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Research Article

Spectra Characterization, In vitro Evaluation of Antibacterial and Hemolytic Activity of Novel Ligand 5-(5-{(2Z)-2-[(2-Hydroxynaphthalen-1- yl)Methylidene]Hydrazinyl}-1,3,4-Oxadiazol-2-yl)Benzene-1,2,3-Triol with some its Transition Metal Complexes

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ABSTRACT

A new series of transition metal (Cr(III), Co(II), Ni(II)and Cu(II) complexes of ligand 5-(5-{(2Z)-2-[(2-hydroxynaphthalen-1- yl)methylidene]hydrazinyl}-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol were synthesized and evaluated for its biological activities. A ligand was synthesized by reaction propyl gallate and hydrazine hydrate in presence of ethanol to give 3, 4, 5- trihydroxybenzohydrazide followed by reaction with potassium hydroxide and carbon disulfide, the resultant was mixed with hydrazine hydrate to produce the ligand. The newly synthesized compounds were characterized by Fourier transform infrared (FTIR)Spectroscopy, Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR), elemental analyses (C, H, N), mass spectral, conductivity measurement, and magnetic susceptibility data. The Hyperchem 7.51 program have been used to draw the ligand geometry optimization and then study the electrostatic potential that given right data about the active site. Antibacterial activity and hemolysis assay of prepared compounds were studied. Antibacterial activity was carried out against *Escherichia coli*, *Salmonella*, and *Staphylococcus aureus* with test compounds at four concentrations of (50,100,250,500µg/ml). Erythromycin was the standard drug utilize. Some of these compounds showed good efficacy, while others ranged from medium to small.

Keyword: 1,3,4-oxadiazole derivative, Antibacterial activity, hemolysis, electrostatic potential.

INTRODUCTION

The history of heterocyclic chemistry started in early 1800s and flourished rapidly with the aid of organic synthesis tools. Heterocyclic compounds comprise the largest division of organic chemistry, which show broad range of pharmacological applications. About two third of organic compounds are heterocyclic in nature[1]. One such important heterocyclic nucleus of medicinal use is oxadiazole. There are four isomers of oxadiazole.

1,3,4-oxadiazol is an important one of these isomers because of its various activities. The capacity of 1, 3, 4-oxadiazole nucleus to undergo variety of chemical reaction have made it medicinal backbone for a large number of medical compound[2-5]. 1,3,4-Oxadiazole has become an important construction motif for the development of new drugs because of its biological activities including anti-inflammatory[6], anticancer[7], antimicrobial[8], cytotoxic[9], anticonvulsant[10], antimalarial[11]. Apart from the biological applications of 1,3,4-oxadiazoles, these are also used as useful oxidation inhibitors[12], important structural motifs in cyanine dyes[13], metal chelating agents and corrosion inhibitors[14].

EXPERIMENTAL

Preparation of the Ligand (L)

Step I: Synthesis of 3,4,5-trihydroxy Benzohydrazide (Galloyl hydrazide)

Propyl gallate (0.05 mol) and hydrazine hydrate (0.1 mol) were mixed gently and heated under reflux for 4 hrs with 100 ml of absolute ethanol[15]. The crude product was filtered and washed with ethanol to give the desired product 3,4,5-Trihydroxybenzohydrazide (A).(m.p:120-122 ºC .

Step II: Synthesis of 5-(5-mercapto-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

A mixture of 3,4,5-trihydroxybenzohydrazide (0.033mol) and (0.033 mol) of potassium hydroxide with 100 ml from ethanol was heated until potassium hydroxide dissolved . The mixture was then cooled at 0 ºC, then (0.033 mol) from carbon disulphide was added. The mixture was heated under reflux for 24 hrs. The resultant mixture was concentrated, and carefully acidified with hydrochloric acid HCl(5%) to give brown precipitate.

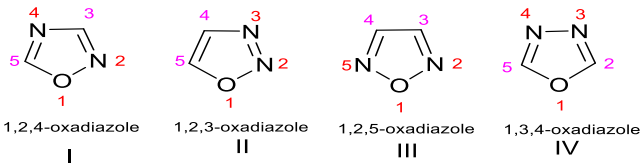

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Table 1: Diameter of the Inhibition Zone (mm) of ligand.

Compound	Concentration (µg/ml)	Type of bacteria	Inhibition zone (mm)
L	50	*Salmonella*	12
L	100	*Salmonella*	11
L	250	*Salmonella*	13
L	500	*Salmonella*	13
Erythromycin	15	*Salmonella*	13

Table 2: Diameter of the Inhibition Zone (mm) of $[Cr(L)_2Cl_2]Cl$.

Compound	Concentration (µg/ml)	Type of bacteria	Inhibition zone (mm)
$[Cr(L)_2Cl_2]Cl$	50	*Salmonella*	18
$[Cr(L)_2Cl_2]Cl$	100	*Salmonella*	15
$[Cr(L)_2Cl_2]Cl$	250	*Salmonella*	17
$[Cr(L)_2Cl_2]Cl$	500	*Salmonella*	No inhibition
Erythromycin	15	*Salmonella*	13

Table 3: Diameter of the Inhibition Zone (mm) of $[Cr(L)_2Cl_2]Cl$.

Compound	Concentraion (µg/ml)	Type of bacteria	Inhibition zone (mm)
$[Cr(L)_2Cl_2]Cl$	50	*Staphylococcus aureus*	No inhibition
$[Cr(L)_2Cl_2]Cl$	100	*Staphylococcus aureus*	No inhibition
$[Cr(L)_2Cl_2]Cl$	250	*Staphylococcus aureus*	No inhibition
$[Cr(L)_2Cl_2]Cl$	500	*Staphylococcus aureus*	13
Erythromycin	15	*Staphylococcus aureus*	12

Table 4: Diameter of the Inhibition Zone (mm) of $[Ni(L)Cl_2]$.

Compound	Concentration (µg/ml)	Bacteria	Inhibition zone (mm)
$[Ni(L)Cl_2]$	50	*Salmonella*	No inhibition
$[Ni(L)Cl_2]$	100	*Salmonella*	16
$[Ni(L)Cl_2]$	250	*Salmonella*	15
$[Ni(L)Cl_2]$	500	*Salmonella*	14
Erythromycin		*Salmonella*	13

then the crude product was filtered and the crystal was recrystallized from ethanol absolute [16], to give the product 5-(5-mercapto-1,3,4-oxadiazole (B) as brown solid, (yield 84%), m.p.(206-208) .

Table 5: Inactive compounds.

