Synthesis, Structural Characterisation and Biological Activity; new Metal Complexes Derived from 4-Ethyl-3-Thiosemicarbazide Ligand

Hala Adnan Dawood[1], Nasry Jasim Hussein[2], Enaam I. Yousif[3]
[1, 2] Department of chemistry,College of Education for pure science, University of Diyala/Iraq
[3]Department of Chemistry, College of Education for Pure Science (Ibn Al-Haitham), University of Baghdad, Baghdad, Iraq
Email: nasry.hussien@uodiyala.edu.iq

Abstract

The research included the preparation and characterization of the new 4-ethyl-3-thiocimecarbazide ligand; N1-(dimethylcarbamoyl)-N2-ethylhydrazine-1,2-bis (carbo-thiomide)(L) .Three transition metal complexes were isolated from the mixing of the title ligand with the metal ions of (Ni(II), Co(II), and Cu(II)).The reaction was performed by mixing metal ligand in a 1:1 mole ratio using EtOH as the medium.The chemical formula of L complexes is presented as follows ;[LNiCl2H2O], [LCoCl2H2O] and [LCuCl2H2O], 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 13C- NMR spectra, elemental analysis(CHNS), chloride content, metal content, melting point, molar conductivity and magnetic susceptibility measurements. The spectral and analytical analyses concluded the isolation of six-coordinate complexes for the (Ni(II), Co(II) and Cu(II) with a distorted octahedral geometry about the centre atom. The anti-bacterial activity (G+ and G-bacterial) was explored

Keywords: Antibacterial activity, metal complexes Synthesis

1. Introduction

The chemistry of nitrogen, oxygen and sulfur heteroatom-containing aromatic compounds represents an interesting area of research [1]. The most important aspect of these compounds is highlighted by their role in being used as chelating agents, as they can interact with transitional elements [2]. Compounds containing nitrogen, oxygen, and sulfur are considered an important class of organic compounds that played an important role in the development of organic chemistry [2] and inorganic and coordination chemistry [3]. Further, researchers have implemented several synthetic routes to improve the preparation methods of organic ligands and their stability including their metal complexes. These factors played role in the development of organic and coordination chemistry [4,5]. Heterocyclic compounds represent materials that contain at least one heteroatom, and the most common heterocyclic atoms are nitrogen, oxygen and sulfur. Compounds that are derived from thiosemicarbazide are interesting reagents as they consist of the hard site (nitrogen) and the soft site (sulfur). Subsequently, these compounds (the organic and their metal complexes) are potential agents that use in medicine and the pharmaceutical industry. These compounds exhibit a wide range of activity against diseases and are used as antimicrobials and insecticide agents [6,7]. More, heterocyclic compounds are used as antifungal [8], antibacterial [9], anticancer [10] and anti-inflammatory [11], anti-tubercular [12] and anti-HIV [13]], as well as analytical and environmental chemistry [14]. The chemistry of heterogeneous organic species and complexes remains one of the hot research areas that influenced the concern of organic, inorganic and coordination chemists. This work represents the synthesis and spectral characterization of a new thiosemicarbazide ligand namely; N1-(dimethylcarbamoyl)-N2-ethylhydrazine-1,2-bis (carbo-thiomide) (L) and its metal complexes with M(II) ions (Co, Ni and Cu). More, the antibacterial evaluation of the ligand and its metal complexes is explored.

