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Synthesis, characterization and biological activity of mixed ligand complexes of some metal ions containing new 2-Thioxoimidazolidine-4- one derivative and amino acid

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Abstract

In the present work, a new derivative of 2- thioxoimidazolidine-4- one (3-{(E)-[(4- hydroxy-3-methoxyphenyl) methylidene] amino} -2- sulfanylideneimidazolidin-4-one) has been synthesized by the reaction of vanillin with thiosemicarbazide then the resulting product reacted with ethelchloroacetate to produce the ligand. This ligand was characterized using different technique such as elemental analysis (C.H.N.S), (FTIR) and (UV.Vis) and HNMR spectra. This ligand and glycine have been used in the characterization of mixed ligand metal complexes ions, using metal ions [Cu(II), Ni(II), Co(II), Zn(II), and Cd(II)] the synthesized complexes have been also synthesized using available technique such as, Accurate analysis of the elements (C.H.N.S) and atomic absorption spectroscopy, (FT-IR) spectra, conductivity measurement, (UV-Visible) spectra, and (magnetic susceptibility). The biological activity of the prepared complexes were investigated against two kind of bacteria (***Escherichia coli*** as gram negative bacteria and ***Staphylococcus haemolyticus*** *as gram positive* bacteria***).***

Key words: compounds of Schiff base, coordination compound of thioxoimidazolidene, mixed ligand complexes, amino acid complexes spectral data, antimicrobial activity***.***

Introduction

Thiohydantion a type of heterocyclic ring compound, its sulfur similar to hydantoins with one or both carbonyl groups substituted by thiocarbonyl groups [1][2], there are many process to prepared these compounds, It can be prepare from the reaction of carbonyl compound with thiosemicarbazide and then the product reacted with ethychloroacetate.

These compounds have many applications in industrial field, agriculture, manufacturing and design of drugs. For example 2- thioxoimidazolidine -4- one derivatives have a variety of biological activity like antitumor, antiviral, antithyroidal [3][4][5] , metal complexes of thiohydantion the most favorable kinds as antitumor drugs because of a wide applications of these compounds. Very little work has been described the behavior of 2-thioxoimidazolidine-4-one and its derivatives with transition metal ions. Metal complexes of 2-thioxoimidazolidine-4-one derivatives most favorable due to their biological activity like antitumor[6].

The structure of thiohydantion and its derivatives exhibit distinctive modifications with different cations, so there have been studies about the structural relationship of these compounds and its derivatives and its metal chelates[7], thioxoimidazolidine molecules have thioamide portion and can suffer thione- thiol tautomerism because of they can be coordinated to metal ions from the lone electron pairs of the oxygen or sulfur or nitrogen atoms [8]. Thioxoimidazolidine compounds can act as neutral or charged ligand moieties.[12][13] The formation and interesting of metal ion complexes from these ligands indicates the amazing development in coordination and bioinorganic chemistry. In this study a thioxoimidazolidine derivatives and some of their metal ion complexes with amino acid were synthesized, then screened toward two type of bacteria (gram positive and gram negative bacteria to observe antibacterial activity of this derivative and its metal complexes.

Experimental

1. Instrumentation

The GC mass spectra were recorded on Shimadzu model GCMSQP 1000 EX Gas Chromatography-MS apparatus, ^{1}H-NMR spectra were obtained with the Varian 400 MHz spectrometer in d6 DMSO solution with the TMS as internal standard, melting point of all synthesized compound were predict using (a GallenkampMF B600 melting point apparatus), Accurate analysis of the elements (C.H.N.S) for ligand and its metal complexes were obtained with EA-034.mth. metal contents have been predicted using the Flame Atomic absorption Spectrophotometer Shimadzu-670 AA. The samples have been measured as CsI disks using a (4000-350)cm-2 FT-IR-8300 Shimadzu infrared spectroscopy. Magnetic Susceptibility measured using Sherwood Scietifi balance. Molar conductivity has been measured using platinum electrode Model MC-1-mark V.