Compound	Concentration (µg/ml)	Inhibition zone (mm)
$[Co(L)]Cl_2]$	50,100,250,500	No inhibition
$[Cu(L)Cl_2]$	50,100,250,500	No inhibition

Step III: Synthesis of 5-(5-hydrazinyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

A mixture B (0.035 mol) (7.9 gm) and hydrazine hydrate (0.035 mol)(1.1 ml) dissolved in (50 ml) of ethanol and reflux for (19 hrs) .The crude product was concentrated and then cooled[17].Solid product was filtered and recrystallized from ethanol to give the product (5-(5-hydrazinyl -1,3,4-oxadiazol- 2-yl)benzene -1,2,3-triol) (C) as brown solid , yield (84%), m.p. (215^0C).

Step IV: -(5-{(2Z)-2-[(2-hydroxynaphthalen-1-yl)methylidene]hydrazinyl}-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

A mixture(C) (0.02mol, 3.8gm) and p-Chloro benzaldehyde was refluxed for (5hrs),the solution is evaporated to half and filtered, the crystallized using absolute ethanol to give crystals of brown color product . Yield: (94%), m.p.(315 ^{0}C), scheme (1).

Preparation of Complexes

The Cr(III), Co(III), Ni(II) and Cu(II) complexes were prepared by refluxing the respective hydrated metal chloride (0.0009mol) in 15 ml ethanol with 50 ml of an ethanolic solution of the ligand (0.0009 mol, 0.3 gm) for 2 hrs. The separated solids were filtered and washed with ethanol to removed unreacted salts or ligand, then precipitated complexes dried in air[18].

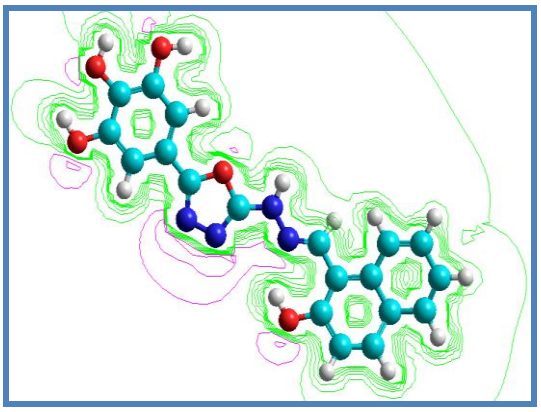
Biological activity

Antibacterial activity measurement

terial isolates which selected for this study were grow overnight or to stationary phase. At the day of the test, the cultures diluted and back to grow to mid-log phase, around an OD of 0.5. While that, a stock solution of the compound to be tested was prepared, and a control antibiotic was provided. A serial dilution of the ligand and its complexes prepared for evaluate which concentration give a powerful action against selected strain of bacteria. A bacterial lawn was performed on plates of Muller Hinton agar and a cup diffusion method was used by making a hole in the Muller Hinton agar plates by a corkscrew then 100 µl of the different concentrations of the compound was added to the holes in addition to use the antibiotic erythromycin as positive control and normal saline as negative control. After incubation of the plates at 37 ºC for 24 hr., the result of inhibition was observed and the diameter of inhibition zone was measured.

Hemolysis assay

The hemolysis assay is used to determine the hemolytic effect of a test compound. The Hemolysis assay was done as described by Henkelman.S. *et al*[19] 5mL of blood was collected in the tubes containing 3 mg of EDTA to prevent coagulation and centrifuged at 1000 rpm for 10 min at 40C. Plasma was removed carefully and the white buffy layer was completely removed by aspiration with a



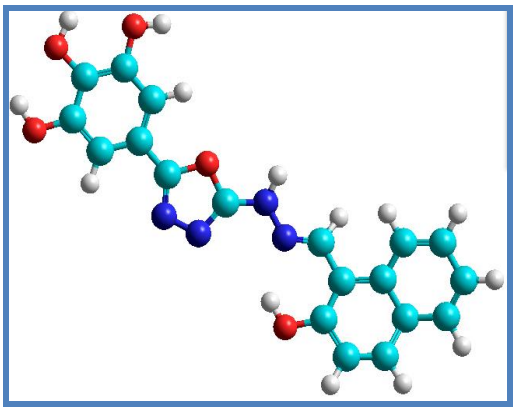


Figure 1: Electrostatic potential 2D for Ligand.

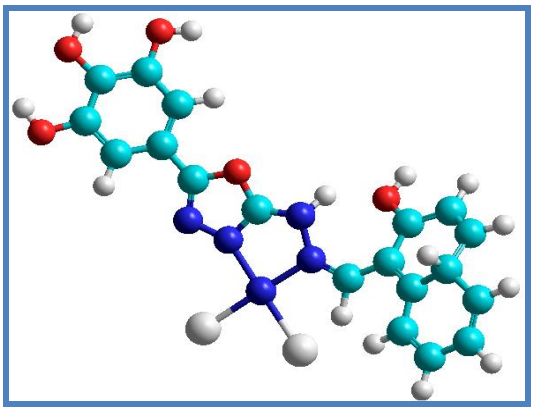


Figure 2: $[Co(L_2)]Cl_2]$

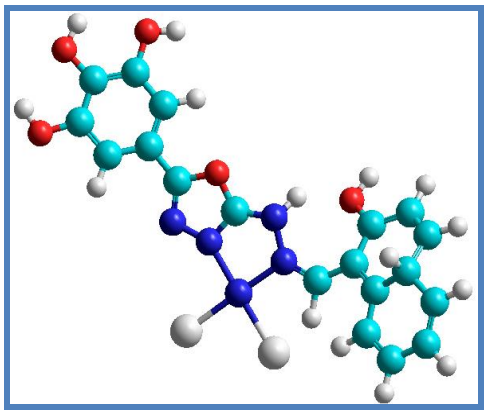


Figure 3: $[Ni (L) Cl_2]$

Table 6: Hemolytic assay of the ligand and its complexes.