Experimental

2. Materials and Methods

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

Masurement techniques

Elemental analysis was carried out using a Carlo Erba 1108 Elemental Analyzer (Milan, Italy). The infrared (IR) spectrum was recorded as KBr and CsI pellets using a Perkin Elmer Spectrum GX spectrophotometer (Perkin Elmer, Waltham, MA, USA). NMR spectra (1H, 13C- NMR) were acquired in DMSO-d6 solutions usinga Bruker-400MHz for 1H-NMR and 100.61 MHz for 13C-NMR with tetramethylsilane (TMS) as an internal reference for

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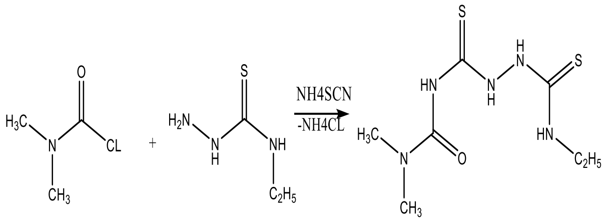
1H NMR.

Synthesis of N1-(dimethylcarbamoyl)-N2-ethylhydrazine-1,2-bis (carbo- thioamide) (L)

The ligand was prepared according to the method reported in [15} and as follows;

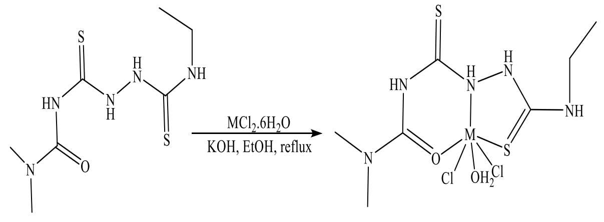
A mixture of dimethyl carbamoyl chloride (1.07g, 10mmol) and ammonium thiocyanate (0.76 g, 10mmol) in acetonitrile (40mL) was heated at reflux for 1h. The reaction mixture was cooled to room temperature and then filtrated off. 4-ethyl-3-thiosemicarbazide (1.19g, 10 mmol) in acetonitrile (20mL) was added to the filtrate and the mixture was refluxed for 2h. Upon cooling, a white solid was formed which was collected by filtration washed with acetonitrile (10mL) and dried in a desiccator over anhydrous silica gel to give the title compound, Scheme 1.



Scheme 1: Synthetic route of ligand.

Synthesis of complexes

In a 100mL of a round-bottomed flask was mixed N^1-(dimethylcarbamoyl)-N^2-ethylhydrazine-1,2-bis(carbothioamide)(L)(0.49g,2mmol)dissolved in ethanol (10mL). A solution of KOH (0.011g, 2mmol) dissolved in ethanol (10mL) was added dropwise to the L solution. The resulting mixture was refluxed for 1h and then an ethanolic solution (10mL) of the title metal ions $MCl_2.6H_2O$ (2 mmol) (M(II)= Co, Ni or Cu) was added dropwise. The resulting coloured solution was allowed to reflux for 2h and then cooled to room temperature. The metal complexes were collected by filtration and air-dried (Scheme 2).



M(II)= Co, Ni or Cu

Scheme 2: *Synthetic route of complexes*

3. Results and Discussion

FT-IR spectrum of L

The solid-state infrared spectrum of the prepared ligand, Figure1, was recorded in the range of 4000-370 cm^{-1}. The main FTIR bands of the ligand are presented in Table (1). The FTIR spectrum of thiosemicarbazide ligand showed bands around(3387-3080)cm^{-1} ,810 and 725 assigned to *v*(N-H) and *v*(C=S)thiosemicarbzid and (C=S)thiocyanat5, respectively [16,17]. Bands detected at 1141,1049 were attributed to *v*(C-N) and *v*(N-N), respectively. The *v*(C=O) of the carbamoyl group appeared at 1658 cm^{-1} [18].

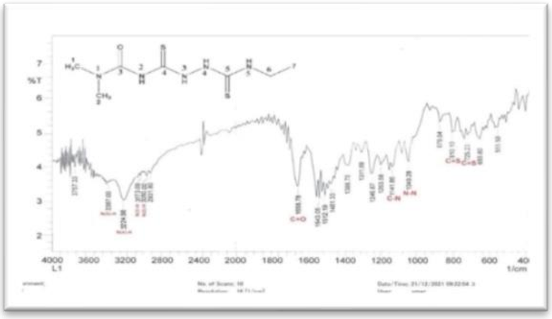


Figure 1. The FTIR spectrum of N1-dimethylcarbamoyl)-N2-ethylhydrazine-1,2-bis (carbo- thioamide)(L)

U.v.-Vis Spectrum of Ligand

The UV spectrum for L, Figure 2, showed a high-intensity absorption peak at 290nm which is attributed to the ligand field (π →π* * transitions)[19,20].

