Synthesis, Characterisation and Antibacterial Activity of Novel Metal Complexes Derived from 4-Methyl-3-Thiosemicarbazide

Laith Shadhin Thamer[1], Nasry Jassim Hussien[2], Siti Fairus M. Yusoff[3,] Mohamad J. Al-Jeboori[4]
[1,,2] Department of chemistry, College of Education for pure science, University of Diyala
[3] School of Chemical Sciences and Food Technology, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, 43600 UKM Bangi, Selangor
[4]Department of Chemistry, College of Education (Ibn Al-Haitham) for Pure Science, Baghdad University, Baghdad, Iraq
Corresponding author: nasry.jh11@yahoo.com

Abstract

The research included the preparation and characterization of the new thiosemicarbazide ligand; N1-(dimethylcarbamoyl)-N2-methylhydrazine-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 HL 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 13 C- 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: Synthesis, antibacterial activity, metal complexes

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-methylhydrazine-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 Mthods

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

doi.org/10.31838/hiv22.02.443 Received: 27.05.22, Revised: 28.05.22, Accepted: 04.08.22

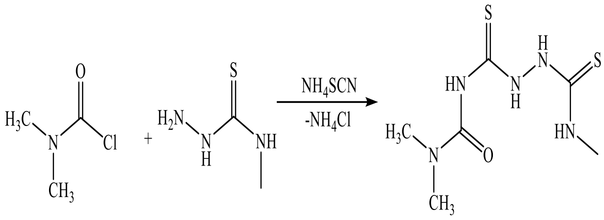
tetramethylsilane (TMS) as an internal reference for

1H NMR

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

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

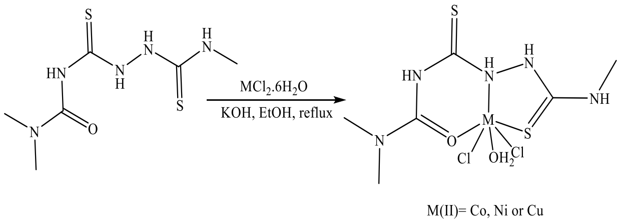
A mixture of dimethyl carbamoyl chloride (1.07g, 10mmol) and ammonium thiocyanate (0.76 g, 10mmol) in acetonitrile (40mL) was heated at reflux for 1h. The reaction mixture was cooled to room temperature and then filtrated off. 4-Methyl-3-thiosemicarbazide (1.05g, 10 mmol) in acetonitrile (20mL) was added 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 N1-(dimethylcarbamoyl)-N2-methylhydrazine-1,2-bis(carbothioamide) (L) (0.470g, 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 MCl2.6H2O (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).



Scheme 2: Synthetic route of complexes

3. Results and Ddiscussion

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 (3347 – 3001), 871 and 779cm-1 assigned to v(N-H) and v(C=S)thiosemicarbzid and (C=S)thiocyanat5, respectively [16,17]. Bands detected at 1188 and 1033cm-1 were attributed to v(C-N) and v(N-N), respectively. The v(C=O) of the carbamoyl group appeared at 1666 cm-1 [18].

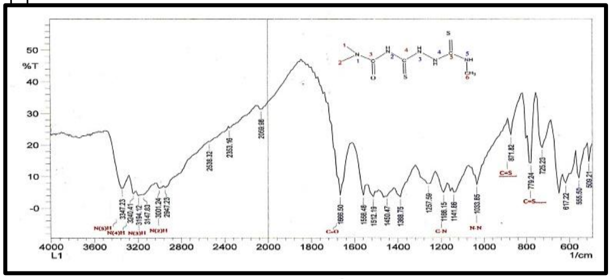


Figure 1. The FTIR spectrum of N1-dimethylcarbamoyl)-N2-methylhydrazine-1,2-bis (carbo- thioamide)(L)

3-1-2 U.v.-Vis Spectrum of Ligand

The UV spectrum for L, Figure 2, showed a high-intensity absorption peak at 275 which is attributed to the ligand field (an overlap of π →π* and n →π* transitions)[19,20].