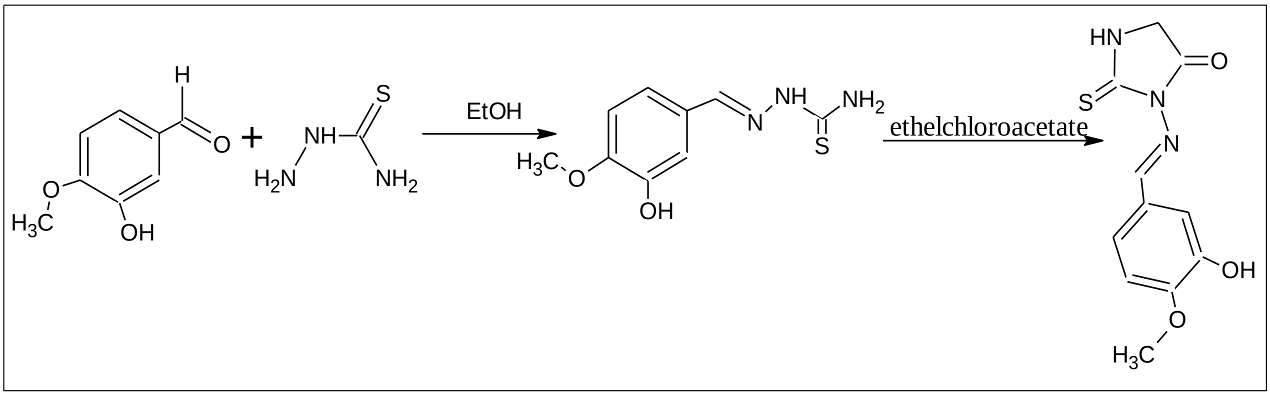
2. Materials and Methods

Synthesis of ligand (L)

Synthesis of Thiosemicarbazone (Shiff's base)

A solution of thiosemicarbazide (0.58gm, 0.0064 mol, 10mL of absolute ethanol) was added to the solution of (1g, 0.0064 mol in 10mL of absolute ethanol) of vanillin. The result mixture had been reflexed for few minutes then a drops of concentrated acetic acid was added, then reflexed for (6 h.). the product poured in crushed ice, filtered, dried and recrystallized from ethanol. (Mp = 196-198C). Scheme(1).

(0.00223mol ,0.5g) of pervious product was dissolved in absolute ethanol, then (0.3g, 0.00223mol) of ethylchloroacetate was added. The mixture was heated under reflux for (3h.), then filtered dried, and recrystallized from ethanol, (M.p =264-262C). Scheme(1).



Scheme (1): preparation of Ligand (L)

preparation of mixed ligand metal complexes (N_1-N_5)

Metal ion complexes were synthesized by reaction of mixed ligand (prepared ligand) and (amino acid) with divalent metal ions in the (1:1:1) molar ratio in ethanol media, The following metal ion salts ethanolic solution (0.1g, 0.00075mol) [$CuCl_2.2H_2O$, $NiCl_2.6H_2O$, $CoCl_2.6H_2O$, $ZnCl_2$, $CdCl_2$]. The ethanol solution of these metal ions had been added to a mixture of prepared ligand solution (0.2g, 0.00075mol) and the amino acid (glycin), (0.056 g, 0.00075 mol). the reaction mixture was reflux for (4h.), through this stage the precipitate was formed, then filtered and washed with absolute ethanol, then by cold distilled water and dried under oven.

