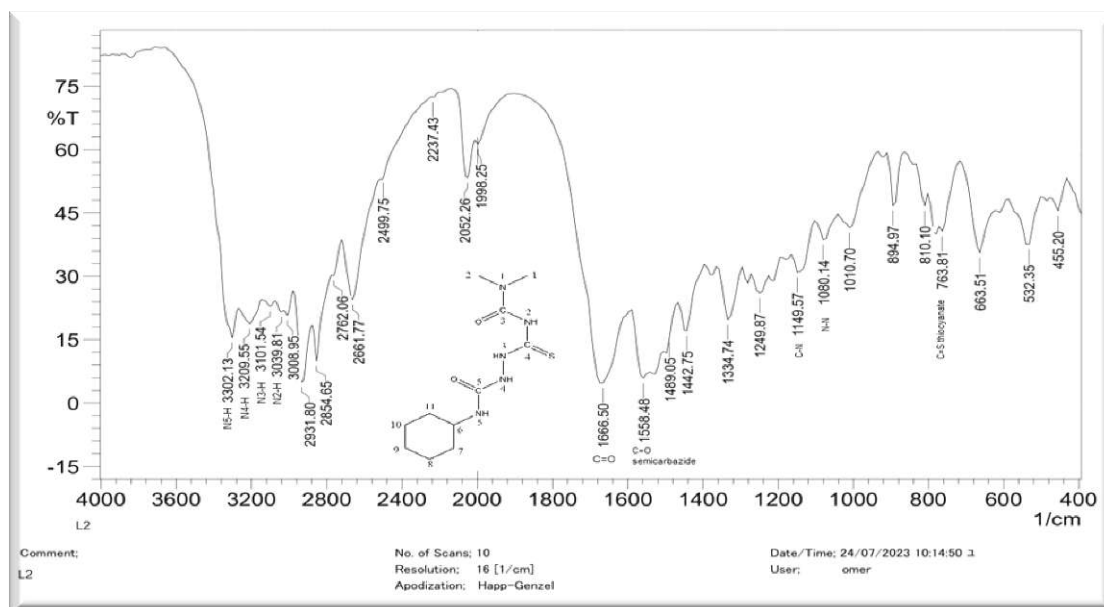


Figure 1. FTIR spectrum of N-cyclohexyl-2- (dimethyl carbamoyl) carbamothioyl) hydrazine-1-carboxamide (L)