Compound	Concentration (µg/ml)	Absorbance at 540 nm	Hemoly **%** sis
Positive control		1.822	99
Negative control		0.914	0
L	50	0.397	78.2
L	100	0.436	76.1
L	250	0.210	88.475
L	500	0.042	97.8
$[Cr(L)_2Cl_2]Cl$	50	o.118	93.52
$[Cr(L)_2Cl_2]Cl$	100	1.055	42.1
$[Cr(L)_2Cl_2]Cl$	250	0.313	82.82
$[Ni(L)Cl_2]$	100	0.837	54.1
$[Ni(L)Cl_2]$	250	0.112	93.85

pipette with extreme care. The erythrocytes were then washed for additional three times with 1X PBS, pH 7.4 for 5 min. 50 uL of 10 dilution (100 uL Erythrocytes suspension: 900 uL 1XPBS) of erythrocytes suspension was taken and mixed with 100 uL of test samples. 100 uL of 1XPBS was used as negative control and 100 uL of triton-X100 as positive controls. Reaction mixture was incubated at 37^0C water bath for 60 min. Then the volume of reaction mixture was made up to 1 ml by adding 850 uL of 1XPB. Finally it was centrifuged at 300rpm for 3min and the resulting hemoglobin in supernatant was measured at 540 nm by spectrophotometer to determine the concentration of hemoglobin. The percentage hemolysis was calculated as follows:

% Hemolysis inhibition= 100-[Sample / Control] x 100

Experimental Section

Infrared absorption spectra were recorded on FTIR spectrophotometer on a model (Shimadzu FT-IR Spectrometer) in the range (200-4000) cm^{-1}. ^{1}H-NMR spectra were recorded at 500 MHZ utilize a model Bruker DRX, TMS use as standard, DMSO-d^6 used as solvent. Mass spectra (MS) were registered in the range (0-800) m/e on 5973 network mass selective detector. Elemental C, H,N and S analysis were carried out on a LECO elemental analyzer/CHNS-932. Melting points were specified in open capillary tubes using an electro thermal melting point/SMP31 device.

RESULT AND DISCUSSION

The purity of 5-(5-{(2Z)-2-[(2-hydroxynaphthalen-1-yl)methylidene]hydrazinyl}-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol and its complexes were checked by TLC .Elemental analysis (C,H,N) tabulated in Table (7).The theoretical values were in a good accordance with the experimental values. Melting point, physical properties of all compounds studied are tabulated in Table (8).

Infra-Red Spectroscopy study

The most important FTIR spectra assignments of **(5-(5-{(2Z)-2-[(2-hydroxynaphthalen-1-**

yl)methylidene]hydrazinyl}-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol) as well as its bonding sites (Table 10) have been determined by careful comparison of the