Biological activity for ligand (L) and its metal complexes ion (N_1 –N_5)

The biological activity of ligand (L) and its mixed ligand metal complexes (N1-N5) have been screened on two categories of bacteria, ***(E.coli)*** as a gram- negative bacteria and ***(staphylococcus haemolyticus)*** as a gram positive bacteria. The disc sensitivity test ***(in vitro)*** techniques were performed for examine antibacterial (activity of ligand and its mixed ligand metal complexes against) these bacteria. used was DMSO as a control and solvent, (10^{-3}M) the concentrations of the compounds in the solvent . The process contains Inhibition Zone Exposition to the dissemination of bacteria on agar plate. These plates incubated for 24hr. at $37C^0$, (the inhibition zone of bacterial growth) about the disc was detected.

The Results and Discussion

1.The Elemental Analyses

"The results of physical and analytical measurement" referred to formation of all mixed ligand metal complexes. One of these measurements melting point, therefore all complexes have a higher melting points than the parent ligand. Table(1). While the results of metal content and metal analysis were satisfactory with the calculated value. Table(1). The novel mixed ligand metal ion complexes (N1-N5) were soluble in (DMSO, CH_2Cl_2, DMF, $CHCl_3$) and not soluble in (CH_3OH and CH_3COCH_3).

Table (1): *physical properties and elemental analysis of ligand and its mixed ligand metal ion complexes* (N1-N5)

Comp. Symbole	**General formula**	**Mwt g.mol-1**	**Color**	**M.P (°C)**	**Elemental analysis(%) Calc. (found)**				
					C	**H**	**N**	**S**	**M**
(L_1)	$C_{11}H_{11}N_3O_3S$	265	Orange	264	49.08 (49.11)	4.18 (4.15)	15.84 (15.66)	12.95 (12.99)	
Glycine	$C_2H_5NO_2$	75.07	White	260	32.00 (32.23)	6.71 (6.65)	18.62 (18.45)		
N1	$[Co(L1)(gly.)(H_2O)_2]Cl_2$.$_4H_2O$	510.57	Red	285	30.57 (30.48)	5.09 (4.54)	10.96 (18.45)	6.26 (3.19)	5.28 (5.52)
N2	$[Ni(L1)(gly)]Cl_2$.	403.57	Pale yellow	265	38.65 (38.54)	3.96 (3.92)	13.87 (10.75)	7.92 (7.88)	6.93 (7.88)
N3	$[Cu(L1)(gly.)]Cl_2$	404.57	Green	283	38.55 (38.47)	3.95 (3.93)	13.84 (13.76)	7.90 (7.82)	6.17 (6.19)
N4	$[Zn(L1)(gly.)]Cl_2.2H_2O$	441.57	Off white	272	35.32 (35.28)	4.52 (4.52)	12.68 (12.48)	7.24 (7.22)	6.79 (6.68)
N5	$[Cd(L1)(gly.)Cl_2].2H_2O$	459.57	Off white	290	33.94 (33.86)	4.35 (5.22)	12.18 (13.16)	6.96 (7.45)	10.44 (10.34)

2.*Mass spectrum of synthesized Ligand(L)*

The mother ion peak of the mass spectrum of ligand, (*m/z*=265), as a base peak, that was related to (M^+)[10] Figure (1).