Diagnostics of the complexes

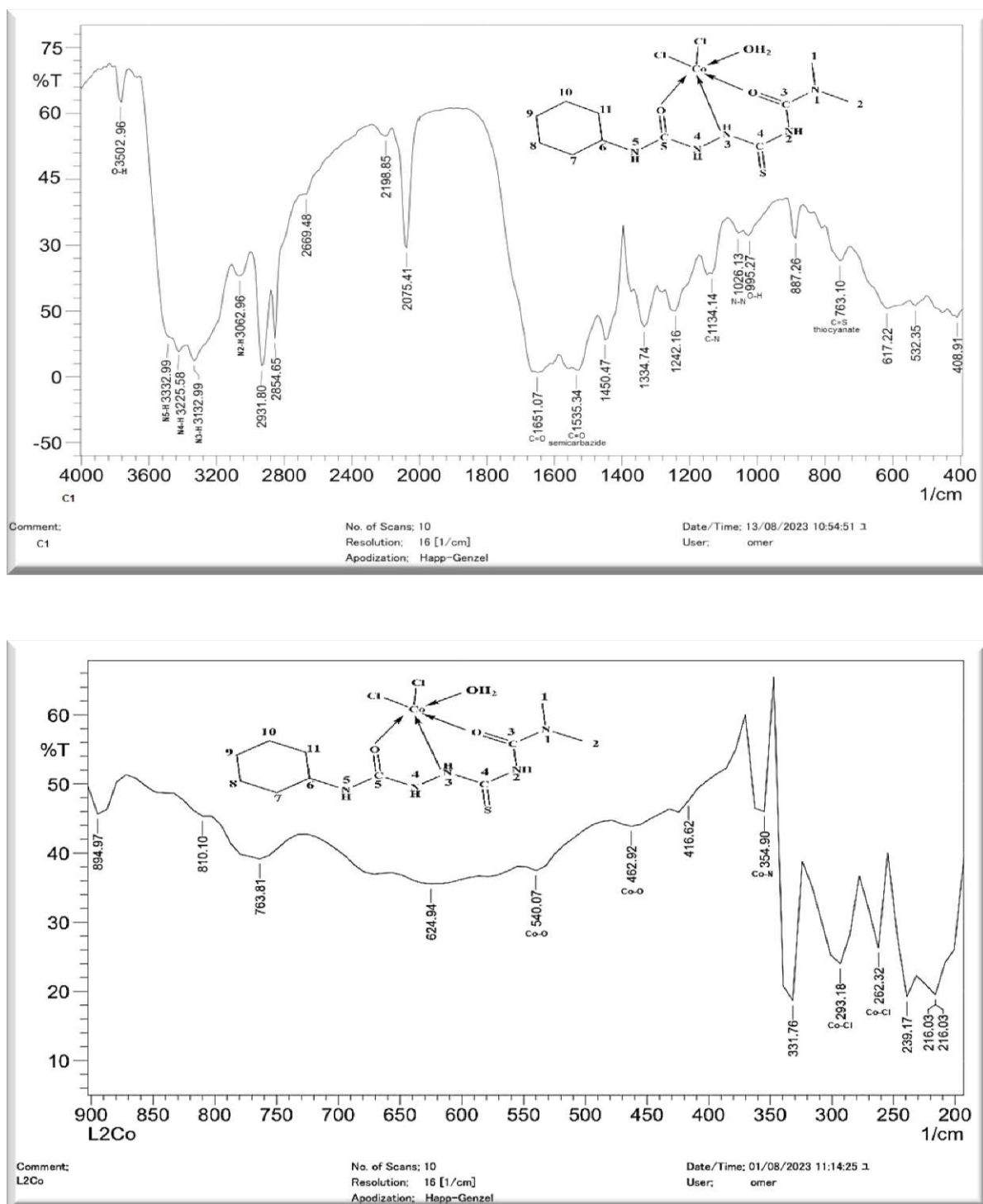
FT-IR spectra of the prepared complexes

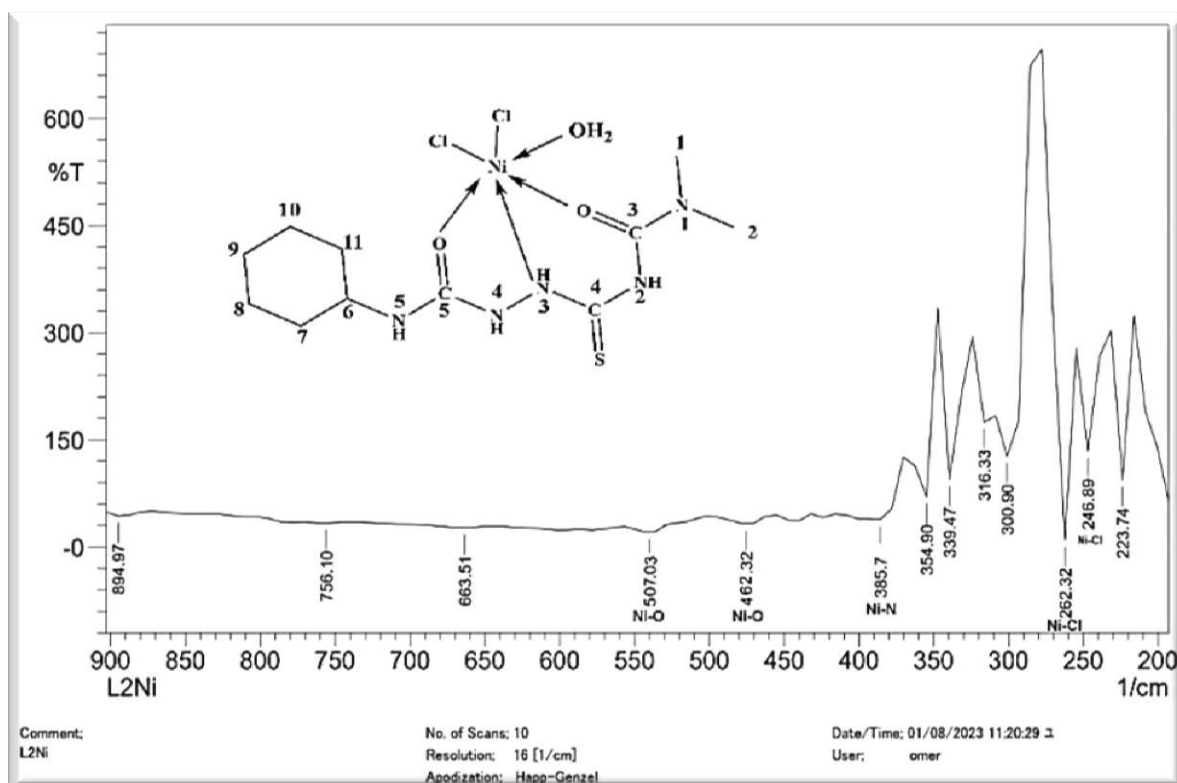
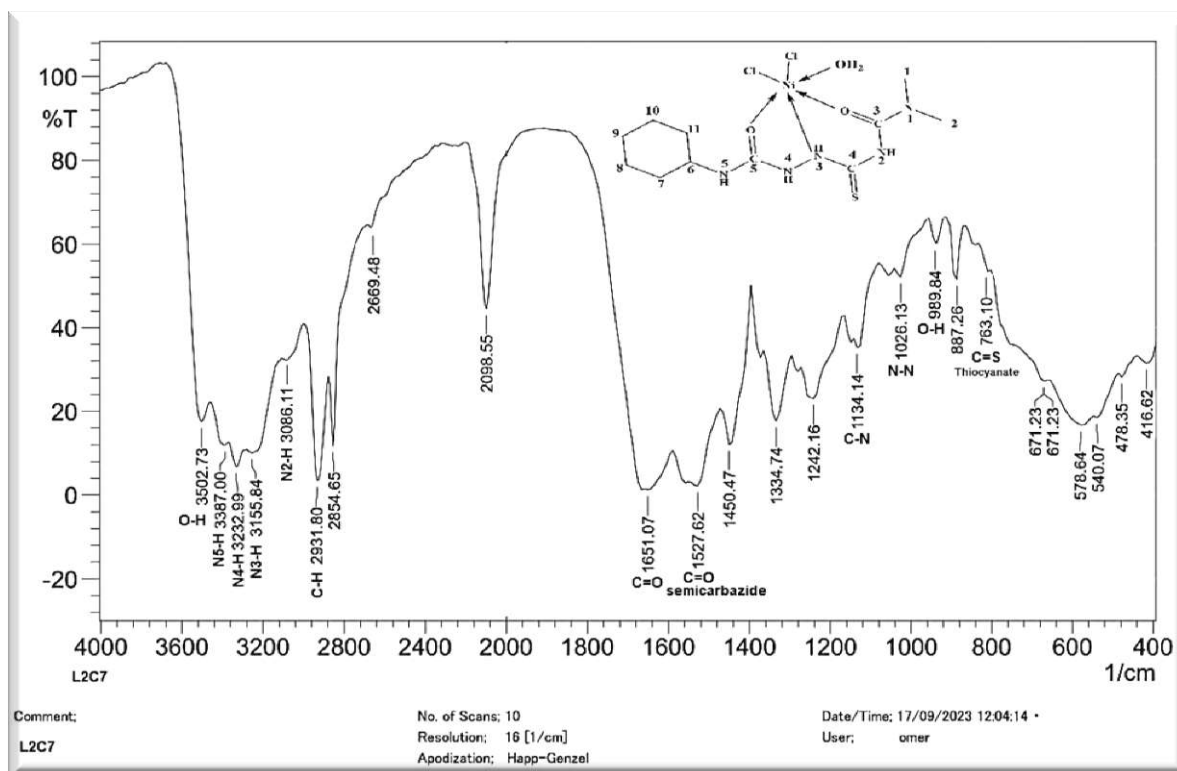
Figures 2 and 3 show the FT-IR spectra of complexes C₁, C₂, and C₃, while Table 1 includes the assignment of the distinct bands. The FT-IR spectra in the complexes (Co⁺², Ni⁺², and Cu⁺²) showed peaks related to $\nu(\text{O-H})$ stretches around (3502-3700) cm⁻¹. These peaks were assigned to the OH of the aqua molecule [18-20]. The spectra exhibited distinct bands ranging from (3332 to 3062) cm⁻¹, which were classified as $\nu(\text{N-H})$ [21] Table 1. A band was found in the free ligand at 1666 cm⁻¹, which was connected to the $\nu(\text{C=O})$ carbamoyl. Figure 1 shows this association. Within the complexes C₁-C₃, the band was observed at the lower shift, which occurred within the region of (1651-1620) cm⁻¹. There is a connection between the involvement of these moieties in the coordination to the metal center and the carbonyl bands [22].