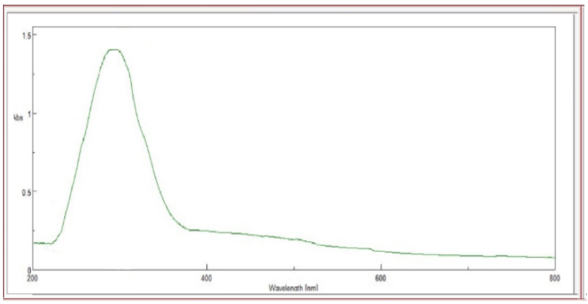


Figure-2. Electronic spectrum of Ligand L in DMSO Solvent

Nuclear Magnetic Resonance (NMR) spectra of Ligand

The 1H-NMR spectrum of N1-dimethylcarbamoyl)-N2-ethylhydrazine-1,2-bis (carbo- thioamide) in DMSO-d6 solvent is presented in Figure 3. The singlet peak at 8.66ppm equivalent to one proton is related to [1H, N(2)H, s]. A singlet peak at 7.74ppm which is equivalent to two protons is attributed to [2H, N(3,4)H, s] [21]. The singlet peak at 7.05ppm equivalent to one proton is related to [1H, N(5)H, s] [21]. The three chemical shifts in the aliphatic that are detected in the range 2.80-0.94ppm are due to [2H, C(6)H, q], [6H, C(1,2)H, s] and [3H, C(7)H, t] [22].

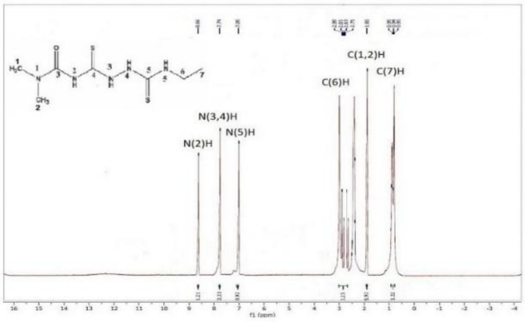


Figure 3. 1H NMR of N1-(dimethylcarbamoyl)-N2-ethylhydrazine-1,2-bis

(carbo- thioamide)(L) The 13C NMR spectrum of the ligand in DMSO-d6 is shown in Figure 4. The spectrum of L1 showed downfield shifts at 181.94 and 177.48 ppm assigned to the thione carbon (C=S) for thiocyanate and thiosemicarbazide, respectively. The slight difference in the chemical shifts of these peaks in the spectrum of the ligand is due to the different environments around the (C=S) groups. The spectrum indicated a signal at 155.02 ppm attributed to the carbonyl of the amide group. The aliphatic carbons signals of the CH3 (C6) , (C1,2) and(C7) appeared as expected in the range 34.71-19.00ppm. All 13C-NMR chemical shift positions of the ligand are in agreement with values reported in other thiosemicarbazide ligands [23].

