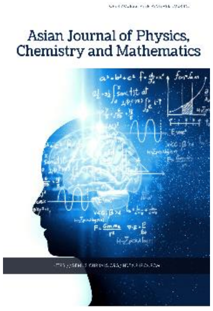

Metal complexes of mixed ligands novel 2- Thioxoimidazolidine-4- one derivative and glycine Synthesis, characterization and biological activity

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ABSTRACT

The present study, a new derivative of 2- thioxoimidazolidine-4- one (3-{(E)-[(4-bromophenyl)methylidene]amino}-2-sulfanylideneimidaz olidine -4-one) has been synthesized by the reaction of 4- bromobenzaldehyde with thiosemicarbazide then the resulting product reacted with ethylchloro acetate to produce the ligand. This ligand was characterized by elemental analysis (C.H.N.S) , (FT-IR) spectra, (UV-Vis) spectra and HNMR spectra. This ligand and amino acid have been used in the preparation of mixed ligand complexes using metal ions Cu(II), Ni(II), Co(II), Zn(II), and Cd(II) the synthesized complexes were characterized using all available technique such as, elemental analysis (C.H.N.S), atomic absorption spectroscopy, (FT-IR) spectra, (UV-Vis) spectra, conductivity measurement , and magnetic susceptibility. Finally The antibacterial activity of metal complexes have been studied in microorganisms such as **Escherichia coli** and **Staphylococcus haemolyticus**

Keywords: Thioxoimidazolidene compounds, metal complexes of thioxoimidazolidine ligands , mixed ligand complexes, amino acid complexes spectral data, antibacterial activity.

Introduction

The chemistry of thioxoimidazolidine has increased interest in synthetic organic chemistry, inorganic chemistry and biological fields.Thioxoimidazolidine is aheterocyclic compound , five- membered ring with two nitrogen atoms that contain two groups at position (2 and 4) thion (C=S) and carbonyl (C=O) groups [1] 2- thioxoimidazolidine-4-one are most known for its wide applications of these compounds many of synthetic methods have been developed to prepare 2-thioxoimidazolidine and its derivatives. Some of the most common methods are using α-amino acids with acetic anhydride followed by ammonium thiocyanate [2]and the coupling reaction between α-amino acid derivatives and isothiocyanate [7]. Other preparation methods to prepare these compounds include the reactions between thiourea and benzil [8], thiourea and α-halo acids [9], oxazolinone and thiocyanate [10], amino amide and diimidazole thiocarbonate [11], carbonyl compound with thiosemicarbazide and then the product reacted with ethychloroacetate [3].Thioxoimidazolidin as apeptide synthesis and structure determination intermidiates , also it is astructure part found in most natural products and is used as basic building block in the stnthesis of amino acids[4][5]. in drug development Thiohydantions are an important class of heterocyclic compounds because they have a wide range of biological properties, including antioxidant, antiparasitic, and antithyroid properties, and are used in a variety of applications such as textile printing, polymerization catalysts, resin and plastic production, and hypolipidemia[5][2][4].Very little work has been reported on 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], antibacterial, antifungal, anticarcinogenic [3], antimutagenic [4], antithyroidal,The structure of thiohydantion and its derivatives exhibit distinctive differences with different cations, so there have been studies concerning the structural relationship of these compounds and its derivatives and their metal chelates[7], thioxoimidazolidine molecules contain thioamide fragment and can undergo thione-thiol tautomerism due to which they can be coordinated to metal ions through the lone electron pairs of the nitrogen or sulfur or oxygen atoms [4]. 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 derivative 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