Table 1. The most important characteristic bands of the (L) and their complexes in the FT-IR spectrum

ON	$\nu(\text{O-H})$	$\nu(\text{N}_5\text{-H})$	$\nu(\text{N}_4\text{-H})$	$\nu(\text{N}_3\text{-H})$	$\nu(\text{N}_2\text{-H})$	$\nu(\text{C=O})$ carbamoyl	$\nu(\text{C=O})$ semicarbazide	$\nu(\text{C-N})$	$\nu(\text{N-N})$	$\nu(\text{c=s})$ thiocyanate	$\nu(\text{O-H})$	$\nu(\text{M-O})$	$\nu(\text{M-O})$	$\nu(\text{M-N})$	$\nu(\text{M-Cl})$
L	-----	3302	3209	3101	3008	1666	1558	1149	1080	763	-----	---	--	---	--
C ₁	3502	3332	3225	3132	3062	1651	1535	1134	1062	763	995	540	478	385	293
C ₂	3502	3387	3232	3155	3086	1651	1527	1134	1026	763	989	507	462	385	262
C ₃	3700	3317	3248	3163	3093	1620	1527	1126	1049	762	933	532	470	378	277

FT-IR spectra of complexes C₁, C₂, and C₃ revealed bands that fall in the range of (1535-1527)cm⁻¹ that attributed to $\nu(\text{C=O})$ semicarbazide group. These bands were shifted to a lower wavenumber when compared to that observed at 1558 cm⁻¹ in the infrared spectrum of ligand (L) confirming the involvement of this $\nu(\text{C=O})$ semicarbazide group upon coordination [23-25]. The spectra of metal complexes showed the presence of extra peaks between 600-200cm⁻¹ whose presence was not demonstrated in the spectra of the ligand. Peaks correlated to $\nu(\text{Co-O})$, $\nu(\text{Ni-O})$, and $\nu(\text{Cu-O})$ were detected at (540,478) cm⁻¹, (507,462) cm⁻¹, and (532,470) cm⁻¹, respectively [26, 27]. Bands detected at 385,385 and 378 cm⁻¹ were assigned to $\nu(\text{Co-N})$, $\nu(\text{Ni-N})$, and $\nu(\text{Cu-N})$, respectively. Peaks detected at 293,262 and 277cm⁻¹ were correlated to $\nu(\text{Co-Cl})$, $\nu(\text{Ni-Cl})$, and $\nu(\text{Cu-Cl})$, respectively [27-29].