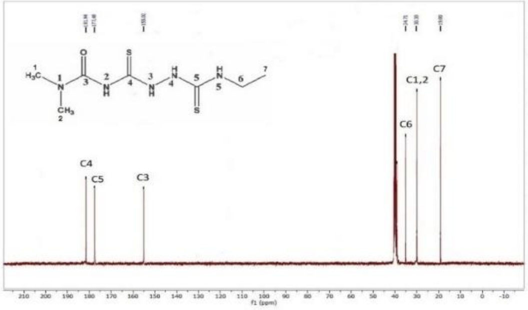


Figure 4. 13C NMR spectrum of N1-dimethylcarbamoyl)-N2-ethylhydrazine1,2- bis

(carbo- thioamide)(L)

Diagnostics of the complexes FT-IR spectra of the prepared complexes

Figures 5-7 show the FT-IR spectra of complexes 1, 2 and 3, while Table (1) includes the assignment of the distinct bands. the FTIR spectra in the complexes of Ni(II), Co(II) and Cu(II) showed peaks related to *v*(O-H) stretches around 3815, 3760 and 3629 cm^{-1}, respectively. These peaks were assigned to the OH of the aqua molecule [24,25,26]. The spectra revealed bands in the range 3375-3040 cm^{-1} that were attributed to the *v(N-H)*. These bands were shifted to lower wavenumber, compared with that observed in the range 3387-3080cm^{-1} in the spectrum of the free ligand [27], Table 1. The band detected at 1658 cm^{-1} in the free ligand, Figure 1, that related to the v(C=O) carbonyl has appeared in the lower range at 1643-1627cm^{-1} in the spectra of the complexes (1, 2 and 3). The shift of the carbonyl bands is related to the involvement of this moiety in the coordination with the metal centre [28,29]. The FTIR spectra of complexes revealed bands in the range 1188-1108 cm^{-1} that attributed to the *v*(C- N) group. These bands were shifted to a lower and higher wavenumber, compared with that observed at 1141cm-1 in the free ligand confirming the involvement of this group in the coordination. The complexes display a band in the range 1056-1002cm−1 due to v(N–N). These band appeared at a higher and lower wavenumber compared with that detected at 1049cm−1 in the free ligand [30]. The band that was assigned to the v(C=S)thiosemicarbazide group was detected in the range 894–804cm-1 in 1, 2 and 3. This band suffered a shift to the lower and higher wavenumber, compared with that observed at 810 cm-1 in the ligand confirming the involvement of this v(C=S) thiosemicarbazide group in the coordination [31]. The band that related to the v(C=S) thiocyanate group at 725 cm-1 in the free ligand appeared at a lower and higher wavenumber, in the range 786-702cm-1, in the spectra of the complexes,. The spectra of metal complexes revealed additional peaks between 600-200cm -1 that were not presented in the spectrum of the ligand. Peaks correlated to v(Ni-N), v(Co-N) and v(Cu- N) were detected at 439, 408 and 401cm-1, respectively [25,26]. Bands detected at 470, 463 and 537, cm^{-1} assigned to *v*(Ni-O), *v*(Co-O) and *v*(Cu-O), respectively.Peaks detected at 370, 385 and 370cm^{-1} were correlated to *v*(Ni-S), *v*(Co-S) and *v*(Cu-S), respectively. The FT-IR spectra revealed bands that belong to *v*(Ni- Cl), *v*(Co- Cl) and *v*(Cu- Cl) at 300, 300 and 293cm^{-1}[32,33].`

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

NO	vN(5)H	vN(4)H	vN(3)H	vN(2)H	v(C=O) carbomyl	v(C-N)	v(N-N)	v(C=S) thiosemicarbazide	(C=S)vthiocyanat	v(O-H)	v(M-O)	v(M-N)	v(M-S)	v(M-Cl)
L	3387	3224	3173	3080	1658	1141	1049	810	725	-	-	-	-	-
C1	3348	3255	3177	3055	1627	1157	1002	804	702	3815 889	470	439	370	300
C2	3375	3248	3194	3062	1635	1108	1018	817	717	3760 902	463	408	385	300
C3	3340	3291	3194	3040	1643	1188	1056	894	786	3629 916	537	401	370	293