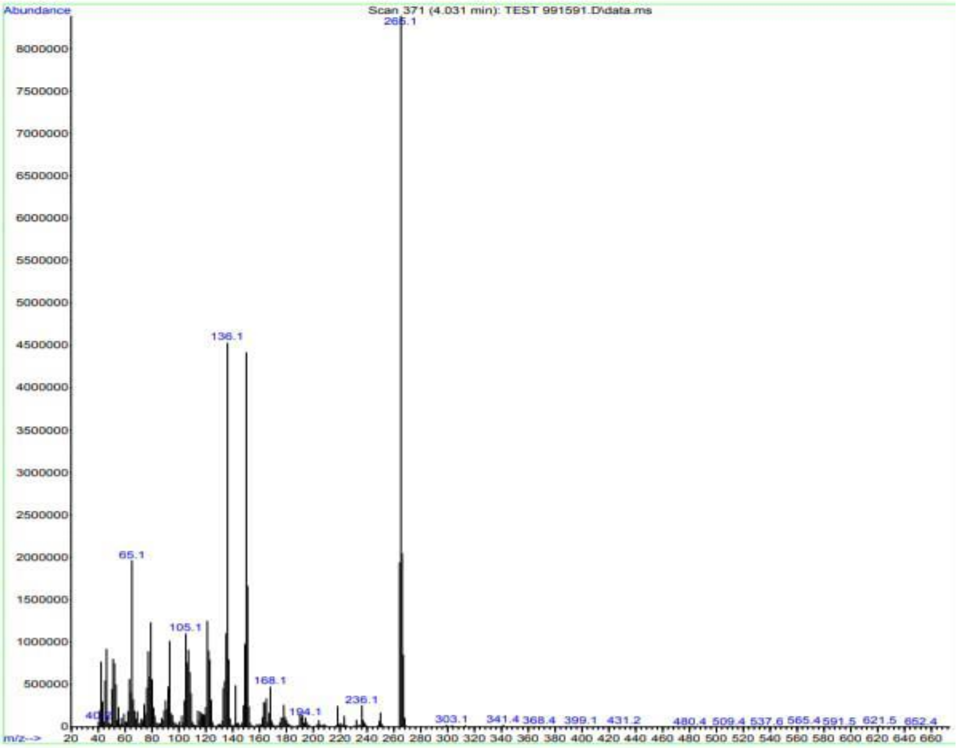
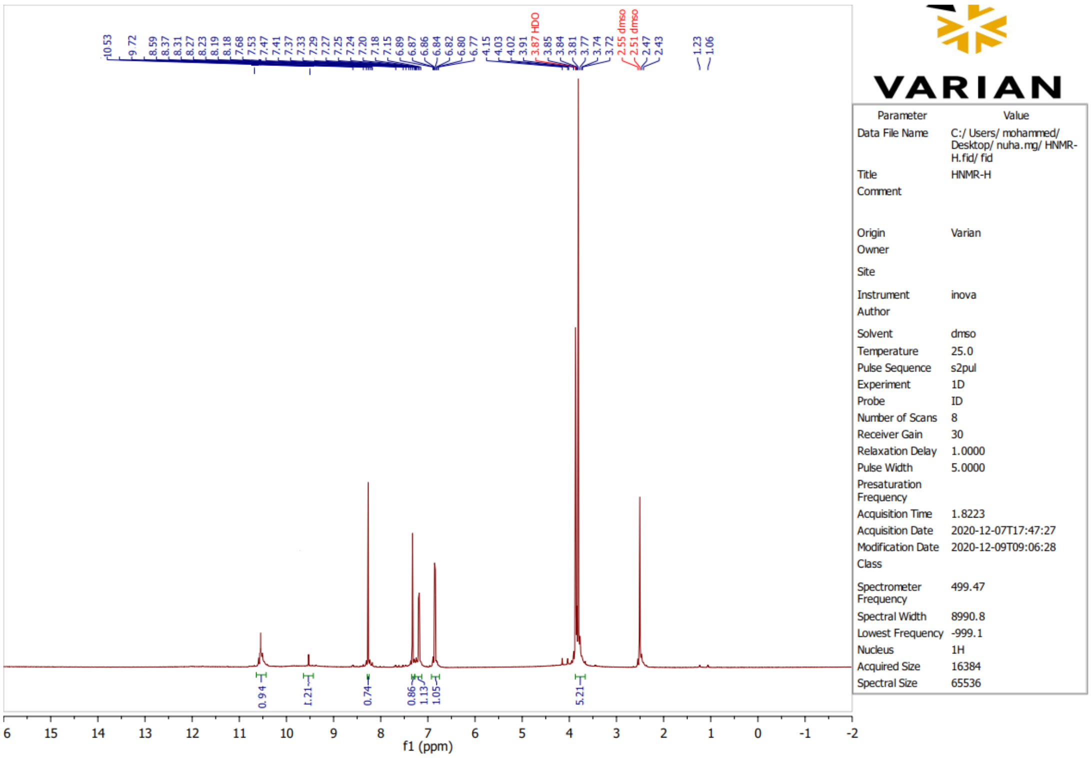