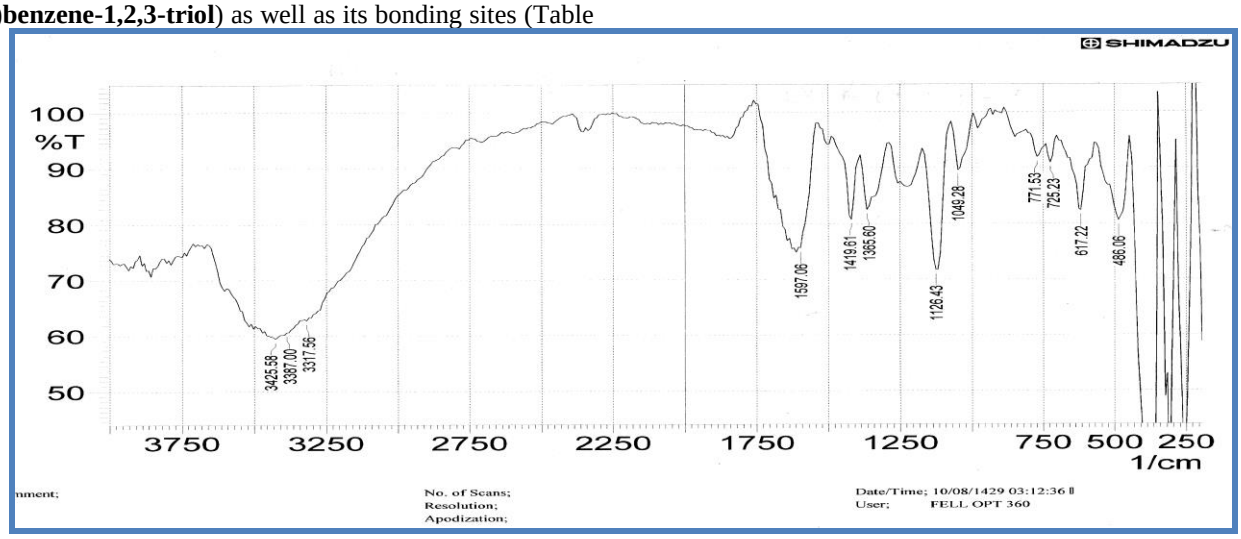


Figure 4: IR Spectra of Ligand $C_{19}H_{14}N_4O_5$

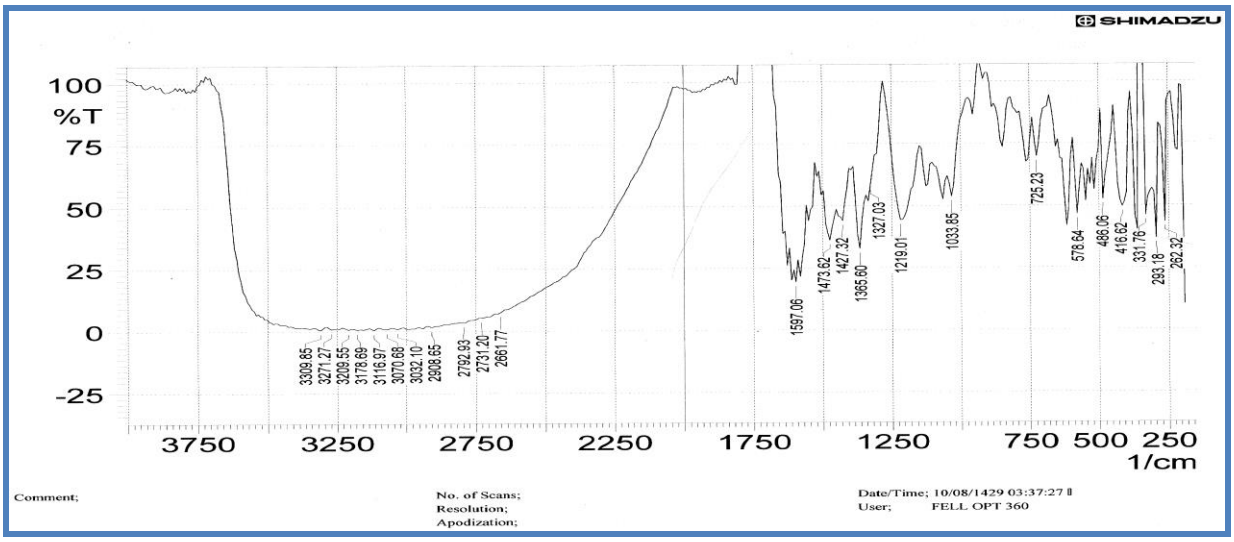


Figure 5: IR Spectra of Complex $[Cr (L)_2Cl_2]$

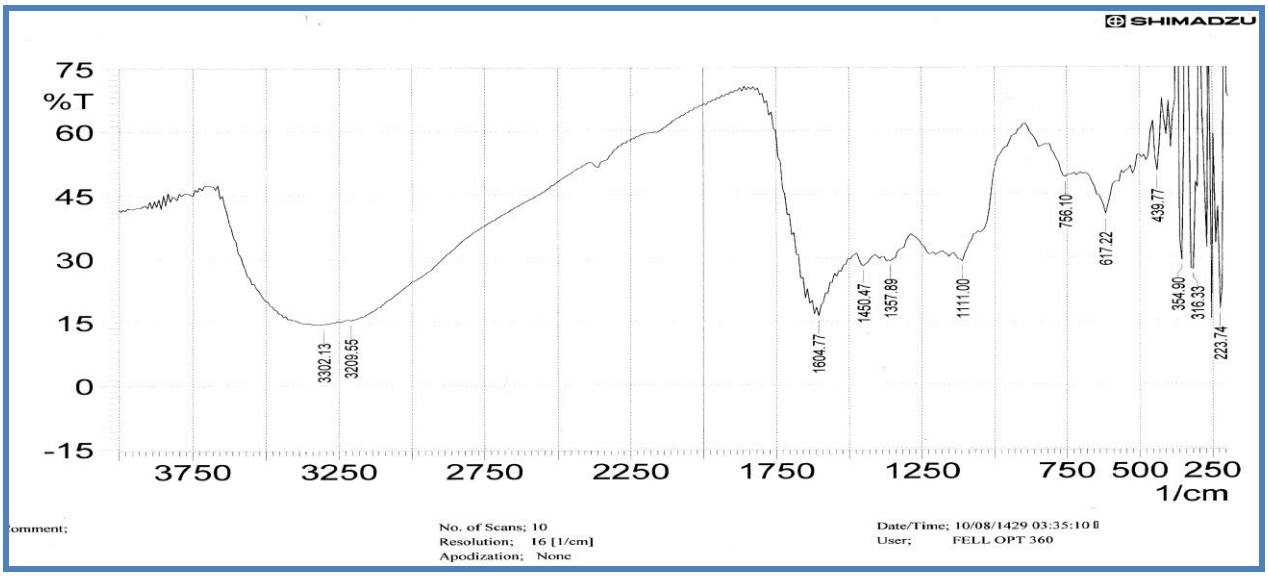


Figure 6: IR Spectra of Complex $[Co(L)Cl_2]$

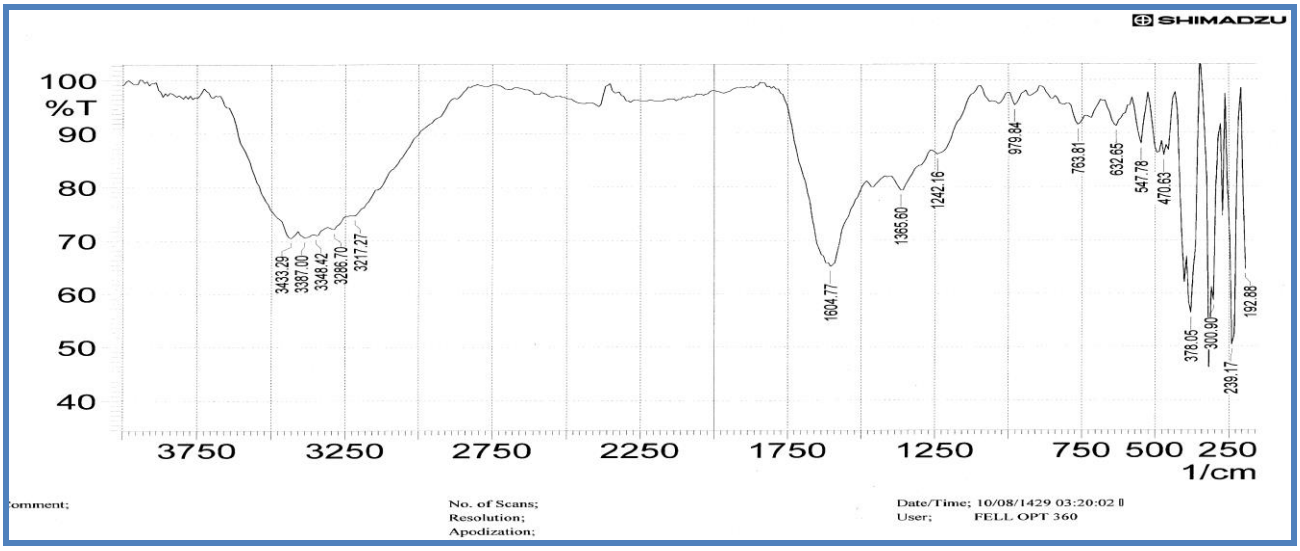


Figure 7: IR Spectra of Complex $[Ni(L)Cl_2]$