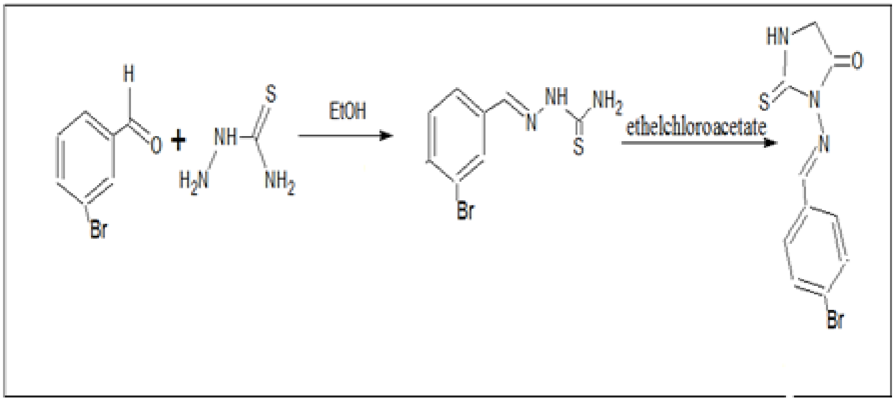
Melting points were recorded on a GallenkampMF B600 melting point apparatus. Elemental analyses (C.H.N.S) were obtained using EA-034.mth. for ligand and their metal complexes. Metal contents of complexes were estimated,Spectrophotometrically using Flame atomic absorption Shimadzu-670 AA Spectrophotometer. Infrared spectra were recorded using FT-IR-8300 Shimadzu in the range of (4000-350)cm^{-1}, samples were measured as (CsI) disc. Magnetic susceptibilities of samples in the solid state were measured by using Magnetic Susceptibility Balance of Sherwood Scietifi. The molar conductivity was measured by using Electrolytic Conductivity Measuring set Model MC-1-Mark V by using platinum electrode(EDC 304) with cell constant(1cm^{-1}), concentration (10^{-3} M) in dimethylformmide as a solvent at room temperature. Electronic spectra were obtained using UV-1650PC-Shimadzu Spectrophotometer at room temperature, the measurement were recorded using a concentration of (10^{-3}M) of the ligand and its metal complexes.

2- Materials and Methods

All chemical were of highest purity and were used as received.

Synthesis of ligand (L)

A solution of thiosemicarbazide (0.58gm, 0.0054 mol, 10mL of absolute ethanol) was added to the solution of (1g, 0.0054 mol in 10mL of absolute ethanol) of 4-bromobenzaldehyde . The resulting mixture were reflexed for few minutes and then drops of concentrated acetic acid was added. The mixture heated under reflux for (6 h.), the reaction mixture cooled and poured into crushed ice, the resulting solid produced was filtered, dried and recrystallized from ethanol. (Mp = 226-224C^0). Scheme(1).***(***0.00168mol ,0.5g) of pervious product was dissolved in absolute ethanol, then (0.205g, 0.00168mol) of ethylchloroacetate was added. This mixture was heated under reflux for (3h.), the resulting solid product was filtered , dried and recrystallized from ethanol , (M.p =274-272C). Scheme(1).



Scheme (1): Synthesis of Ligand (L)

Preparation of metal complexes (M_1-M_5)

Metal complexes have been synthesized by the reaction of mixed ligand (prepared ligand) and (amino acid) with divalent metal ions in the (1:1:1) molar ratio in ethanol media , an ethanolic solution of the following metal ions salts (0.1g, 0.00075mol) [$CuCl_2.2H_2O$, $NiCl_2.6H_2O$, $CoCl_2.6H_2O$, $ZnCl_2$, $CdCl_2$] was added to the ethanolic solution of 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 time the precipitate was formed, then, filtered and washed several times with hot absolute ethanol , and then by cold distilled water , dried under the oven , the prepared metal complexes were thermally stable. Can be stored at room temperature and unaffected by moisture.

4.Study of biological activities for (L) ligand and their Metal Complexes(M_1 –M_5)

The biological activities of the prepared ligand (L) and their metal complexes (M_1-M_5) were studied against two types of bacteria which include ***(E.coli)***as agram- negative bacteria and ***(staphylococcus heamolyticus)*** as agram –positive bacteria cultivated in Nutrient agar medium, DMSO was used as a solvent and as a control, the concentration of the compounds in this solvent were (10^{-3}M).

Results and Discussion

1:Elemental Analyses

The physical and analytical data of the ligand (L) and its metal complexes (N_1-N_5) are given in Table (1). The results obtained from elemental analysis are in acceptable agreement with the calculated value. The new complexes (M_1-M_5) were soluble in (CH_2Cl_2, $CHCl_3$, DMF and DMSO). They are thermally stable and unaffected by and moisture.