Figure (1):[Mass spectrum of the Ligand(L)]

3. ***^{1}H-NMR Spectrum of Ligand (L)***

^{1}H-NMR spectrum of synthesized ligand, figure (2), at DMSO-d6, displayed signals at (10.53ppm, 1H, 9.72ppm, 1H) related to (OH) group proton and (NH) group proton of imidazolidine ring respectively, while the signals at (8.59ppm, 1H, 7.20ppm, 1H and 6.89ppm, 1H) assigned to protons of aromatic ring, finally signals at (6.77, 1H, 3.81, 5H) belonged to (C-H) proton of Schiff bas, (CH_2) group protons of imidazolidine ring and (OCH_3) group protons respectively[11].



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Experiment	1D
Probe	ID
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Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	5.0000
Presaturation Frequency	
Acquisition Time	1.8223
Acquisition Date	2020-12-07T17:47:27
Modification Date	2020-12-09T09:06:28
Class	
Spectrometer Frequency	499.47
Spectral Width	8990.8
Lowest Frequency	-999.1
Nucleus	1H
Acquired Size	16384
Spectral Size	65536

Figure (2): ^{1}H-NMR spectrum of synthesized ligand (L) in DMSO-d_6

5. FTIR Spectra of ligand (L) and their metal complexes (N_1-N_5)

The free ligand showed band at (3257cm^{-1}) in FTIR spectrum due to ν(O-H) group, while band at (3209cm^{-1}) related to ν(N-H) group, also The spectrum showed another bands at (2939cm^{-1}) due to ν(C-H) aliphatic and (3126cm^{-1}) related to ν(C-H) aromatic While band at (1684 cm^{-1}) belonged to carbonyl group ν(C=O), this band undergoes a small variation in shape and position because of formation of metal complexes this indicate that this group was not participates in the coordination process[9].

υ(C=N) of Azomethine group appeared band at (1637cm^{-1}) in FTIR spectrum of the synthesized ligand , this group were shifted by(18 cm^{-1}) to highest wave number in all spectra of metal ion complexes.

A medium band of thion group ν(C=S) observed at (1033cm^{-1}) in FTIR spectrum of free ligand, this band was shifted by (20 cm^{-1}) to highest frequency in FTIR spectra of the metal ion complexes. From the changing in FTIR spectrum of the synthesized ligand deduce the ligand coordinated to all bidentate ions from Azomethine (C=N) group and thion (C=S) group and act as bidentate ligand [12].

FTIR spectrum of amino acid (glycine) showed band at (3279cm^{-1}) due to υ(OH) group, this band shifted by (30cm^{-1}) to highest wave number in all spectra of metal complexes , this indicate the (OH) group participate in coordination process. While a broad bands at (3151, 3167cm^{-1}) due to υ (NH_2) group, these bands were shifted to higher wave number by (23 cm^{-1}) in all spectra of metal complexes [N_1- N_5], propose that the amino acid was coordinated with the metal ion through nitrogen atom.

Band at (1606cm^{-1}) related to υ (C=O) group, this band was suffered small variation in shape and position as a result of coordination process this main that this group does not participate in coordination process.

A broad band at (3450 and 3430cm^{-1}) showed in (N_1, N_4) metal complexes indicating the presence of coordinated water in these complexes.