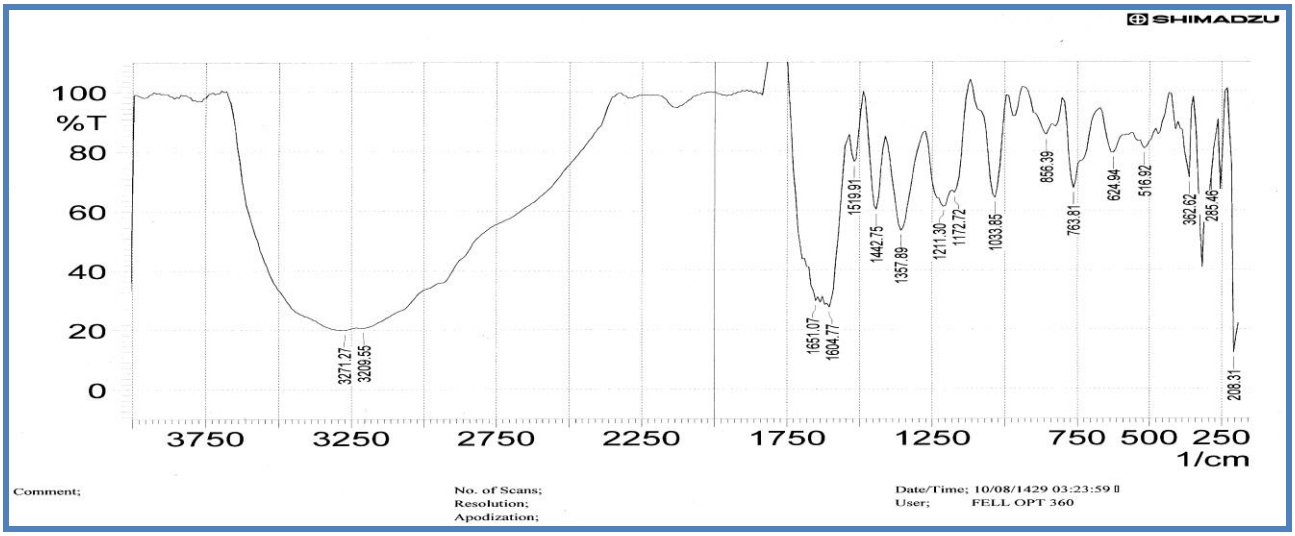


Figure 8: IR Spectra of Complex $[Cu(L)Cl_2]$

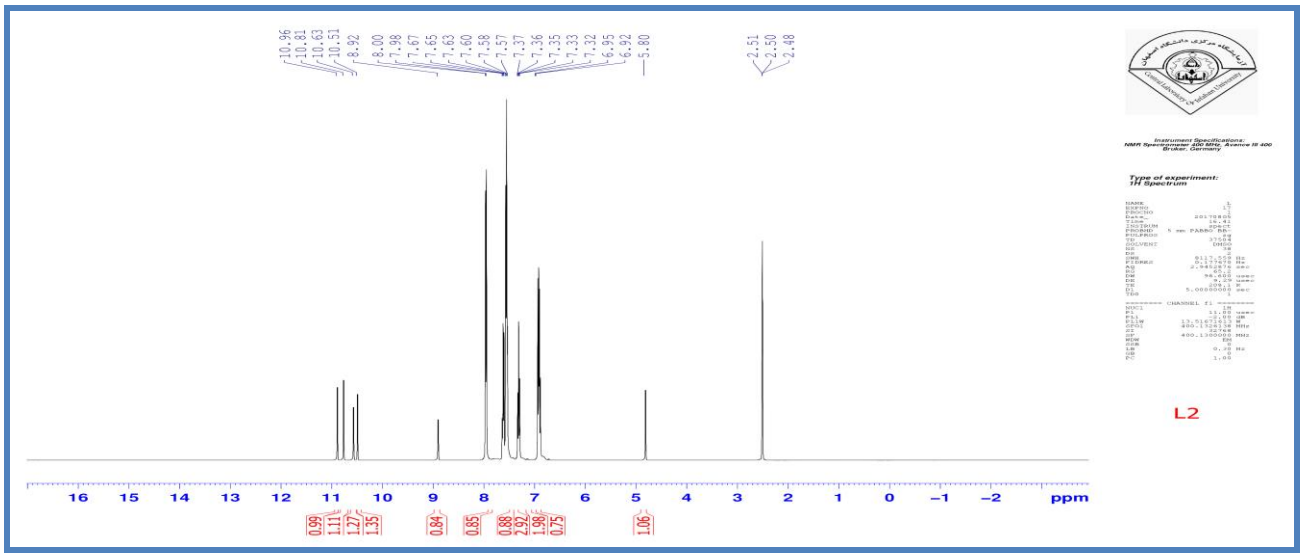


Figure 9:NMR Spectra of Ligand $C_{19}H_{14}N_4O_5$

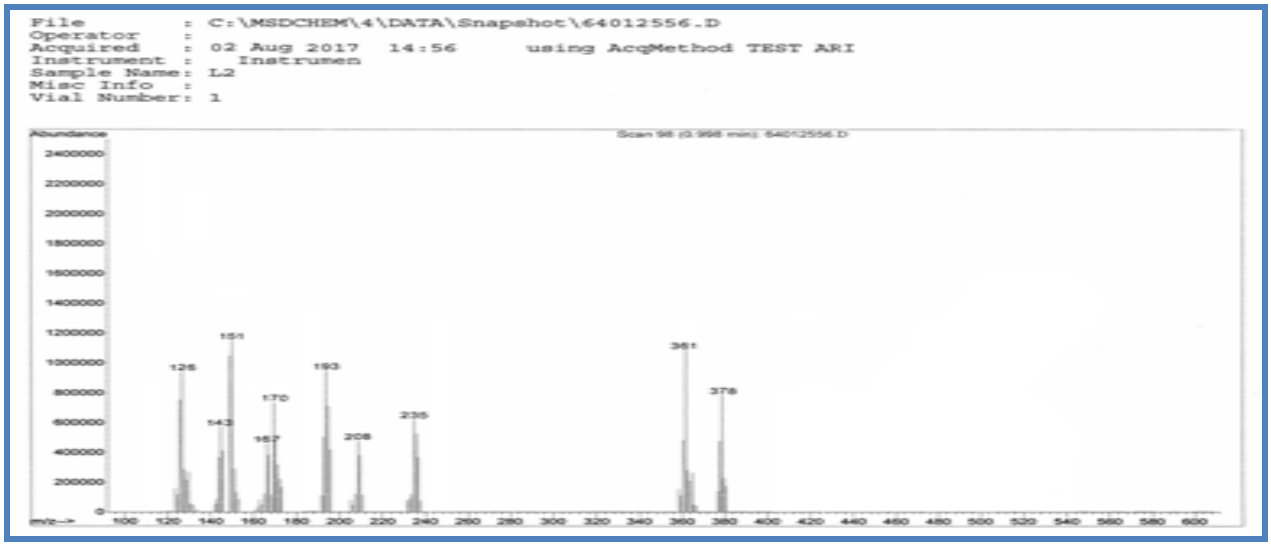


Figure 10: Mass spectra of ligand

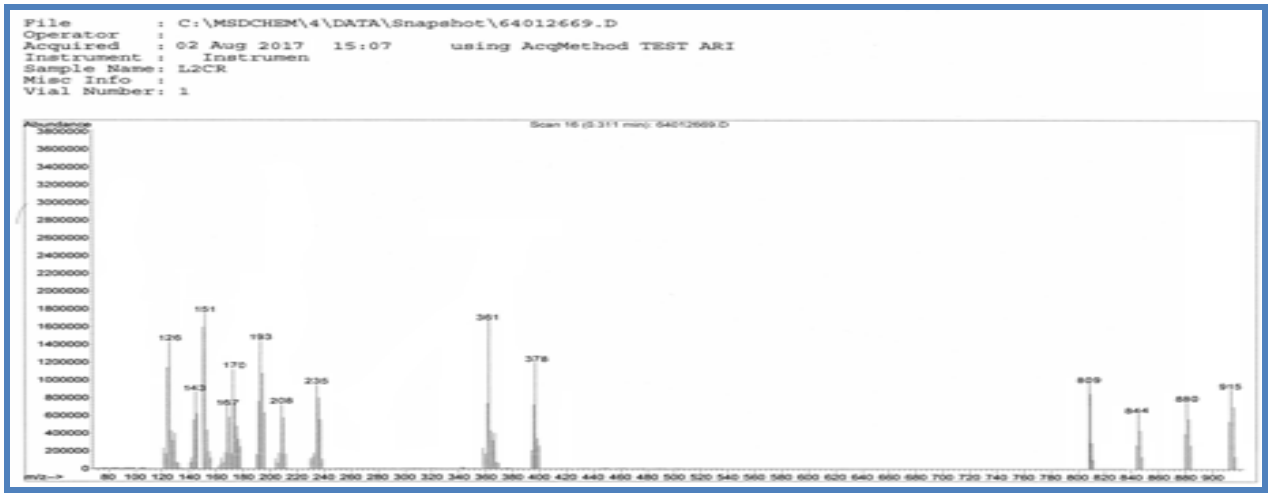


Figure 11: Mass spectra of [Cr(L)Cl_2]