Figure 2. The Infrared spectrum of [LCoCl₂.H₂O](C₁)

Figure 3. The Infrared spectrum of $[LNiCl_2H_2O](C_2)$

3.2. U.v.-Vis Spectrum of Ligand

The UV spectrum for N-cyclohexyl-2-(dimethyl carbamoyl) carbamothioyl hydrazine-1-carboxamide (L) Figure 4, shows a high-intensity absorption peak at 259 nm and 293 nm and were ascribed to the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ electron transitions, sequentially [30].

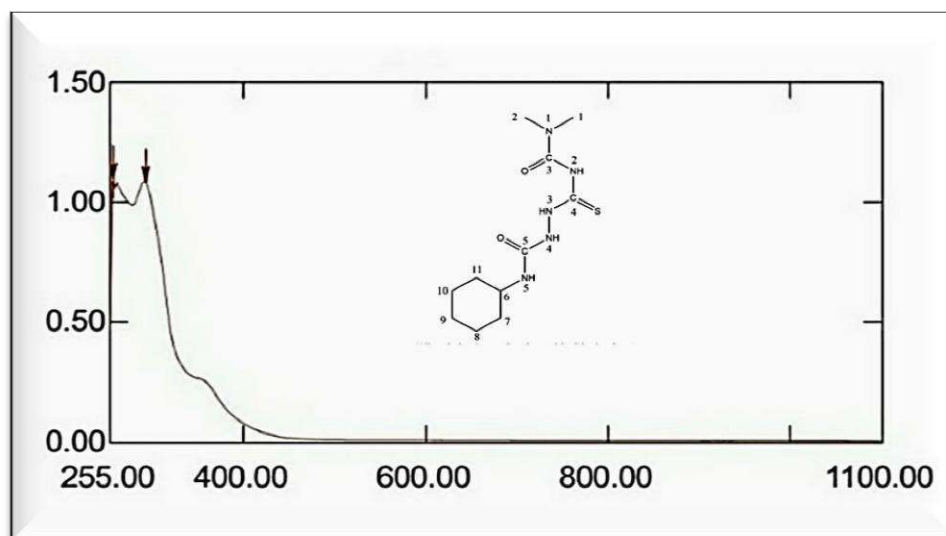


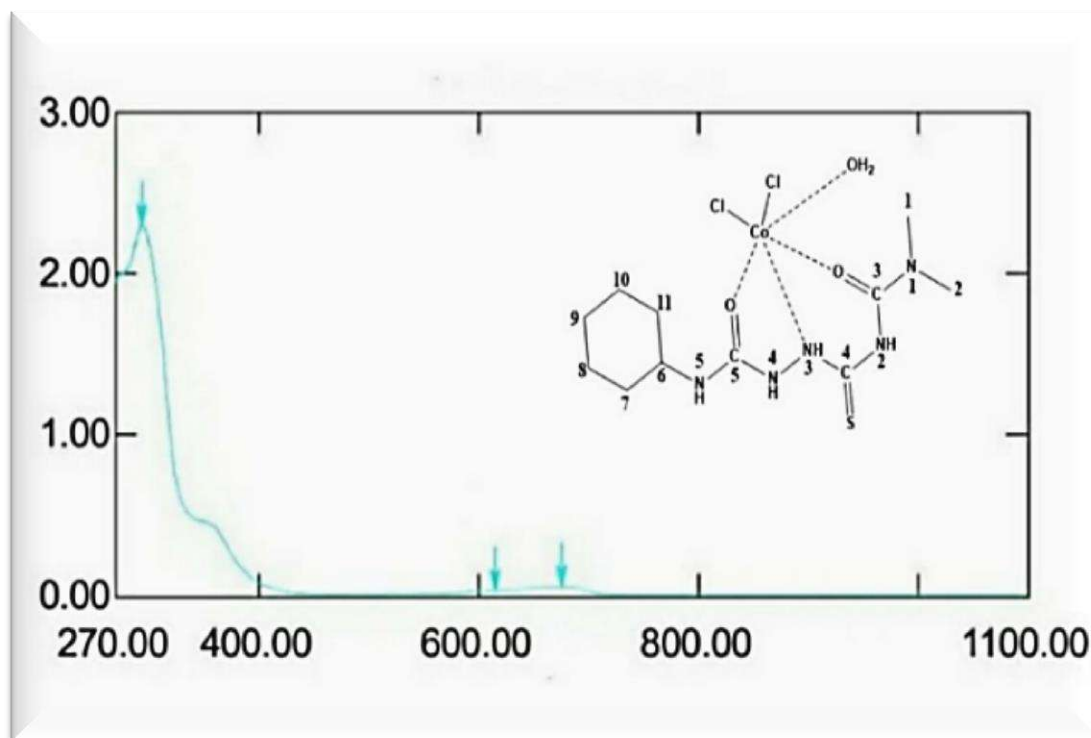
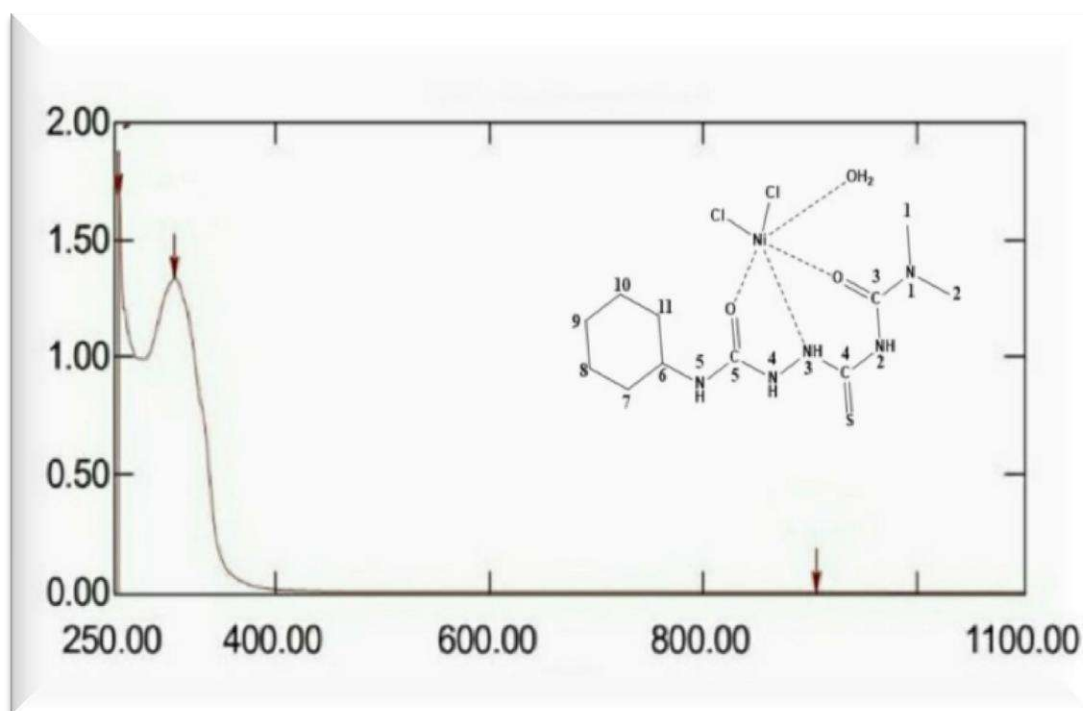
Figure 4. Electronic spectrum of Ligand (L)