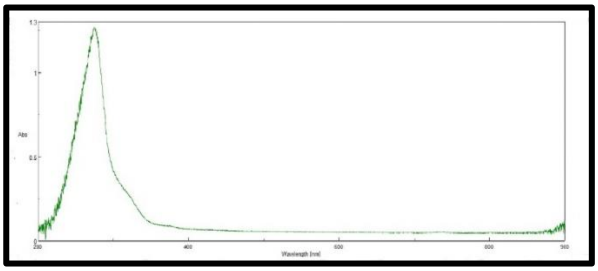


Figure-2. Electronic spectrum of Ligand L in DMSO Solvent

3.1.3 Nuclear Magnetic Resonance (NMR) spectra of Ligand

The 1H-NMR spectrum of N1-dimethylcarbamoyl)-N2-methylhydrazine-1,2-bis (carbo- thioamide) in DMSO-d6 solvent is presented in Figure 3. The singlet peak at 8.24ppm equivalent to one proton is related to [1H, N(2)H, s]. A singlet peak at 7.70ppm which is equivalent to two protons is attributed to [2H, N(3,4)H, s] [21]. The singlet peak at 5.85ppm equivalent to one proton is related to [1H, N(5)H, s] [22]. The two chemical shifts in the aliphatic that are detected as a singlet in the range 2.20-1.82ppm are due to [6H, C(1,2)H, s] and [3H, C(6)H, s], respectively [21].

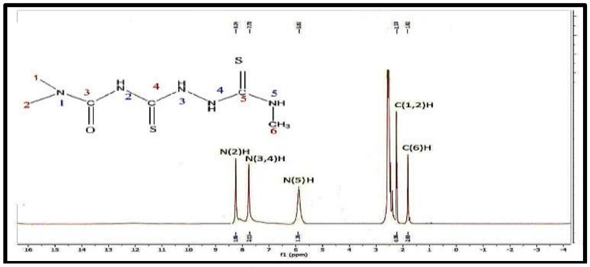


Figure 3. 1H NMR of N1-(dimethylcarbamoyl)-N2-methylhydrazine-1,2-bis

(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 185.89 and 180.22 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 155.00 ppm attributed to the carbonyl of the amide group. The aliphatic carbons signals of the CH3 (C1,2) and (C6) appeared as expected in the range 34.74-30.67ppm. All 13C-NMR chemical shift positions of the ligand are in agreement with values reported in other thiosemicarbazide ligands [23].

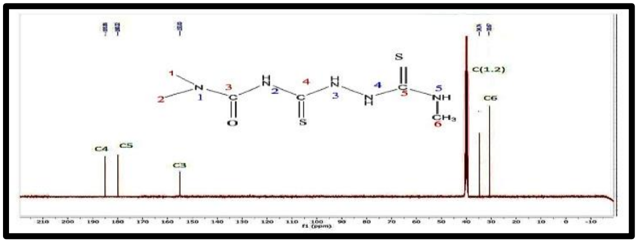


Figure 4. 13C NMR spectrum of N1-dimethylcarbamoyl)-N2-methylhydrazine-1,2-(carbothioamide)

FT-IR spectra of the prepared complexes

Figures 3-5 to 3-7 show the FT-IR spectra of complexes 1, 2 and 3, while Table (3-1) 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 3600, 3621 and 3522 cm-1, respectively. These peaks were assigned to the OH of the aqua molecule [24,25,26]. The spectra revealed bands in the range 3392-3093 cm-1 that were attributed to the v(N-H). These bands were shifted to lower and higher wavenumber, compared with that observed in the range 3347-3001cm-1 in the spectrum of the free ligand [27], Table 3-1. The band detected at 1666 cm-1 in the free ligand, Figure 1, that related to the v(C=O) carbonyl has appeared in the lower range at 1635-1627cm-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 1181-1165 cm-1 that attributed to the v(C- N) group. These bands were shifted to a lower wavenumber, compared with that observed at 1188cm-1 in the free ligand confirming the involvement of this group in the coordination. The complexes display a band in the range 1080-1026cm−1 due to v(N–N). This band appeared at a higher and lower wavenumber compared with that detected at 1033cm−1 in the free ligand [30]. The band that was assigned to the v(C=S)thiosemicarbazide group was detected in the range 851–807cm-1 in 1, 2 and 3. This band suffered a shift to the lower wavenumber, compared with that observed at 871cm-1 in the ligand [31]. The band that related to the v(C=S) thiocyanate group at 779 cm-1 in the free ligand appeared at a lower wavenumber, in the range 740-732cm-1, in the spectra of the complexes, confirming the involvement of this v(C=S)thiocyanate group in the coordination. 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 455, 432 and 439cm-1, respectively [25,26]. Bands detected at 594, 547 and 578, cm-1 assigned to v(Ni-O), v(Co-O) and v(Cu-O), respectively.Peaks detected at 347, 354 and 339cm-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 316, 316 and 300cm-1, respectively [32,33].`