Table (2): FTIR spectral data (cm^{-1}) of synthesized ligand and its mixed ligand metal ion complexes

Comp.	*L*	*N1*	*N2*	*N3*	*N4*	*N5*	*Glycin*
(OH)	*3257*	*3551*	*3263*	*3385*	*3500*	*3500*	*3279*
υ(N-H)	3209	3126	3180	3149	3167	3100	
(NH_2)	_	3141 3247	3242 3247	3242 3247	3049 3247	3141 3157	3151 3167
(C-H) aliphatic	2939	2958	2789	2953	2970	2951	2820
(C-H) aromatic	3126	3126	2943	3068	2789	2779	3057
υ(C=O)	1552	1555	1155	11500	1555	1596	1606
C=N	1637	1647	1650	1649	1655	1649	_
C=S	1033	1023	10020	10049	10047	10043	_

6.*"The electronic spectra, magnetic and conductivity measurements*"

The electronic spectrum of ligand were recorded in the absolute ethanol, while, the spectra of all mixed ligand metal complexes recorded in ($CHCl_3$). The spectrum of the synthesized ligand displayed three bands at (220 nm, 41152cm^{-1}), (280 nm, 36363 cm^{-1}) were related to ($\pi\rightarrow\pi^*$) transitions, while band at (310nm, 39063 cm^{-1}) belonged to ($n\rightarrow\pi^*$) transitions[13]. The complexation process of mixed ligands [(L) and glycine] to divalent ions in the d-d and UV region showed anovel band. These new bands were characteristic to MLCT and to ligand field transitions[14] Table (3) refer to maximum absorption bands of mixed ligand metal ion complexes (N_1-N_5) in (CH_3Cl) with its assignments.

Uv/ visible spectrum of the **(N_1)** complex exhibited (two transitions) bands at (530 nm, 18868 cm^{-1}) and (410nm, 24390 cm^{-1}), that related to $^{4}T_{1}g\rightarrow{}^{4}A_{2}g_{(F)}$ **(ν_2)** and "$^{4}T_{1}g\rightarrow{}^{4}T_{1}g_{(P)}$ **(ν_3)** transitions respectively"[15]. The position of these band point to an octahedral geometry. While the first transition(**ν_1**) was calculated for **d^7** of (Tanaba- Sugano) diagram, it was (8108)cm^{-1} belonged to $^{4}T_{1}g\rightarrow{}^{4}T_{2}g_{(F)}$ transition. While (magnetic susceptibility) and measured conductivity showed that the complex has a paramagnetic properties (4.20 B.M) and electrolytic nature.

The spectrum of **(N_2)** complex, display two bands (600nm,14493cm^{-1}) and (420nm, 23810 cm^{-1}) allocated to $^{1}A_{1}g\rightarrow{}^{1}A_{2}g_{(F)}$ and $^{1}A_{1}g\rightarrow{}^{1}B_{1}g$ transitions[16]. While band at (380cm^{-1}, 26316 cm^{-1}) belonged to charge transfer transition, These bands point to a square planer geometry round Ni (II)ion [17]. Diamagnetic properties and conductivity measurements of this complex approve with a square planer geometry round Ni(II) ion[18].

Uv-vis spectrum of mixed ligand cupper complex (N3) showed one wide band at (697nm, 14347.20 cm^{-1}) which belonged to $^{2}B_{1}g\rightarrow{}^{2}B_{2}g+{}^{2}Eg$ transition, while shoulder band at (416nm, 24038 cm^{-1}) which related to $^{2}B_{1}g\rightarrow{}^{2}A_{1}g$ transition[18]. While band at (368nm, 27174 cm^{-1}) related to charge transfer transition. The location of bands is in a good approve with that described for highly distorted oct. geometry. Another indication for a square planer was value of magnetic moment (2.03 B.M), this value that coincide with this geometry round Cu(II) complex[19]. Conductivity measurement indicated that Cu complex has electrolytic behavior.

The electronic spectrum of Zn(II) off white complex (N4) no absorption bands shown at range (365-1000nm). This approve to no electronic transition was detected related to (d^{10}) in visible region that is a good result for Zn(II) tetrahedral complex [20]. The (Uv-Visible) spectrum of (N4) showed three bands at (259, 330 and 350nm) assigned to ($\pi \rightarrow \pi^*$), ($n \rightarrow \pi^*$) and (MLCT) transition respectively[14], the diamagnetic properties of this complex and conductivity measurements indicate ionic conducting behavior of it.