Table (1):Some Physical properties and elemental analysis of ligand and its metal complexes (M_1-M_5)

Comp. Symbol	General formula	Mwt. $g.mol^{-1}$	Color	M.p	Elemental analysis(%) Found(calc.)				
					C	H	N	S	M
L	$C_{10}H_8$ OBr N_3S	297	Yellow	274-272	40.40 (40.35)	2.69 (2.72)	14.14 (14.20)	10.77 (10.80)	-
M_1	$[Co(L_2)(gly.)Cl_2]._2H_2O$	452.57	Brown	285	31.80 (31.85)	3.7 (3.10)	12.3 (12.59)	7.0 (7.15)	5.9 (5.12)
M_2	$[Ni(L_2)(gly)]Cl_2.2H_2O$	471.57	Yellow	265	30.53 (30.56)	3.61 (3.63)	11.87 (11.92)	6.81 (6.79)	6.4 (6.9)
M_3	$[Cu(L_2)(gly.)]Cl_2$	436.57	Green	283	31.98 (31.95)	3 (3.05)	12.82 (12.80)	7.32 (7.30)	6.64 (6.66)
M_4	$[Zn(L_2)(gly.)Cl_2]$	437.57	Off white	272	32.90 (32.92)	2.9 (2.12)	12.79 (12.82)	7.31 (7.35)	6.85 (6.87)
M_5	$[Cd(L_2)(gly.)(H_2O)_2]Cl_2$	491.57	Off white	290	29.29 (29.32)	3.45 (3.47)	11.39 (11.43)	6.50 (6.52)	9.76 (6.74)

Dec= decomposition

2: Mass spectrum of Ligand(L)

The mass spectrum of ligand (L) figure (1), showed the mother ion peak at (m/z=299), as a base peak, which is corresponds to (M^+).

