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Syntheses, Characterization and biological Activity of a new ligand [N-(5-sulfanyl-1,3,4-thiadiazol-2-yl)acetamide with some transition metal complexes

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Abstract:-

A-new series of transition metal (Cr(III),Fe(III), Co(II) , Ni(II)and Cu(II)) complexes of ligand [N-(5-sulfonyl-1,3,4,thiadiazol-2-yl)acetamide were synthesized. All the synthesized complexes were characterized by analytical techniques, magnetic susceptibility measurements, elemental analyses, conductance, IR , 1HNMR and mass spectra. The electrolytic behavior were confirmed from their conductance data . It may be concluded that the ligand coordinate through Nitrogen and sulfur atoms as shown in figure (6). for all complexes. The ligand acts as a didentate ligand coordinating through the sulfur[S^6] and the nitrogen atom of shiff base [N^5]. This view is further supported by the appearance of a band corresponding to the metal–nitrogen stretching vibration at(547–563) cm^{-1} in the complexes. From results it was suggested tetrahedral geometry for Ni(II) and Cu(II) complexes, while Cr(III),Fe(III) and Co (III)complexes were assigned octahedral geometrics. All complexes and their parent organic moiety have been screened for antibacterial by using spread method and measurement inhibition zone by using (DMSO). this study showed positivity results, by comparison of inhibition zone with E-coli and staph aurens.

تحضير وتشخيص ودراسة الفعالية البايولوجية لليكاند
مع بعض معقدات العناصر الانتقالية[N-(5-sulfanyl-1,3,4-thiadiazol-2-yl)acetamide

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الخلاصة

تم تحضير سلسلة جديدة من معقدات العناصر الانتقالية(Cr(III),Fe(III),Co(III),Ni(II) و Cu(II) مع الليكاند [N-(5-sulfanyl-1,3,4,thiadiazol-2-yl) acetamide تم تشخيص الليكاندات والمعقدات المحضرة باستخدام تحليل العناصر الدقيق ،التوصيلية المولارية، اطياف الاشعة تحت الحمراء، وبروتون الرنين النووي المغناطيسي وطيف الكتلة. السلوك الالكتروليتي للمعقدات تم تاكيده باستخدام تقنية التوصيل المولاري .وتم الاستنتاج بان الليكاند يتناسق من خلال ذرتي النتروجين والكبريت كما موضح في الجدول (٣)،في جميع المعقدات وجد ان الليكاند يعمل كليكاند ثنائي السن ويتناسق من خلال [S^6]و[N^5]وهذه الرؤية تضيف دعما اخر من خلال ظهور حزمة تقابل حزمة امتصاص M–N بحدود cm^{-1} (547–563).من النتائج التي تم الحصول عليها اقترح الشكل الرباعي السطوح للـNi(II) وCu(II) بينما لمعقدات Cr(III),Fe(III),Co(III) شخصت على انها ثمانية السطوح.وتم اختبار الفعالية البايولوجية لليكاند المحضر ومعقداته باستخدام طريقة الانتشار وذلك بقياس منطقة التثبيط وباستخدام مذيب ثنائي مثيل اوكسيد الكبريت (DMSO) ، وأعطت اختبارات الفعالية نتائج ايجابية حيث لوحظ ظهور تثبيط جيد ضد بكتريا E–coli و Staphylococcus .

1- Introduction

Over the past decade, drug resistance has become a growing problem in the treatment of infectious disease caused by bacteria, fungi and viruses. In particular, resistance of bacterial pathogens to current antibiotic has emerged as a major health problem. This is especially true in case of infectious diseases such as pneumonia,meningitis and tuberculosis.The search for new antimicrobial agent is one of the most challenging tasks to the medicinal chemist . Heterocyclic moieties can be found in a large number of compounds which display biological activity. The biological activity of the compounds is mainly dependent on their molecular structures (1) .Thiadiazoles are very interesting compounds due to their important applications . In recent years 1, 3, 4-Thiadiazole derivatives have received significant attention and have been increasingly investigated due to their diverse range of biological properties. They exhibit for example, antimicrobial (2), anti-micro bacterial(3) , anticancer (4), anti-inflammatory (5) .The compounds containing azomethine group (-CH=N-) are known as Schiff bases. They are used as substrates in the preparation of number of industrial and biologically active compounds *via* ring closure, cyclo-addition and replacement reactions (6) Schiff base ligands are potentially capable of forming stable complexes with most transition metal ions, which served as model compounds for biologically important species .aimed at searching for novel antibacterial antiviral agents with high activity and low toxicity, a synthetic route has been developed to the title compounds.