U.v.-Vis Spectra of the complexes

In the range of (200-1100) nanometers, the electronic spectra of the metal complexes that were prepared were recorded with DMSO (con. = 1×10^{-3} M) as the solvent. The electronic data, which are presented in Table 2 and illustrated in Figures (5) and (6). illustrate absorption peaks in the (254) and (306-293) nm range that are associated with $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ (ligand field transitions) [31-33]. Within the d-d area of the C₁ complex's structure, the band at (615 and 676 nm), sub ${}^4T_{1g} \rightarrow {}^4T_{1g(P)}$, and ${}^4T_{1g} \rightarrow {}^4A_{2g}$ provided evidence of a deformed octahedral geometry about the metal center [34]. In the C₂ complex peak at 906 nm, it is attributed to ${}^3A_{2g} \rightarrow {}^1E_g$ the metal center is surrounded by a deformed distorted octahedral shape [35].

Table 2. UV-visible spectrum of ligand and complexes

Complex	nmλ	cm ⁻¹ λ	ΣMax (dm ³ mo ⁻¹ cm ⁻¹)	Assignment	Suggested geometry
L	259 293	38610 34129	1850 1099	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	
C ₁ [LCo]	293 615 676	34129 16260 14792	1304 32 47	$n \rightarrow \pi^*$ ${}^4T_{1g} \rightarrow {}^4T_{1g(P)}$ ${}^4T_{1g} \rightarrow {}^4A_{2g}$	Distorted Octahedral
C ₂ [LNi]	254 306 906	39370 22679 11037	1688 1335 3	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$ ${}^3A_{2g} \rightarrow {}^1E_g$	Distorted Octahedral

Figure 5. Electronic spectrum of $[LCoCl_2.H_2O]Cl_1$ Figure 6. Electronic spectrum of $[LNiCl_2.H_2O]Cl_2$

3.3. Nuclear Magnetic Resonance (NMR) spectra of Ligand

The ^1H -NMR spectrum of **N-cyclohexyl-2-((dimethyl carbamoyl) carbamothioyl) hydrazine-1-carboxamide (L)** in DMSO-d_6 solvent is presented in Figure 7. The singlet peak when (9.54 ppm) is equal to a single the proton as a result of $[1\text{H}, \text{N}(2)\text{H}, \text{s}]$. The singlet peak at (9.03 ppm) equivalent to the proton is due to $[1\text{H}, \text{N}(3)\text{H}, \text{s}]$ [38]. A singlet peak at (5.02 ppm) which is equal to a proton is due to $[1\text{H}, \text{N}(4)\text{H}, \text{s}]$ [39]. The singlet peak when (4.52 ppm) is equal to the proton is due to $[1\text{H}, \text{N}(5)\text{H}, \text{s}]$. The chemical shift due to the $\text{H}_{\text{aliphatic}}$ was detected as a multiplet when (3.22-2.59) ppm which is due to $[11\text{H}, \text{C}_{(6,11)}\text{-H}_{\text{aliphatic}, \text{m}}]$ and the chemical shift at (1.10 ppm) which is due to a single peak of $[6\text{H}, \text{C}_{(1,2)}\text{-H}_{\text{aliphatic}, \text{s}}]$.