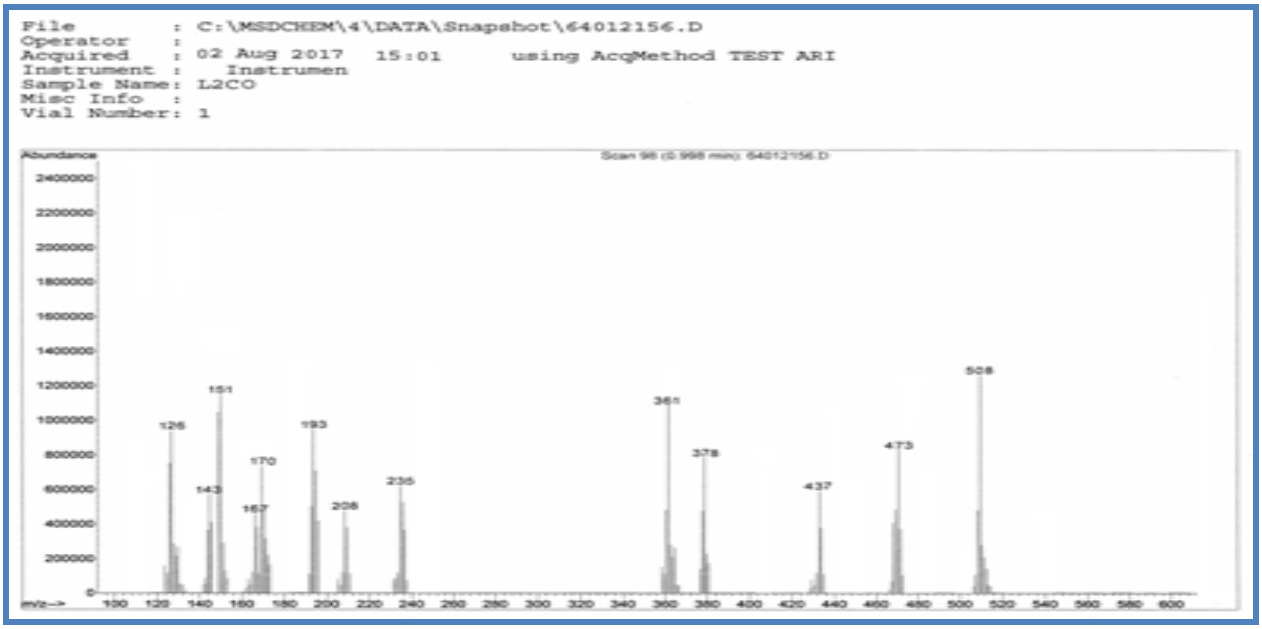


Figure 12: Mass spectra of [Co(L)Cl_2]

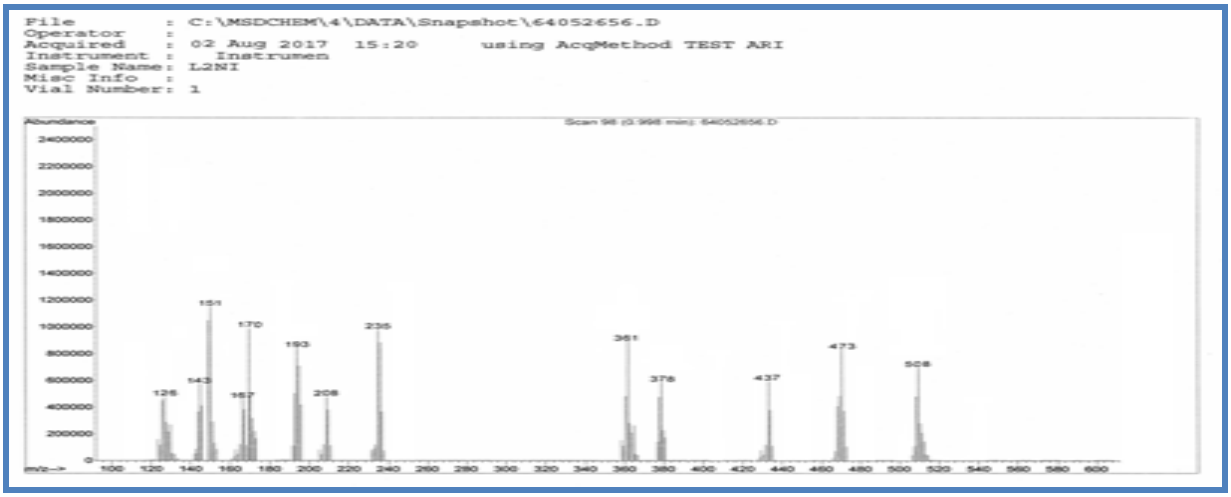


Figure 13: Mass spectra of [Ni(L)Cl

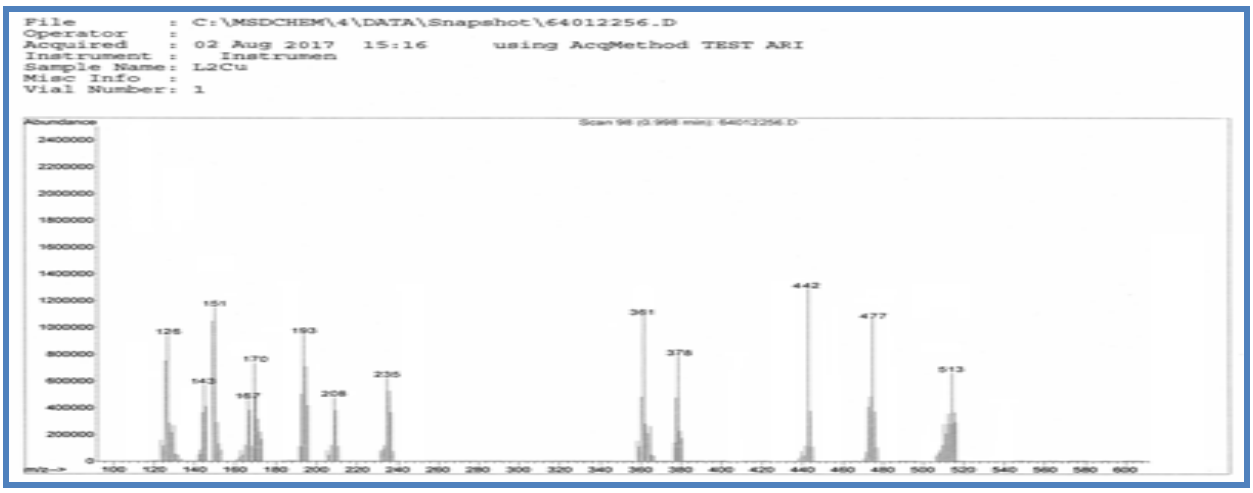


Figure 14: Mass spectra of $[Cu(L)Cl_2]$

Table 7: Elemental analysis for the ligand.