Table 3.1 Principal FTIR bands of ligand and complexes (cm^{-1})

N O	O-H	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) Thiocyanat	v(M- O)	(M-N) v	v(M- S)	(M- Cl) v
L_1	-	3347	3240	3194	3001	1666	1188	1033	871	779	-	-	-	-
C_1	3600	3392	3232	3155	3093	1635	1165	1080	807	740	594	455	347	316
C_2	3621	3388	3278	3151	3078	1635	1172	1056	848	732	547	432	354	316
C_3		3382	3242	3147	3032	1627	1181	1026	851	732	578	439	339	300

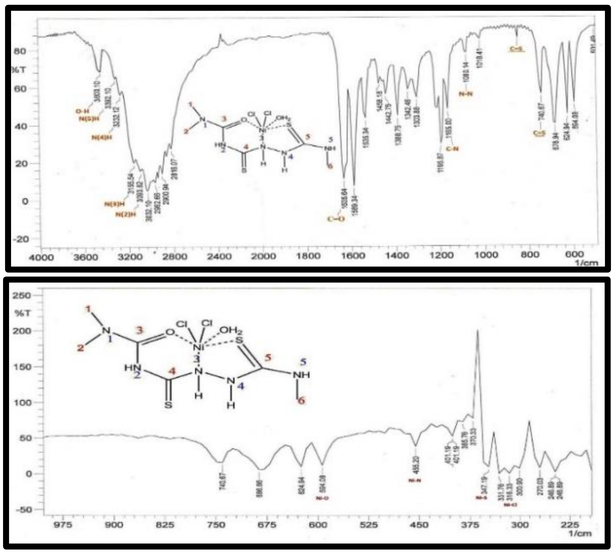


Figure (3-5) The Infrared spectrum of [(HL1)NiCl2H2O

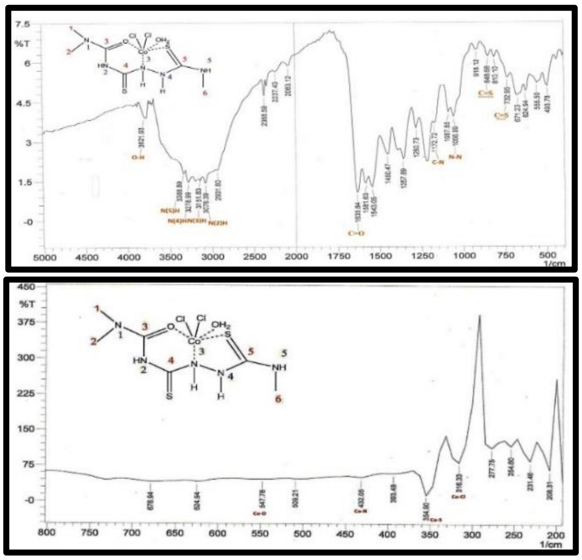


Figure (3-6) The Infrared spectrum of [(HL$_1$)CoCl$_2$H$_2$O]

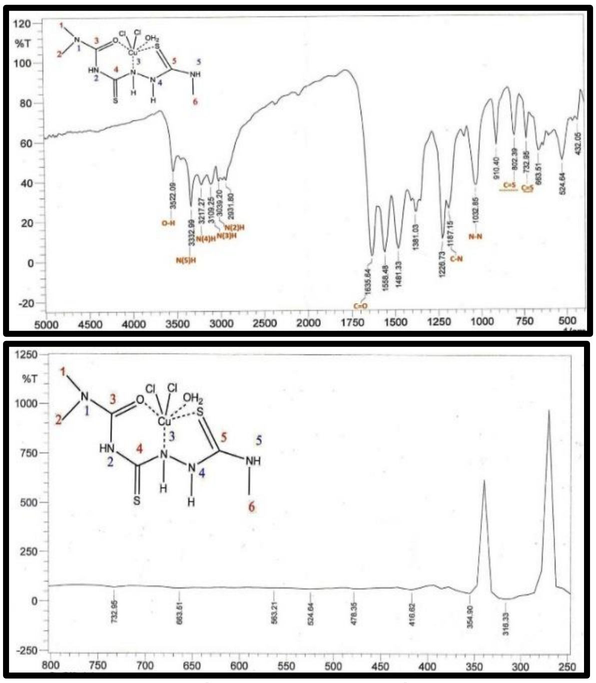


Figure (3-7) The Infrared spectrum of [(HL1)CuCl2H2O]