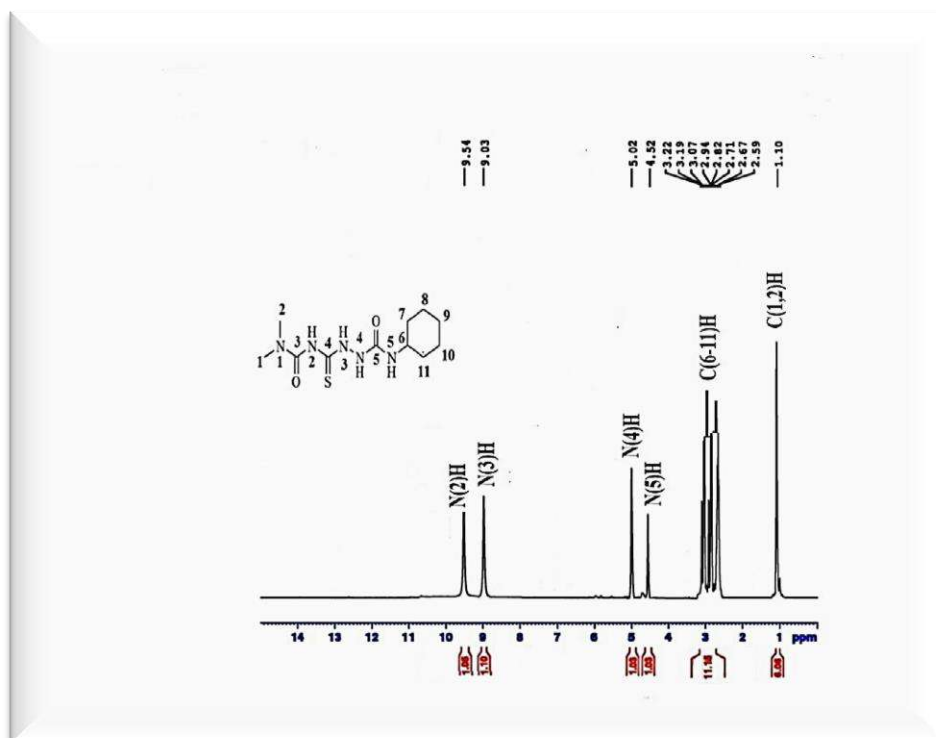


Figure 7. ^1H NMR of N-cyclohexyl-2-((dimethyl carbamoyl) carbamothioyl) hydrazine-1-carboxamide (L)

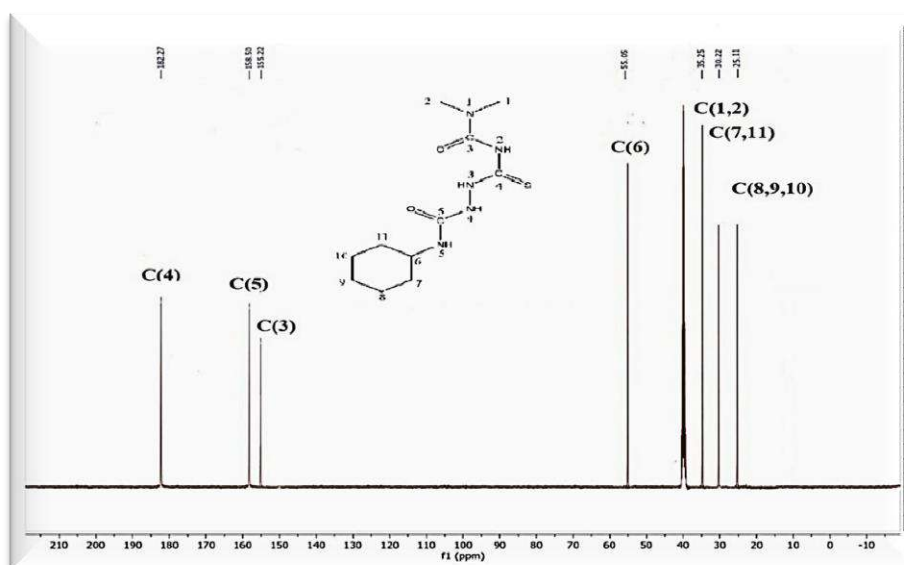


Figure 8. ^{13}C NMR spectrum of N-cyclohexyl-2-((dimethyl carbamoyl) carbamothioyl) hydrazine-1-carboxamide (L)

Figure 8 illustrates the ^{13}C NMR spectrum of the ligand in DMSO-d_6 . The ligand spectrum shows downfield shifts at 158 and 155 ppm assigned to carbonyl carbon ($\text{C}=\text{O}$) for semicarbazide and carbonyl, respectively. The slight differences in the chemical shifts of these peaks in the spectrum of ligands are probably due to different environments around them ($\text{C}=\text{O}$). The spectrum showed an indicated ($\text{C}=\text{S}$) signal at 182 ppm, attributed to the thiocyanate group. The aliphatic carbon signals of the (C_6), ($\text{C}_{1,2}$), ($\text{C}_{7,11}$), and ($\text{C}_{8,9,10}$) appeared as expected in the range of 55-25 ppm, respectively. All ^{13}C -NMR chemical shift positions of the ligand (L) are in agreement with values reported by other semicarbazide ligands [40].