Uv-vis spectrum of cadmium complex **(N_5)** , [no (d-d) transition] is existing related to (d^{10}), the (Uv-Vis) spectrum of (N5) revealed three bands (230, 270 and 350nm), allocated to ($\pi \rightarrow \pi^*$), ($n \rightarrow \pi^*$) and ($M \rightarrow LCT$) transition respectively [3]. This approve with (O.h) geometry round Cd(II) ion [21], the measured conductivity showed nonionic behavior of this metal ion complex.

Table (3): Electronic spectra, Magnetic moment (B.M) and Conductance in (DMF) for (N_1-N_5) complexes

No.	**Maximum absorption υ_{max}(cm^{-1})**	**Band assignment**	**Molar Cond. S.cm^2.mol^{-1}**	**μeff. B.M**	**Suggested geometry**
(N_1)	18868 24390 8108	$^4T_1g \rightarrow -^4A_2g(F)$ $^4T_1g \rightarrow {}^4T_1g(P)$ $^4T_1g- \rightarrow {}^4T_2g(F)$	170	4.18	Octa hedral
(N_2)	14493 23810 26316	$^1A_1g- \rightarrow {}^1A_2g(F)(v2)$ $^1A_1g- \rightarrow {}^1B_1g$ M-LCT	167	0.00	Square planner
(N_3)	14347.20 24038 27174	$^2B_1g \rightarrow {}^2B_2g + {}^2Eg$ $^2B_1g \rightarrow {}^2A_1g$ M-LCT	168.85	2.03	Square planner
(N_4)	38610.04 30303.03 28571.43	$\pi \rightarrow -\pi^*$ $n \rightarrow \pi^*$ MLcT	172	0.00	Tetra hedral
(N_5)	43478.26 37037.04 28571.43	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$ MLCT	20.3	0.00	Octahedral

Suggested metal complex chemical structure (N_1-N_5)

The structure of the all mixed ligand complexes compounds can be shown in the following figures according to the results gotten from physical and analytical measurements.