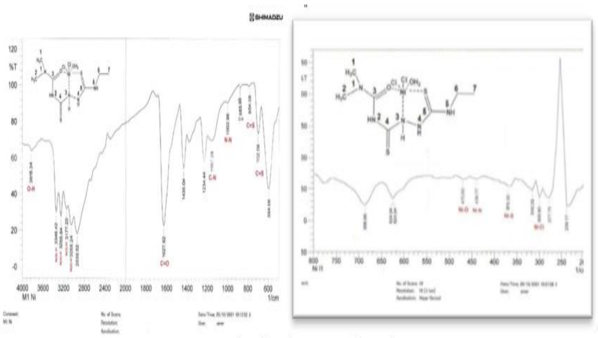
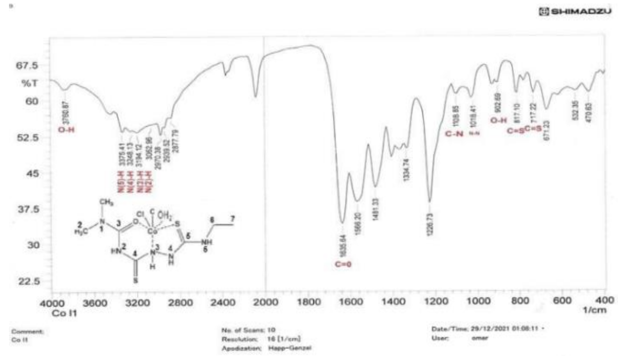


Figure (5)The Infrared spectrum of[(L)NiCl2H2O]



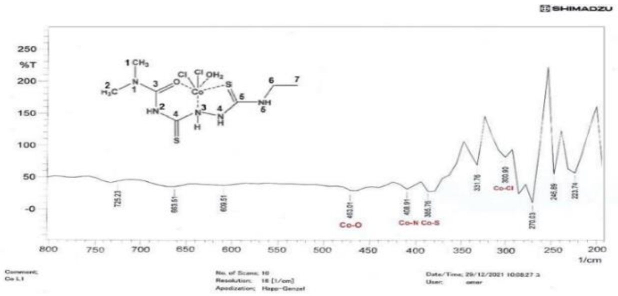


Figure (6) The Infrared spectrum of [(L)CoCl$_2$H$_2$O]

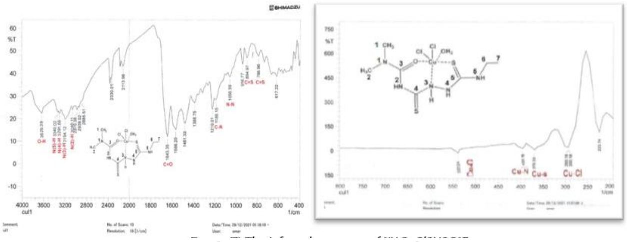


Figure (7) The Infrared spectrum of [(L)CuCl2H2O]

U.v.-Vis Spectra of the complexes

The electronic absorption spectra of complexes were determined in DMSO solutions (con. = 1x 10^{-3} M) . The electronic spectra of the metal complexes of Ni(II) , Co(II) and Cu$^{(II)}$ are exhibited in Figures (8), (9) and (10), respectively. The spectra indicated peaks, see Table (2), around 297-283nm related to the π → π* (ligand field transitions) [34,37]. In the d-d region of the Ni(II) complex, bands observed at 601 and 1019 nm correlated to $^3A_2g \rightarrow {}^3T_1g$ and $^3A_2g \rightarrow {}^3T_2g$, respectively indicating a distorted octahedral geometry about the metal centre [38]. Peak at 545 nm in the spectrum of C$_o$ referred to $^4T_1g \rightarrow {}^4T_1g(p)$ confirming a distorted octahedral geometry around the metal centre [39,40]. Peak at 643 nm in the spectrum of Cu$^{(II)}$ is referred to $^2B_2g \rightarrow {}^2A_1g$ confirming a distorted octahedral geometry around the metal centre[41].