3-2-2 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 (3-8), (3-9) and (3-10), respectively. The spectra indicated peaks, see Table (3-2), around 290-254nm related to the overlap of π → π* and πn→ π* (ligand field transitions). The spectra of 1, 2 and 3 showed an extra peak about ca.315nm assigned to charge transfer (C.T) [34-37]. In the d-d region of the Ni(II) complex, bands observed at 518, 692 and 1023nm correlated to 3A2g→1T1g, 3A2g→1Eg and 3A2g→3T2g, respectively indicating a distorted octahedral geometry about the metal centre [38]. Peaks at 595 nm in the spectrum of Co referred to 4T1g→4A2g, confirming a distorted octahedral geometry around the metal centre [39,40]. The peak at 695nm in the spectrum of Cu(II) is referred to 2B2g →2A1g transition confirming a distorted octahedral geometry around the metal centre [41].

Table (3-2): UV-visible spectrum of complexes

Complex	λ nm	cm-1 λ	Ɛmax (dm3 mo-1cm - 1)	Assignment	Suggested geometry
L_1	275.8	36258	1250	π → π*	
C_1	274 301 518 692 1023	36496 33222 19305 14450 9770	1000 950 30 30 35	π → π* n → π* $^{3}A_{2}g\rightarrow{}^{1}T_{1}g$ $^{3}A_{2}g\rightarrow{}^{1}Eg$ $^{3}A_{2}g\rightarrow{}^{3}T_{2}g$	Octahedral
C_2	254 595	39370 16806	1400 50	π → π* $^{4}T_{1}g\rightarrow{}^{4}A_{2}g$	Octahedral
C_3	290 396 695	34482 25252 14388	1100 006 **30**	π → π* n → π* $^{2}B_{2}g\rightarrow{}^{2}A_{1}g$	Octahedral

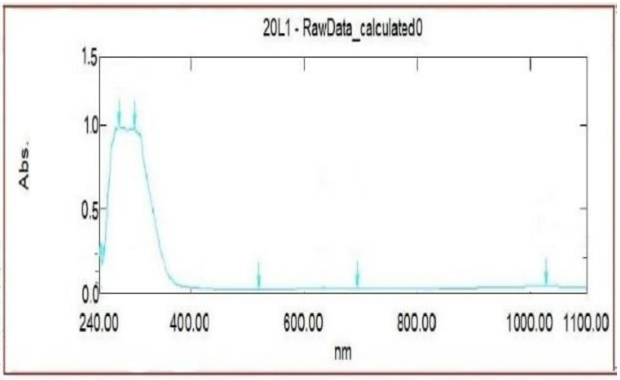


figure (3-8): Electronic spectrum of of [(HL1)NiCl2H2O]

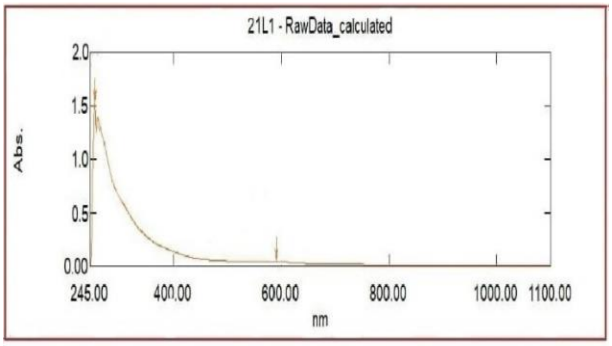


figure (3-9): Electronic spectrum of of [(HL1)CoCl2H2O]

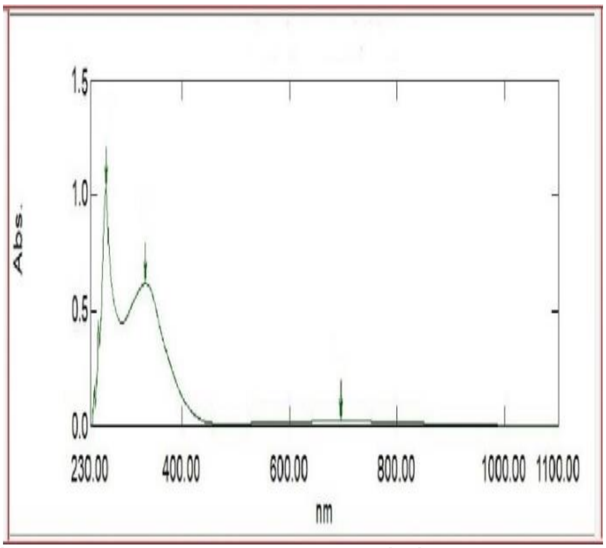


figure (3-10): Electronic spectrum of of [(HL1)CuCl2H2O]

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).