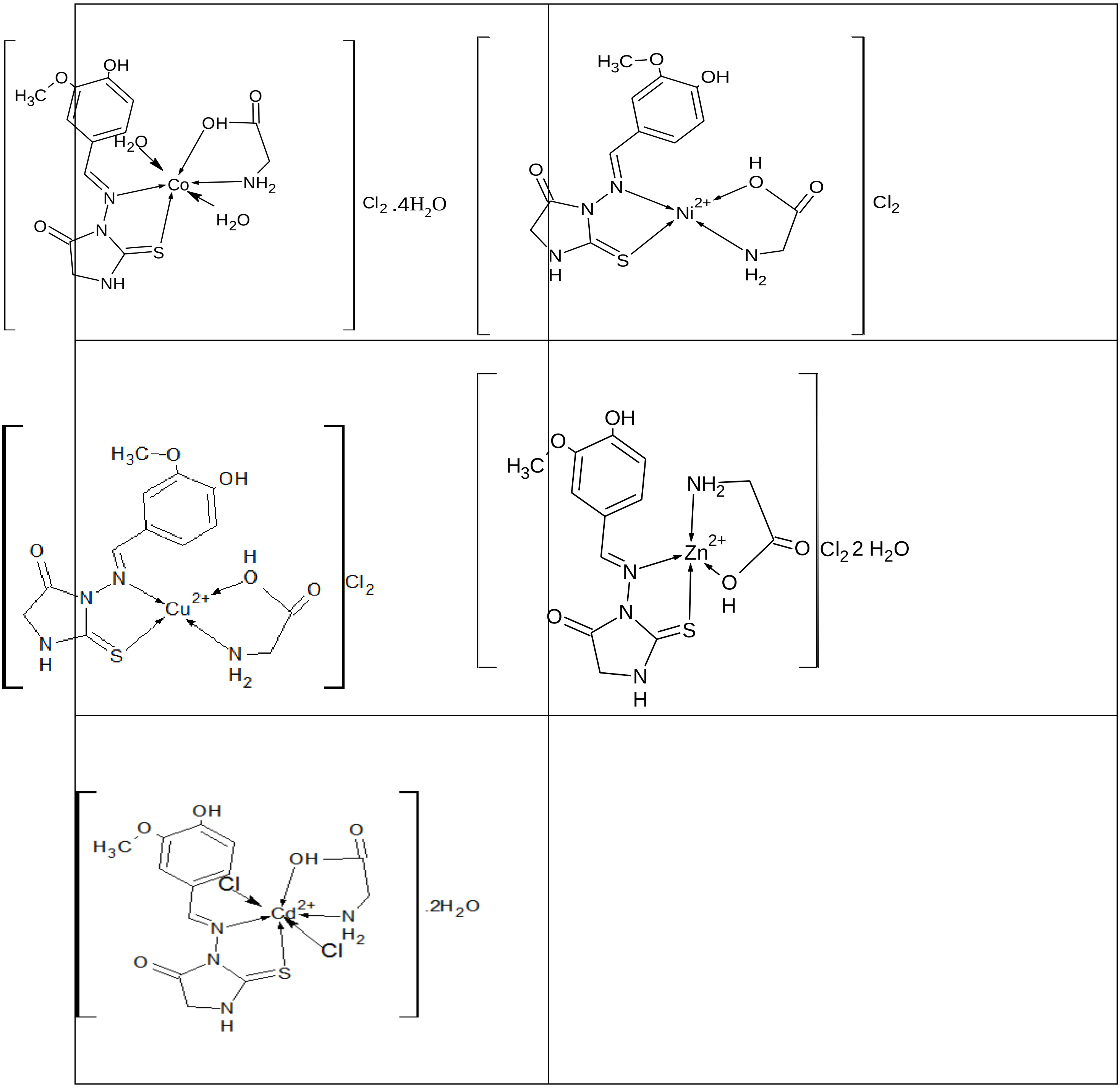

Figure (4): Suggested Chemistry Structure of Metal complexes (N$_1$-N$_5$)

Biological activity

The free ligand(L) was screened in ***vitro*** with its complexes (N1-N5) for the capacity to prevent representative [***(E. coli***) and (***Staphylococcus haemolyticus*** as a gram positive] growth are shown in the Table (4). as a solvent in DMSO, table (4). The following points were concluded as a result of the above studies:

1) the synthesized ligand was inactive against ***E.coli.***

2) All mixed ligand metal ion complexes except (N$_{1)}$ and (N4) were inactive against two types of bacteria .

3) complex (N1) show high antibacterial activity against *(**E.coli***) compared *(**staph***).

4) Finally complex (N4) display significant antibacterial activity against *(**E.coli***), but inactive against *(**staph***)

Table (4): Ligand (L) and its metal complexes (N1-N5) inhibition zone diameter "mm"

Comp. No.	***E. coli***	***Staph.***
Control DMSO	------	--------
(L)	NO inhibition	No inhibition
(N_1)	16	15
(N_2)	No inhibition	No inhibition
(N_3)	No inhibition	No inhibition
(N_4)	11	No inhibition
(N_5)	No inhibition	No inhibition

Conclusions

The new ligand of 2-thioxoimidazoline (L) and its mixed ligand metal complexes were synthesized and characterized in a simple method, the preparation process give a good yield. The structure of complexes were proven by many physical and analytical methods. Synthesized ligand (L) and its mixed ligand metal complexes showed low antibacterial activity, excepted cobalt and zinc mixed ligand complexes were displayed significant antibacterial activity.

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