Table(2) UV-visible spectrum of ligand and complexes

Complex	nmλ	λ cm-1	ΣMax (dm3 mo-1 cm-1)	Assignment	Suggested geometry
L	290	34482	1400	π→π*	
C$_1$	293	34192	1103	π→π*	Octahedral
	601	16638	40	3A2g→3T1g	
	1019	9813	99	3A2g→3T2g	
C$_2$	297	33670	1009	π→π*	Octahedral
	545	18348	33	4T1g→4T1g(p)	
C$_3$	283	35335	1078	π→π*	Octahedral
	643	15552	88	2B2g→2A1g	

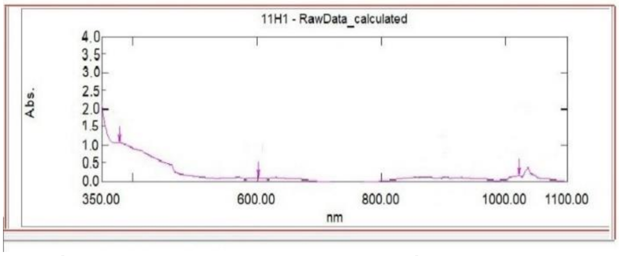


figure (8): Electronic spectrum of [(L)NiCl2H2O]

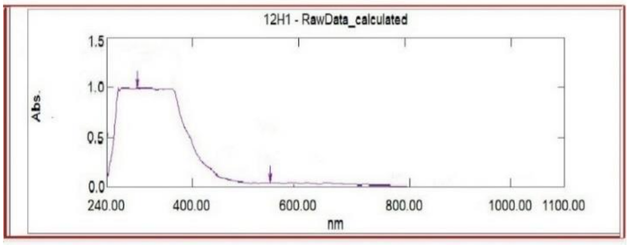


figure (9): Electronic spectrum of [(L)CoCl2H2O]

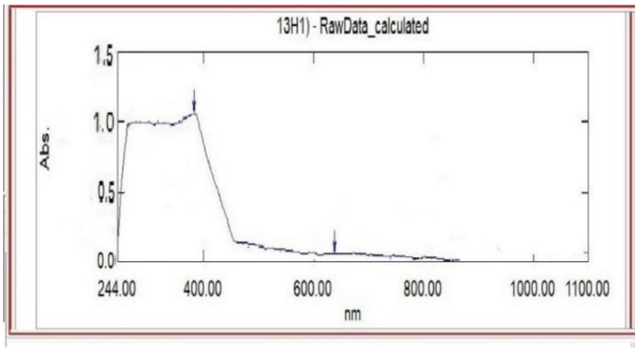


figure (10): Electronic spectrum of of [(L)CuCl2H2O]

Biological Activity

The ligand and its metal complexes were examined for their microbiological activity against a type of isolate of Gram-positive bacteria (*Staphylococcus aureus*) and a dye-negative bacteria (*Escherichia Coli*).

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

Compound	Concentration (mg/ml)	Staphylococus aureus (G+)	Escherichia Coli (G-)
L	50	22	R
	25	17	R
	12.5	12	R
C1	50	18	21
	25	15	14
	12.5	R	14
C2	50	23	20
	25	20	R
	12.5	14	R
C3	50	26	17
	25	20	13
	12.5	17	14