3.4. Mass Spectrum of of Ligand (L)

The electrospray (+) mass spectroscopy of L figure (9) shows the molecular ion peak at $m/z = (287.14)$ amu (22%) this peak is related to (L) + calculated (287.38) amu for ($\text{C}_{11}\text{H}_{21}\text{N}_5\text{O}_2\text{S}$)

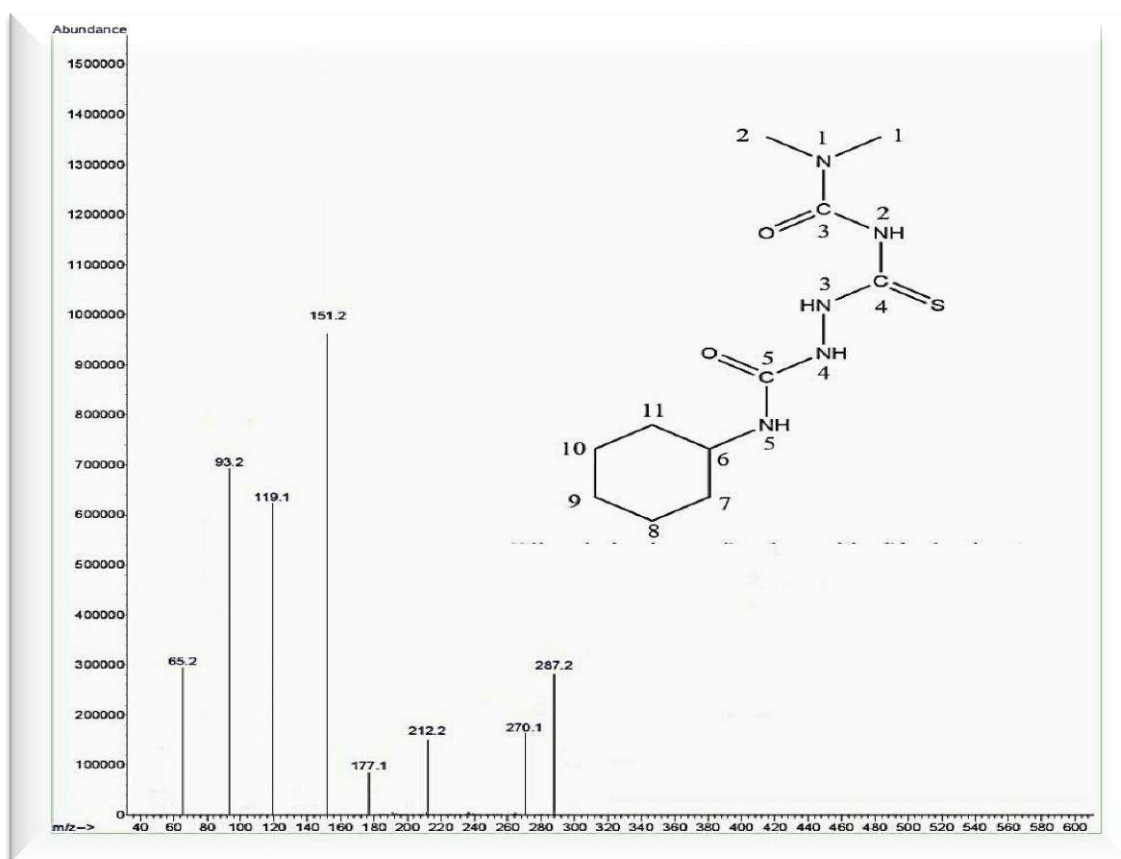


Figure 9. The mass spectrum of (L)

Biological Activity

Determine the antibacterial activity of the ligand and its metal complexes, a dye-negative bacteria strain and a specific strain of Gram-positive bacteria isolate (*Staphylococcus aureus*) and (*Escherichia coli*) were used as test organisms. To determine whether or not ligand and its complexes possessed antibacterial properties, the disc diffusion method was utilized. The *in vitro* antibacterial studies were conducted at a range of concentrations of 50mg/ml, 25mg/ml, and 12. mg/ml against pathogenic bacterial strains. Levofloxacin ($10 \mu\text{g}/\text{disc}$), was used as a positive control, and (CFU $10 \mu\text{g}$) a negative control. The nutrient agar solution was poured into the sterilized petri plates to create the agar medium. Following an incubation period of twenty-four hours at 37 degrees Celsius in the nutrient broth, all of the bacteria were cultivated and then distributed throughout the nutritional agar's surface. Whatman No. 1 filter paper was cut into 5 mm diameter discs, which were then autoclaved for 15 minutes at 15 psi in an aseptic environment. The chemicals diffuse from a filter paper disc onto agar when it is impregnated with the chemical and placed on the agar. The chemical in the