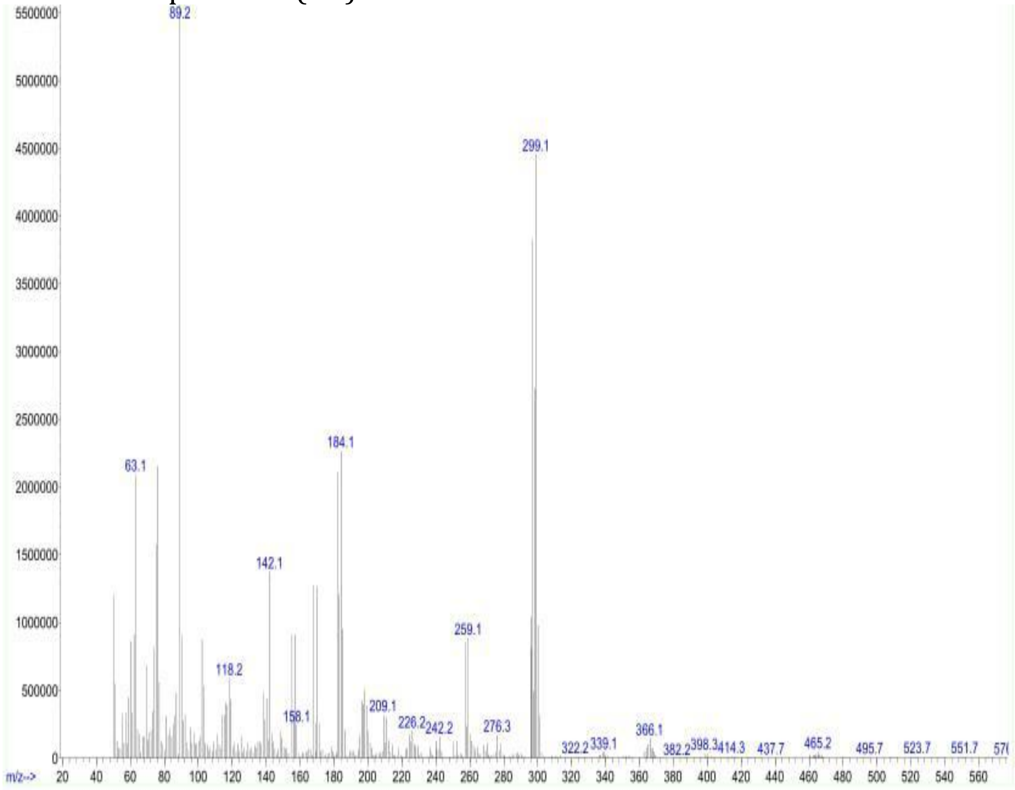
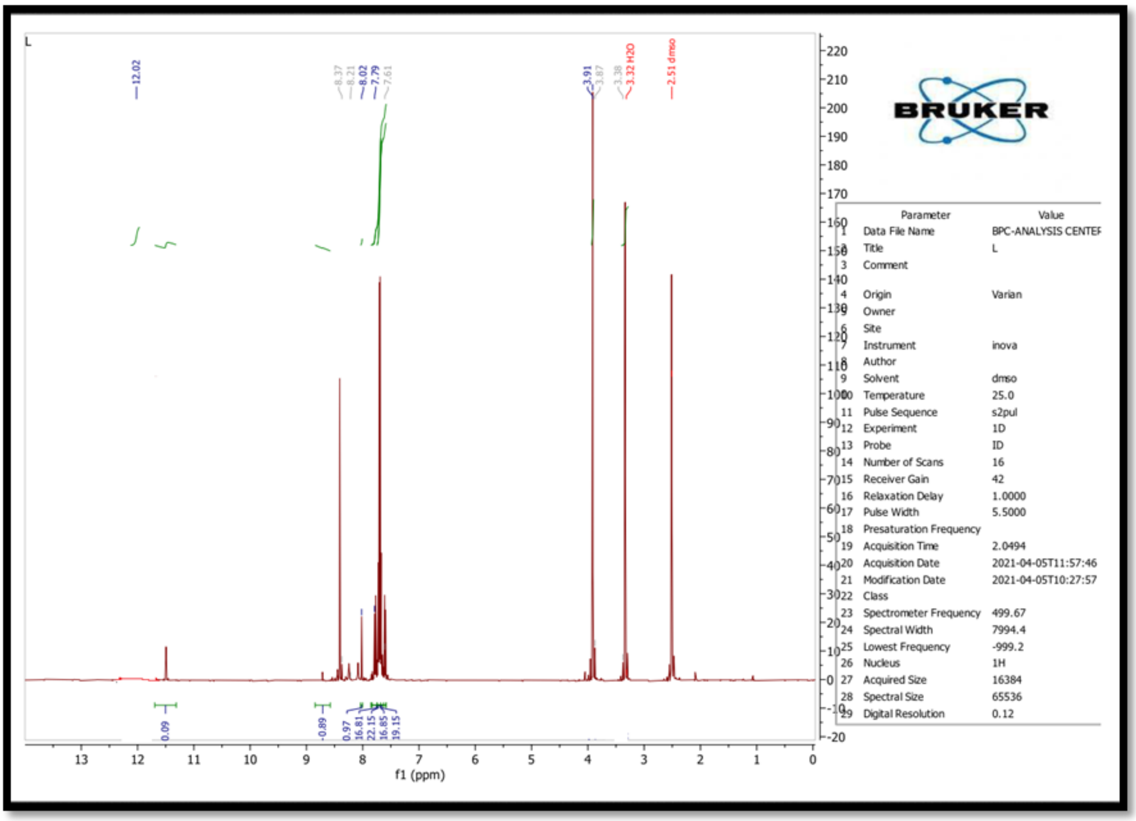


Figure (1): Mass spectrum of Ligand(L)

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

H-NMR spectrum of (L2), Figure (3.8) in (DMSO-d6) showed the signals at (11.5ppm) 1H for (NH) group of imidazolidine ring, and (8ppm) 4H related benzene ring and (9.3ppm,1H) proton of Schiff base and signals at (2.5ppm,2H) for (CH_2) group of thioxoimidazolidin ring

, fig.(2)[8].