Compound	Theoretical data			Practical data		
	C %	H %	N %	C %	H %	N %
L	60.32%	3.73%	14.81%	60.41%	3.67%	14.98%

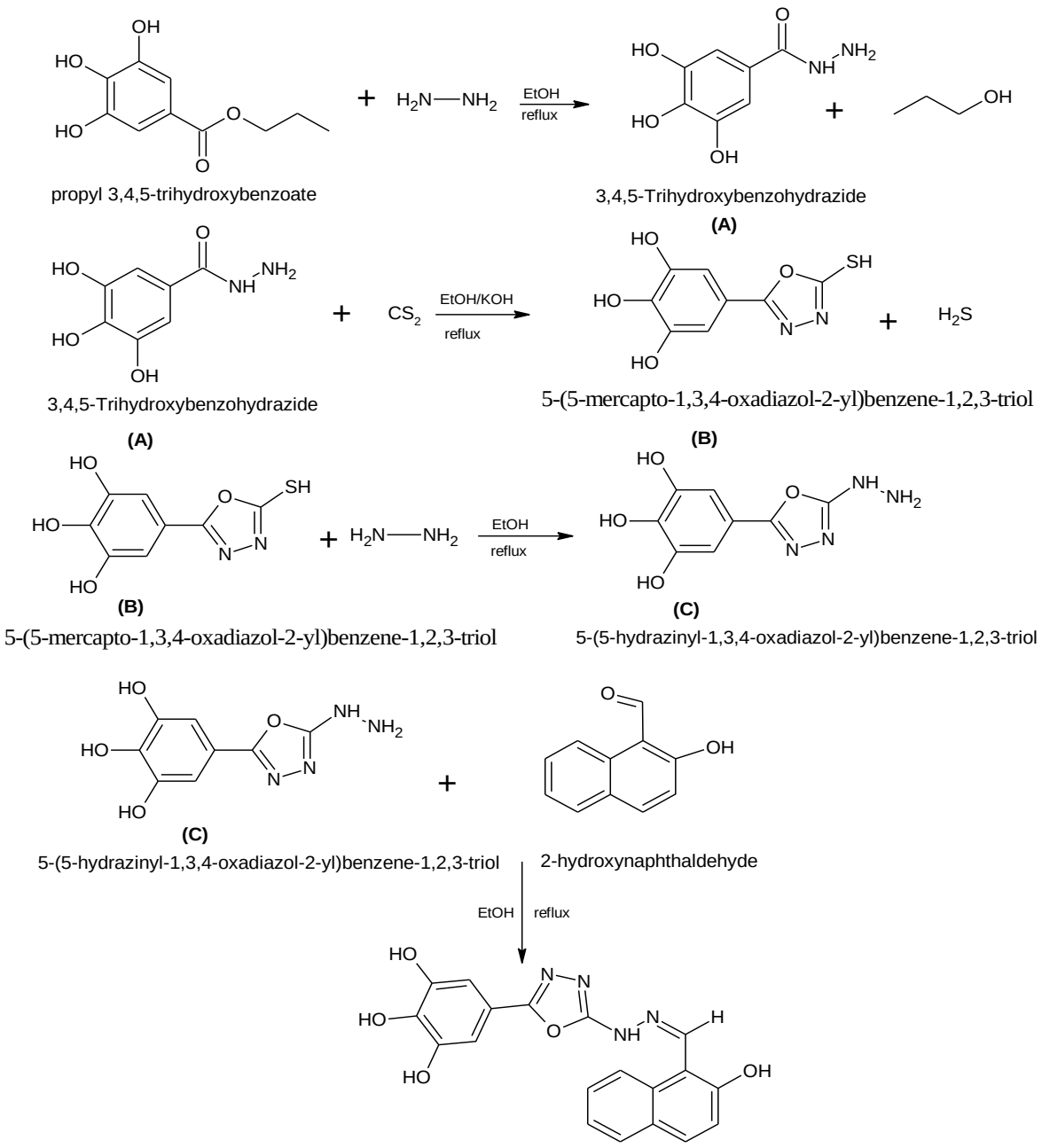
spectra of the ligand with those of its metal complexes and by considering our previous publications [20,21]. The ligand spectrum in KBr shows band at{3425cm^{-1}, 3387cm^{-1} 1597.06 , 1505.55} assigned to υ(O-H, N-H,C=N-azomethine, C=N-Oxa. ring, the spectra shows anther bands at {1049.28, 1126.43 ,1249.00}cm^{-1} due to(structural movement , symmetrical and asymmetrical C-O-C stretching) respectively[22]. There are some bands appeared in the complex spectra which are attributed to M-Cl and M-N, this bands are confirm presence the complex formation. The IR data are shown in table (10) and figures (4-8)**.**

Nuclear Magnetic Resonance

The 1H-NMR spectrum of the ligand showed signals at 4.9 (1H,s,NH), 6.92-8 (2H,m, aryl protons), 8.92 (1H,s, N=CH proton), 10.51-10.96 (4H,s, OH). The proton NMR of the ligand shown in figure (9).