agar will only be distributed across the disc by diffusion. If the disc is chemically sensitive, the extent of the chemical infiltration around it will depend on the chemical's solubility and molecular size. The "zone of inhibition" is the region that does not expand. To create a consistent suspension, a loopful of the test organism's overnight slant culture was injected with 5 μ L of sterile physiological saline. To create a homogeneous grass culture, this suspension culture was surface distributed over a nutrient agar plate using a sterile cotton swab. Using sterile forceps, the discs containing the test samples that were prepared as previously indicated were put on the plates' swabbed surfaces (five discs per plate). After an incubation time of twenty-four hours at 37 degrees Celsius, the plates were examined to look for zones of inhibition surrounding the discs. Regarding the biological activity of *Escherichia coli*, the L in the third and second concentrations 50,25 showed stronger activity, while the complexes C₆, and C₇, in all concentrations, gave medium activity against this bacteria strain. The examined chemicals' biological action against *Staphylococcus aureus* indicated that the L in the third concentration 50 showed a stronger activity against this type of bacteria. C₁, in the second and third concentrations 25,50 showed a stronger activity against this type of bacteria. activity in the third, first, and second concentrations C₂ showed medium activity, but did not give activity against this type of bacteria.

Table 3. Antibacterial activity values of some prepared compounds against isolates of pathogenic bacteria

Compound	Concentration (μ g/ml)	Staphylococcus aureus (G+)	Escherichia Coli (G-)
L	50	R	26
	25	27	32
	12	48	36
C ₁	50	R	11
	25	R	15
	12	30	25
C ₂	50	R	17
	25	R	18
	12	21	19
C ₃	50	R	11
	25	17	14
	12	21	18

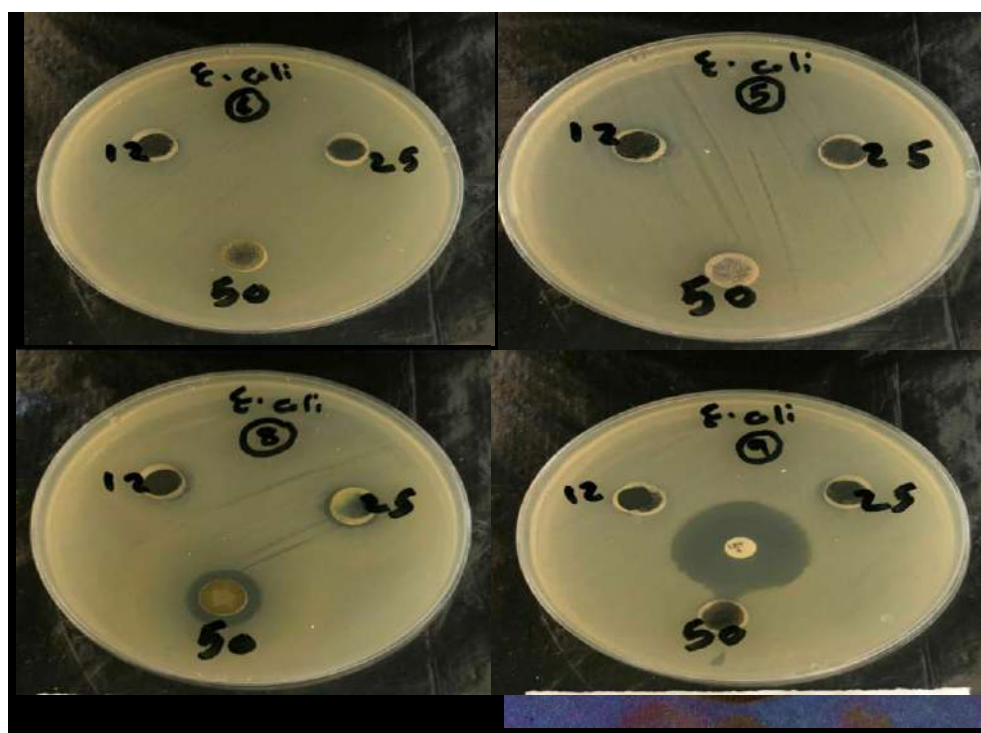


Figure 12. Antibacterial I activity of the compounds against *Escherichia aureus* of the L ligand and its complexes [C₁, C₂, C₃]



Figure 13. Antibacterial activity of the compounds against *Staphylococcus* *Escherichia coli* of the L ligand and its complexes [C₁, C₂, C₃]

4. CONCLUSION

The synthesis of a new ligand N-cyclohexyl-2- ((dimethyl carbamoyl) carbamothioyl) hydrazine-1-carboxamide (L) and the new metal complexes are recorded. The monomeric complexes were formed by the interaction of the ligand with Co⁺², Ni⁺², and Cu⁺² metal ions in a 1:1 (ligand - metal) mole ratio. The chemical structure of compounds and the bonding behavior of complexes were confirmed using physicochemical methods. Six-coordinate monomeric complexes with the formula [LCoCl₂H₂O], [LNiCl₂H₂O], and [LCuCl₂H₂O] were isolated and confirmed through characterization. An assessment of the ligand and its complexes was conducted to determine their antibacterial activity against both Gram-positive and Gram-negative bacteria.

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