	Parameter	Value
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2	Title	L
3	Comment	
4	Origin	Varian
5	Owner	
6	Site	
7	Instrument	inova
8	Author	
9	Solvent	dmso
10	Temperature	25.0
11	Pulse Sequence	s2pul
12	Experiment	1D
13	Probe	ID
14	Number of Scans	16
15	Receiver Gain	42
16	Relaxation Delay	1.0000
17	Pulse Width	5.5000
18	Presaturation Frequency	
19	Acquisition Time	2.0494
20	Acquisition Date	2021-04-05T11:57:46
21	Modification Date	2021-04-05T10:27:57
22	Class	
23	Spectrometer Frequency	499.67
24	Spectral Width	7994.4
25	Lowest Frequency	-999.2
26	Nucleus	1H
27	Acquired Size	16384
28	Spectral Size	65536
29	Digital Resolution	0.12

Figure (2): 1H-NMR spectrum of (L) in DMSO-d$_6$

5. FTIR Spectra of ligand (L) and their metal complexes (M_1-M_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. 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 showed 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 υ (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[10]

FTIR spectrum of amino acid (glycine) showed abroad bands at (3151, 3167cm^{-1}) due to N-H(asymmetric) and N-H(symmetric) vibrations of free amino acid moiety are shifted to higher wave numbers,in the range 3279-3265cm^{-1} and 3150- 3125cm^{-1}, respectively in the spectra of metal complexes , suggesting coordination of the amino group through nitrogen with the metal ion.The asymmetric υ (COO-) band of the free amino acid, that is 1610-1590cm^{-1} group,is shifted to lower wave number , in the range of 1571-1566cm^{-1}, and the symmetric υ(COO-) mode observed at ~1400cm^{-1} in the spectra of free amino acids is found to be shifted to lower wave number 1378cm-1, in the spectra of complexes indicating the coordination of the carboxylic acid group through Oxygen with the metal ions in all complexes, A broad band at (3450 and 3430cm^{-1}) showed in (M_1, M_4) metal complexes indicating the presence of coordinated water in these complexes.

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

Comp.	L	M_1	M_2	M_3	M_4	M_5	Glycine
(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	1683	1712	1710	1691	1699	1606
C=N	1637	1635	1641	1639	1637	1641	_
C=S	1033	1037	1008	1008	1037	1037	_

6. Electronic absorption spectra, Magnetic susceptibility, and Conductivity measurements

The (U.V-Vis) spectrum of ligand, in absolute ethanol exhibited three absorption bands at (250 nm, 40000.00 cm^{-1}), (270 nm, 37037.04 cm^{-1}) were assigned to ($\pi \rightarrow \pi^*$) transitions , and band at (340 nm, 29412 cm^{-1}) assigned to ($n \rightarrow \pi^*$) transitions[11]Complexation of (L) with metal ions appearance a new bands in the visible and UV. These bands were attributed to M-L charge transfer and to ligand field transitions[12] Table (3) describes bands of maximum absorption of (M_1-M_5) complexes in chloroform with their assignments

The electronic spectrum of the cobalt complex(M_1) showed two transition at (500nm,20000.00cm^{-1}) and (401nm,24937cm^{-1}) which might be assigned to the transition ($^4T_{1}g \rightarrow {}^4A_{2}g$)(F)($v_2$) , and($^4T_{1}g \rightarrow {}^4T_{1}g$) (P)($v_3$) respectively[13]

these indicate an (octahedral geometry) but the first transition (v_1) due to the transition ($^4T_{1}g \rightarrow {}^4T_{2}g$)(F) did not appear. The magnetic susceptibility and molar conductivity measurement indicated that the complex to be a paramagnetic (4.18 B.M) and non-ionic behavior

The electronic spectrum of nickel complex (M_2) showed two bands. at (521nm, 19193cm^{-1}) and (349nm, 28653.30cm^{-1}) assigned to$^1A_{1}g \rightarrow {}^1A_{2}g$ (f) and $^1A_{1}g \rightarrow {}^1B_{1}g$ transition , while band at (329nm, 30395.14cm^{-1}) belonged to charge transfer transition , these bands refers to a sequare planer geometry around Ni(II) [1]the diamagnetic properties and conductivity measurements of this complex indicate with a sequare planer geometry around Ni(II) ion[8][14] .