Mass spectra

the mass spectrum of the ligand exhibits a molecular ion peak $[M]^{+\cdot}$ at 378 m/z ,the ligand spectra shows fragments at (126, 143, 151, 167, 170, 193, 208, 235, 361) m/z due to $[C_{10}H_6]^{+\cdot}$, $[C_{10}H_7O]^{+\cdot}$, $[C_7H_5NO_3]^{+\cdot}$, $[C_7H_5NO_4]^{+\cdot}$, $[C_{11}H_8NO]^{+\cdot}$, $[C_8H_5N_2O_4]^{+\cdot}$, $[C_8H_6N_3O_4]^{+\cdot}$, $[C_9H_7N_4O_4]^{+\cdot}$, $[C_{19}H_{13}N_4O_5]^{+\cdot}$, $[C_{19}H_{14}N_4O_5]^{+\cdot}$} respectively as shown in figure (7). The mass spectrum of the complex $[Cr(L)_2Cl_2]$ shows a molecular ion peak $[M]^{+\cdot}$ at(915) m/z which is equivalent to molecular mass of the complex. This complex shows another a fragment ion peak with loss of three chlorine atom at (880,844, 809) due to $[Cr(L)_2Cl_2]^{+\cdot}$, $[Cr(L)\ _2Cl]^{+\cdot}$, and $[Cr(L)_2]^{+\cdot}$ respectively. The mass spectrum of the complex $[Co(L)Cl_2]$ shows a molecular ion peak $[M]^{+\cdot}$ at(508) m/z which is equivalent to molecular mass of the complex .This complex shows another a fragment ion peak with loss of chlorine atom at (473,437) due to $[Co(L)Cl]^{+\cdot}$ and $[Co(L)]^{+\cdot}$ respectively. The mass spectrum of the complex $[Ni(L)Cl_2]$ shows a molecular ion peak $[M]^{+\cdot}$ (508) m/z which is equivalent to



scheme 1

Table 8: Melting point, Physical properties data for the ligand and its complexes.

No	Formula	M.Wt	Color	M.P(°C)	Yield
L	$C_{19}H_{14}N_4O_5$	378	Umber	315	90%
1	$Cr[(L_2)_2Cl_2]Cl$	915	Dark brown	352	85%
2	$[Co(L_2)Cl_2]$	508	Brown	329	95%
3	$[Ni(L_2)Cl_2]$	508	Brown	342	95%
4	$[Cu(L_2)Cl_2]$	513	Brown	361	94%

molecular mass of the complex. This complex shows another a fragment ion peak with loss of chlorine atom at (473,437) due to $[Ni(L)Cl]^{+\cdot}$ and $[Ni(L)]^{+\cdot}$ respectively. The mass spectrum of the complex $[Cu(L)Cl_2]$ shows a molecular ion peak $[M]^{+\cdot}$ (513) m/z which is equivalent to molecular mass of the complex. This complex shows another a fragment ion peak with loss of chlorine atom at (477,442) due to $[Cu(L)Cl]^{+\cdot}$ and $[Cu(L)]^{2+\cdot}$ respectively.

Table 9: Molar Conductance, Magnetic susceptibility of all complexes.

Complex no.	Complexes	Λm ($S.cm^2.mole^{-1}$)	Electrolyte Type	μ_{eff}
1	$[Cr(L_2)Cl_2]Cl$	30	1:1	4.1
2	$[Co(L_2)Cl_2]$	17	Non electrolyte	3.8
3	$[Ni(L_2)Cl_2]$	15	Non electrolyte	0.6
4	$[Cu(L_2)Cl_2]$	17	Non electrolyte	1.8

Table 10: IR Spectra for Ligand and its complexes.

	Wave numbers (cm^{-1})				
Assignment	L	$[Cr(L)_2Cl_2]Cl$	$[Co(L)]Cl_2]$	$[Ni(L)Cl_2]$	$[Cu(L)Cl_2]$
OH	3425	3309	3363	3433	3271
NH	3387	3271	3201	3387	3209
C=N (azo.)	1597.06	1597.06	1604.77	1604.77	1651.07
C=N(oxa.)	1505	1473	1450	1511	1519
C-O-C	1225 (sy)	1219.01 (sy)	1211 (sy)	1242 (sy)	1211 (sy)
	1365 (asy)	1365.60 (asy)	1357 (asy)	1365 (asy)	1357 (asy)
Structural movement	1049.28	1033.85	1033.85	1035.00	1033.85
C-H(Aromatic)		2908.65			
M-N	———	578.64	547.78	547.78	516.92
M-Cl	———	331.76	370.33	378.05	362.2

The mass spectra of the complexes shown in figures (10-14).

Magnetic susceptibility

The magnetic susceptibility (μ_{eff} B.M) for metal complexes and conductivity data are tabulated in table (9). The magnetic data give an information about the electronic state of central ion (transition metal ion) of the complexes. The (μ_{eff} B.M) value of Cr(III) complex was 3.9 BM, this value is likely to be octahedral geometry. The (μ_{eff} B.M) value of Co(II) complex was 3.9 BM suggesting tetrahedral geometry. The (μ_{eff} B.M) value was 0.6 BM for Ni(II) complex, This value confirms existence eight paired electrons, This value confirms that Ni(II) is square planer geometry. The 1.9 BM for Cu(II) proposition tetrahedral geometry.

Antibacterial activity

The practical results of in vitro antibacterial activity of 5-(5-{(2Z)-2-[(2-hydroxynaphthalen-1-yl)methylidene]hydrazinyl}-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol exhibits at concentrations of (50,100,250,500) µg/ml against *Salmonella* ,observed that increasing of inhibition zone when concentration increased, but , there is no inhibition zone for the same compound against *E.coli* and *Staphylococcus aureus* in the same concentrations. The two complexes $[Cr(L)_2Cl_2]Cl$ and $[Ni(L_2)Cl_2]$ used at concentrations (50,100,250,500) µg/ml against *Salmonella* , observed that decreasing of inhibition zones when the concentration increased, thought that this happens because when concentration increased hydrogen bonding increased, then compounds were engaged in hydrogen bonding rather than inhibiting bacteria. The complex $[Cr(L)_2Cl_2]$ exhibited biological activities at concentration of 500µg/ml and does not appeared biological activity in other concentrations, can be attributed that, this concentration was active concentration which the compound inhibiting bacteria. The two complexes $[Co(L)]Cl_2]$ and $[Cu(L)Cl_2]$ didn't have any antibacterial activities for all types of bacteria utilize. Tables (1,2,3,4,5)

Hemolytic activity

The hemolysis activity of the compounds was tested at different concentrations ranging from 50 - 500µg/ml and the results showed high percentage of hemolysis for all these compounds and these gave a conclusion about the contraindication use of these compound *in vivo*. The details showed in table (6).

Molecular Electrostatic potential (MEP).

Hyperchem 7.5 program was used to draw optimization structure of the ligand and then find the Electrostatic potential Which is considered very important to finding the active site in the free ligand as shown in figure (1)[23]

CONCLUSIONS

The ligand 5-(5-{(2Z)-2-[(2-hydroxynaphthalen-1-yl)methylidene]hydrazinyl}-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol was successfully synthesized. The techniques analysis observations suggest the octahedral geometry for the Cr(III) complex, tetrahedral geometry for Co(II) and Cu(II) complexes. Square planar geometry was proposed for Ni (II) complex. The antimicrobial activity revealed that some of the test compounds showed perfect inhibition, but other compounds weren't revealed any antibacterial activity. At measuring the ratio of hemolysis for these compounds, it is noticed that the ratio is very high, and thus, these compounds shouldn't be used inside the human body.

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