Table3.3 Biological activity values of some prepared compounds against isolates of pathogenic bacteria

Escherichia Coli (G-)	Staphylococus aureus (G+)	Concentration (mg/ml)	Compound
13	38	50	L1
R	35	25	
R	20	12.5	
28	28	50	C1
25	24	25	
16	18	12.5	
38	33	50	C2
26	26	25	
18	22	12.5	
15	22	50	C3
14	19	25	
	19	12.5	

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, complexes 1 and 2, in the first concentration 50, showed a stronger activity, while the ligand in the third concentration did not give activity against the examined bacteria., The biological activity of the tested compounds against Staphylococcus aureus indicated the free ligand and complex 2 showed good activity against this type of bacteria, while the rest of the complexes showed medium activity and the free ligand in the third concentration indicated no activity against this type of bacteria

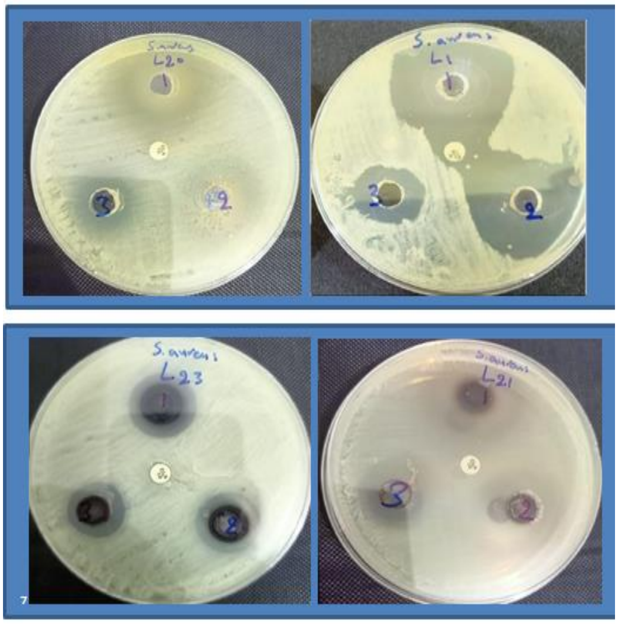


Figure (3-11): Antiviral activity of the compounds against Staphylococcus aureus of the L ligand and its complexes [C1, C2, C3

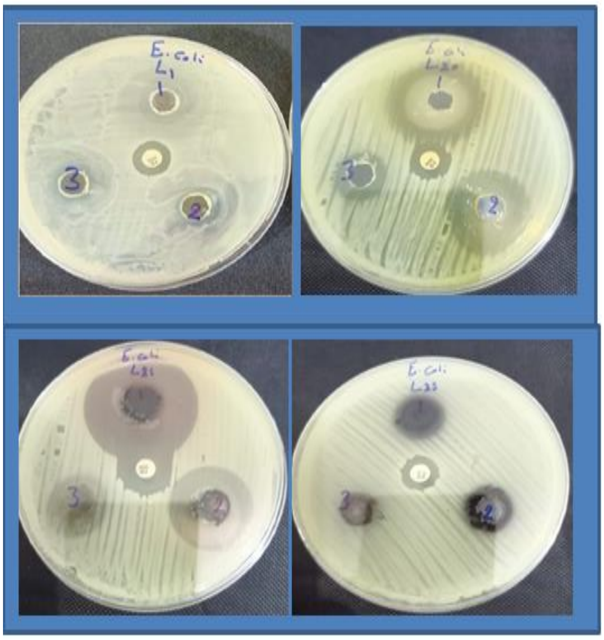


Figure (3-12): Antiviral activity of the compounds against Escherichia coli of the L ligand and its complexes [C_1, C_2, C_3]

4. Conclusions

The synthesis and characterisation of N^1-(dimethylcarbamoyl)-N^2-methylhydrazine-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

The authors would like to thank University of Diyala for its continued support

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