2.Experimental

Materials

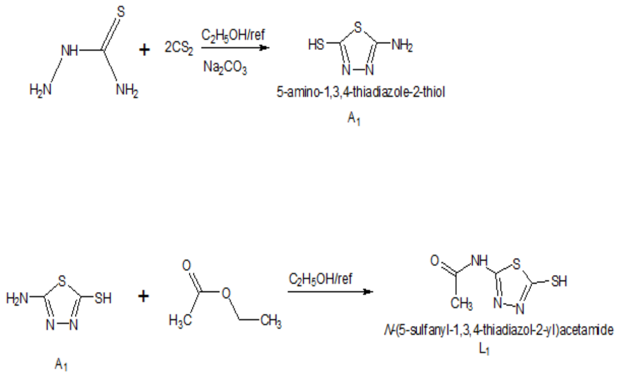
All the employed chemicals were of reagent grade, Thiosemicarbazide (Fluka) Hydrazine hydrate(BDH), anhydrous sodium carbonate (Fluka), absolute ethanol (BDH), Hydro chloride acid(BDH), Ethyl acetate (BDH) and carbon disulphide (BDH) were used. All the metal chlorides ($NiCl_2.6H_2O$, $CuCl_2.6H_20$, $CrCl_{3.}6H_2O$, $CoCl_3.6H_2O$, $FeCl_36H_2O$) were purchased from (BDH) fine chemicals.

Analytical methods and physical measurements

Elemental C, H and N analysis were carried out on a Thermofinigan flash analyzer, the FTIR spectra in the range (200-4000) cm^{-1} were recorded as CsI discs using a Shimadzu FTIR spectrophotometer, molar conductance measurements were made in anhydrous DMSO at 25 ^oC using Inolabcond 720.The ^1H NMR spectra were recorded on a Mercury-300BB NMR 300 spectrometer, relative to the internal standard tetra methyl silane (TMS) , d6-DMSO used as solvent. Melting points were determined in open capillary tubes using an electro thermal melting point /SMP3Iapparatus. Mass spectra were recorded in the range (0-800) m/e on a 5973 network mass selective detector .

2.1 Preparation of the ligand

New ligand [N-(5-sulfonyl-1,3,4,thiadiazol-2-yl) acetamide (Scheme 1) was prepared as follows:
A mixture of (9.1 g, 0.1mol) of thiosemicarbazide and (4 g, 0.1mol) of anhydrous sodium carbonate was dissolved in (70ml) absolute ethanol, to this solution (6 ml, 0.1mol) of carbon disulfide was added. The resulting mixture was heated under reflux for (6 hours).The resultant mixture was concentrated , and carefully acidified with hydrochloric acid HCl(10%) to give pale yellow precipitate. The crude product was filtered and washed with cold water, recrystallized from ethanol to give the desired product5-Amino-1,3,4-thiadiazole-2-thiol (A1) as White needles(7,8), yield (81%),m.p(9).233-235C.A mixture(A1) (0.02mol, 2gm) and Ethyl acetate (0.02mol, 2ml) dissolved in ethanol (50ml) was refluxed on a water bath for(3) hrs, .The resultant mixture[ligand] was concentrated and the Yellow solid which separated was filtered and recrystallised from ethanol. Yield: (86 %), m. p. 272-274°C.(scheme1)



Scheme (1) preparation of ligand

2.2 Preparation of complexes

The Cr(III), Co(III), Fe(III), Ni(II) and Cu(II) complexes were prepared by refluxing the respective hydrated metal chloride (1 mmol, 0.28gm) in 15 ml ethanol with 50 ml of an ethanolic solution of the ligand (1mmol, 0.3 gm) for 4 hrs. The resultant solids which separated were filtered, washed with ethanol and dried in air.

3. Results & Discussion

The purity of the ligand and its complexes were checked by TLC using silica gel-G as adsorbent., elemental analysis tabulated in Table (1), Melting point, physical properties and molar conductance of all the compounds studied are tabulated in Table (2). The calculated values were in a good agreement with the experimental values.

Table 1.Elemental analysis for the ligand

Experimental			Theoretical		
C%	H%	N%	C%	H%	N%
27.42	2.937	24.064	27.42	2.88	23.98

Table 2. conductance, physical properties data of the ligand and its complexes

No	Compound	Molecular formula	Color	Λ Scm2 mol-1	Melting Point
1	Ligand	$C_4H_5N_3S_2O$	Yellow	-------	272-274
2	[Cr(L)2Cl2]Cl	$Cr(C_4H_5N_3S_2O)_2Cl_3$	Light green	39.2	294-296
3	[Co(L)2Cl2]Cl	$Co(C_4H_5N_3S_2O)_2Cl_3$	Dark brown	31.2	310 d*
4	[Fe(L)2Cl2]Cl	$Fe(C_4H_5N_3S_2O)_2Cl_3$	Light Brown	34.7	288-290
5	[Cu(L) Cl2]	$Cu(C_4H_5N_3S_2O)Cl_2$	Greenish yellow	9.8	335-337
6	[Ni(L) Cl2]	$Ni(C_4H_5N_3S_2O)Cl_2$	Light green	10.1	266-268