The electronic spectrum of cupper complex (M_3) shows one broad band at (750nm, 13333.33 cm^{-1}) which corresponds to $^2B_{1}g \rightarrow {}^2B_{2}g$+ ^2Eg transition, and a shoulder band at (469nm, 21321.96 cm^{-1}) which assigned to $^2B_{1}g \rightarrow {}^2A_{1}g$ transition[15]. While band at (368nm, 27174 cm^{-1}) related to charge transfer transition.also band at(368nm, 27174cm^{-1})related to charge transfer transition . (The position of bands is in a good approve with that described for highly distorted octahedral geometry. The value of magnetic moment at room temperature was found to be (2.03 B.M), which agree well with square planer geometry around Cu (II) complex[16] Conductivity measurement in DMF showed that the complex has electrolytic nature.

The electronic spectrum of Zinc complex Zn(II) off white complex (M_4) no absorption bands shown at range (365-1000nm).This indicate no transition is located which belongs to (d10) in visible region that is a good result for Zn(II) octahedral complex [9], the prepared complex is an off white in color with the diamagnetic being expected [17]

The (Uv-Vis) spectrum of (M_4) in ($CHCl_3$) showed three bands at (259, 280, 350nm) respectively assigned to ($\pi \rightarrow \pi^*$) ($n \rightarrow \pi^*$) and (M→LCT) transition [12], the conductivity measurements indicate non conductivity behavior of the complex .

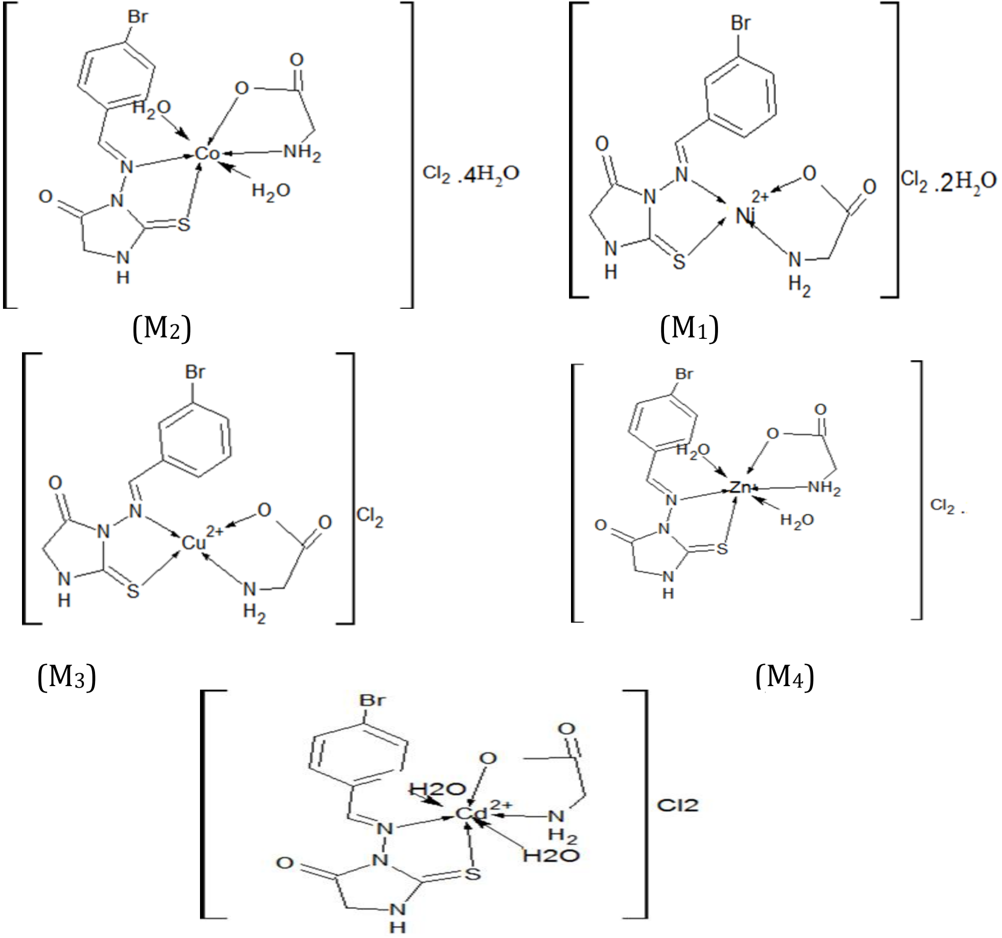
The electronic spectrum of cadmium complex **(**M_5**)** , no (d-d) transition is located belongs to (d10) , the (Uv-Vis) spectrum of (M_5) in ($CHCl_3$), displayed three bands (277, 256, 311 nm) respectively , assigned to ($\pi \rightarrow \pi^*$) , ($n \rightarrow \pi^*$) and (M→LCT) transition[1].This agree with octahedral geometry around Cd(II) ion [18], the conductivity measurements indicate ionic conducting of the complex .