The antibacterial activity was performed using a disc diffusion method. The in vitro antibacterial studies were conducted at a range of concentrations of 50mg/ml, 25mg/ml, and 12.5mg/ml, against pathogenic bacterial strains. Clarithromycin (10 µg/disc) was used as a positive control and polymyxin B as the negative control. The agar media was prepared by pouring the nutrient agar solution into the sterilized Petri dishes. All bacteria were cultured in the nutrient broth and incubated at 37°C for 24 h, and then the cultures were spread on the surface of the nutrient agar. Discs of 5mm diameter were cut out of Whatman No.1 filter paper and autoclaved at 15psi for 15 min under aseptic conditions. When a filter paper disc is impregnated with a chemical and placed on agar, the chemical will diffuse from the filter paper into the agar. The diffusion will place the chemical in the agar only around the disc. The solubility of the chemical and its molecular size will determine the size of the area of chemical infiltration around the disc if it is susceptible to the chemical. The area of no growth is known as the 'zone of inhibition'. A loopful of an overnight slant culture of the test organism was inoculated to 5µL of 140 sterile physiological salines to make a uniform suspension. This suspension culture was surface spread on a nutrient agar plate by swabbing with a sterile cotton swab to get a uniform lawn culture. The discs with test samples prepared as mentioned above were placed on the swabbed surfaces of the plates (5 discs per plate), using sterile forceps. The plates were incubated at 37°C for 24 hours and then checked for zones of inhibition around the discs.Regarding the biological activity of Escherichia coli comsplexes C1and C2 in the first concentration 50, showed a stronger activity ,while the ligand L and C2, in the third concentration did not give activity against the examined bacteria.L did not give any efficacy in the first, second and third concentrations. The biological activity of the tested compounds against Staphylococcus aureus indicted the complexes(C3) in the first concentration 50 showed good activity against this type of bacteria, (C1)in the third concentration no activity against this type of bacteria while the rest of the complexes and the free ligand showed medium activity against this type of bacteria

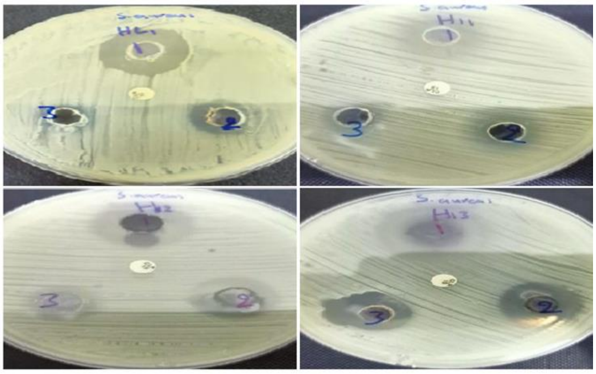


Figure (11): Antiviral activity of the compounds against Staphylococcus aureus of the L ligand and its complexes [C1, C2, C3]

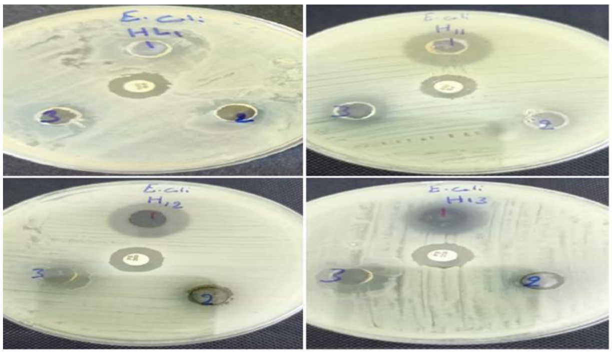


Figure (12): Antiviral activity of the compounds against Escherichia coli of the L ligand and its complexes [C1, C2, C3]

4. Conclusions

The synthesis and characterisation of *N*^{1}-(dimethylcarbamoyl)N^{2}-ethylhydrazine-1,2-bis (carbo-thiomide) (L) and its new metal complexes are reported. The reaction of the ligand with $Ni^{(II)}$, $Co^{(II)}$ and $Cu^{(II)}$ metal ions in a 1:1 (L:M) mole ratio resulted in the isolation of monomeric complexes. The chemical structure of compounds and overall bonding behaviour of the complexes were confirmed through physicochemical techniques. The characterisation data confirmed the isolation of six-coordinate monomeric complexes of the general formula; $[LNiCl_2H_2O]$, $[LCoCl_2H_2O]$ and $[LCuCl_2H_2O]$. The biological activity of the ligand and its complexes against (G+ and G-) bacterial was tested.

Acknowledgements

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