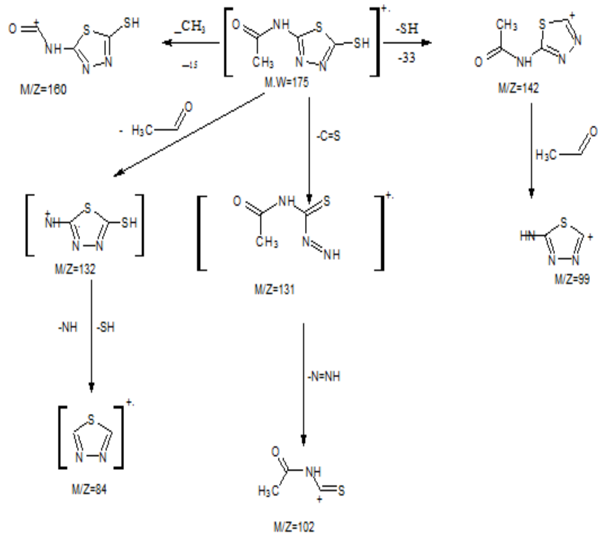
d*=decomposition

The FTIR spectrum for L shows a characteristic stretching absorption bands at 3286cm^{-1},2700 cm^{-1},1593 cm^{-1},1504cm^{-1},1365 cm^{-1} and 1323 cm^{-1} assigned to υ(N-H) ,υ(S–H)،(C=O),υ(C=N), asymmetrical C-S-C and symmetrical C-S-C stretching respectively(10). The C=N and S-H stretching are important to predict the bonding mode of the ligand ,these bands shift lower wavelength in the spectra of complexes compare with ligand, observed changes are the evidences of complexation had happened . The IR data of the ligand and complexes are shown in Table (3) and figure(8),(9)and(10). The Table lists the wave number (υ) for some of the characteristics groups exhibited by the ligand and complexes.

Table 3: Characteristic absorption bands of ligand and its complexes

NO	υN - H	υS - H	υC=O	υC=N	υ C-S-C	الحركة الهيكلية	υM-N	υM-S	υM-Cl
L	3286	2700	1593	1504	1365 asy 1323sy	1026			
1	3263	2800	1608	1554	1365 asy 1334sy	1056	550	432	250
2	3275	2805	1639	1504	1392asy 1319sy	1138	547	412	212
3	3309	2750	1589	1523	1392asy 1338sy	1037	559	412	231
4	3286	2802	1608	1523	1400asy 1354sy	1053	563	412	270
5	3255	2750	1620	1516	1354asy 1320sy	1049	563	412	277

The data of proton NMR of the ligand[N-(5-sulfanyl-1,3,4,thiadiazol-2-yl) acetamide displayed good solubility in DMSO. The proton nuclear magnetic resonance spectral data gave additional support for the suggested structure of the ligand. The spectra also exhibit a singlet –CH3 peaks at 2.504ppm due to methyl group, another singlet peaks exhibit at 3.845ppm and 5.793ppm due to–SH and –NH respectively(11). the proton NMR of the ligand shown in figure(11) .The mass spectrum of the ligand exhibits a molecular ion peak [M]+. at m/z175,the ligand spectra shows fragment the spectra peaks at m/z(160, 142,131,102,99 and 84)due to [(C3H2N3S2O)+. ،(C4H4SN3O)+. ،(C3H5N3SO)+. ،(C3H4NSO)+. ،(C3H5N3O)+. ،(C3H4N2O) +.]respectively as shown in Figure(12)and(Scheme2).The mass spectrum of the complex [Cr(L)2Cl2]Cl shows a molecular ion peak at m/z [M•](507)which is equivalent to molecular mass of the complex. This complex shows another a fragmentation peak with loss of chlorine atom at m/z(471). the complex spectrum shows fragment ion peak with loss two chlorine atom at m/z (436,400) due to[Cr(L)2Cl]and [Cr(L)2] respectively. the complex spectrum shows fragment ion peak at m/z (225) due to ([Cr (L1)]+.).The mass spectrum of the complex [Fe(L)2Cl2]Cl shows a molecular ion peak at m/z [M•](511)which is equivalent to molecular mass of the complex. This complex shows another a fragment ion peak with loss of chlorine atom at m/z(475). the complex spectrum shows fragment ion peak with loss two chlorine atom at m/z (440, 404) due to [Fe(L)$_2$Cl]and [Fe(L)$_2$] respectively. the complex spectrum shows fragment ion peak at m/z (336) due to [Fe (L$_1$) Cl$_2$]$^{+\cdot}$Cl .The mass spectrum of the complex [Co(L)$_2$Cl$_2$]Cl shows a molecular ion peak at m/z [M•](514)which is equivalent to molecular mass of the complex. This complex shows another a fragment ion peak with loss of chlorine atom at m/z(478). the complex spectrum shows fragment ion peak with loss two chlorine atom at m/z (443, 407) due to [Co(L)2Cl]and [Co(L)2] respectively. the complex spectrum shows fragment ion peak at m/z (232) due to ([Co (L1)]+.).The mass spectrum of the complex [CuLCl2] shows a molecular ion peak at m/z [M•](309), This complex shows another a fragment ion peak with loss of chlorine atom at m/z (273)and (238), the spectrum shows another peak at m/z (133)due to[Cu Cl2]+.The mass spectrum of the complex [NiLCl2] shows a molecular ion peak at m/z [M•] (304), This complex shows another a fragment ion peak with loss of chlorine atom at m/z (267)and (233), the spectrum shows another peaks at m/z (129,93) due to[Ni Cl2]+. ,[Ni Cl]+.. the mass spectra of the complexes shown in figure(13), (14),(15)(16)(17).