Table (3): Electronic spectra, Magnetic moment (B.M) and Conductance in (DMF) for (M_1-M_5) complexes

No.	Maximum absorption υ_{max}(cm^{-1})	Band assignment	Molar Cond. $S.cm^2.mol^{-1}$	μeff. B.M	Suggested geometry
M_1	20000.00cm^{-1} 24937.66cm^{-1}	${}^4T_1g \rightarrow {}^4A_1g(F)$ ${}^4T_1g \rightarrow {}^4T_1g(p)$	18.11	4.18	O.h
M_2	19193cm^{-1} 28653.30cm^{-1}	${}^1A_1g \rightarrow {}^2A_2g(F)$ ${}^1A_1g \rightarrow {}^1B_1g$	172.48	0.00	S.p
M3	13333.33cm^{-1} 20408.16cm^{-1} 2941176cm^{-1}	${}^2B_1g \rightarrow {}^2B_2g+\ 2Eg$ ${}^2B_1g \rightarrow {}^2A1g$ M → LCT	186.51	2.03	S.p
M_4	38610cm^{-1} 35714.29cm^{-1} 28571.43cm^{-1}	$\pi \rightarrow \pi^*$ $n \rightarrow \pi$ M→ LcT	17.25	0.00	O.h
M_5	36101.08cm^{-1} 39062.50cm^{-1} 32154.34cm^{-1}	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$ M →LCT	172.58	0.00	O.h

Suggested Chemistry Structure of Metal complexes (M_1-M_5)

According to the results obtained from elemental and spectral analysis as well as magnetic moment and conductivity measurements, the structure of the above mentioned compounds can be illustrated as follows, figure(4).



(M2) (M1)

(M3) (M4)

(M5)

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

Biological Studies

The free ligand (L) and its complexes (M$_1$-M$_5$) were screened in vitro for their ability to inhibit the growth of representative ***[(E.coli***)as gram negative] and [(***Staphylococcus haemolyticus*** as gram positive] are shown in table (4). in DMSO as a solvent, table(4). As a result from the above mentioned studies, the following points were concluded:-

1)(L) was inactive against ***E.coli*** and ***staph*** .

2) complexes (M$_3$) ,(M$_4$) (M$_5$) showed good aresult biological activity against two types of bacteria

3) complex (M$_3$) show high effect against (***E.coli***) compared (***staph***).

4) complex (M$_4$) show active against (***E.coli***) , compared against activity ***(staph***).

5) complex (M$_5$) showed highest avtivity against (***E.coli***) compared (***staph***) bacteria

Table (4): Antibacterial activities for ligand (L) and their metal complexes (M$_1$-M$_5$) inhibition zone diameter"mm"

Comp. No.	***E. coli***	***Staph.***
Control DMSO	-	-
(L)	NO inhibition	No inhibition
(M$_1$)	No inhibition	No inhibition

(M_2)	No inhibition	No inhibition
(M_3)	15	11
(M_4)	17	12
(M_5)	25	19

Conclusions

The new 2-Thioxoimidazoliine (L) ligand and its metal complexes were successfully synthesized and characterized. The mode of bonding and overall structure of the complexes was determined through physio-chemical and spectroscopic methods. Hyperchem-8 program has been used to predict structural geometries of all compounds in gas phase. The free ligand (L) and its metal complexes show significant antimicrobial activity. The all complexes are found more effective than the free ligand.

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