Scheme2(frigment of ligand)

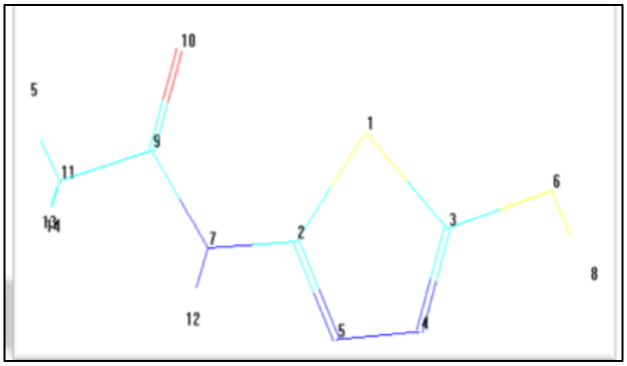


Figure 1:The stereochemistry of the Ligand

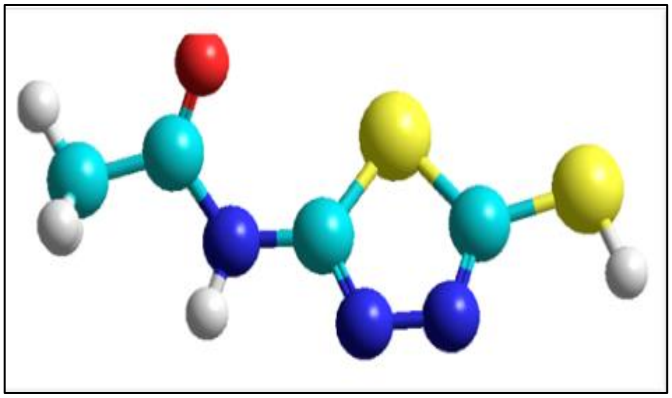


Figure 2: Graphical presentation of stereochemistry of the Ligand ($C_4H_5N_3S_2O$)

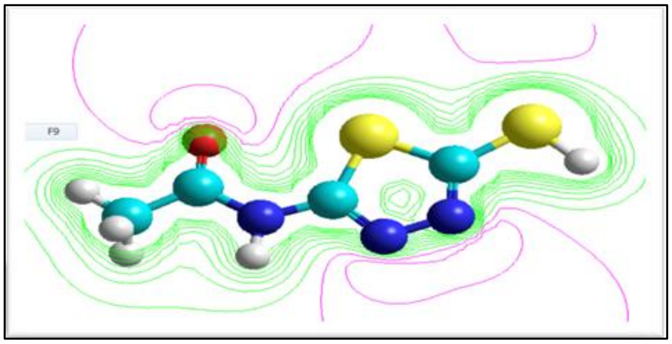


Figure 3:Electrostatic potential 2D for Ligand

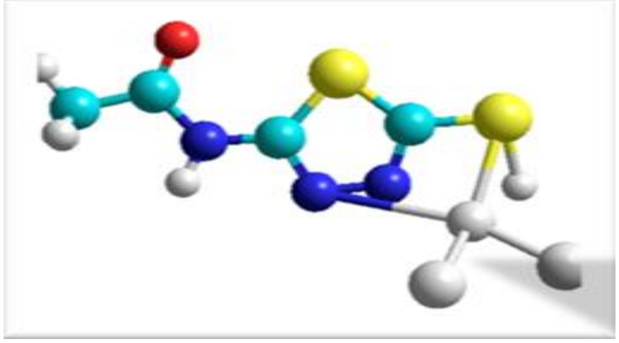


Figure 4: [Ni(L) Cl2]

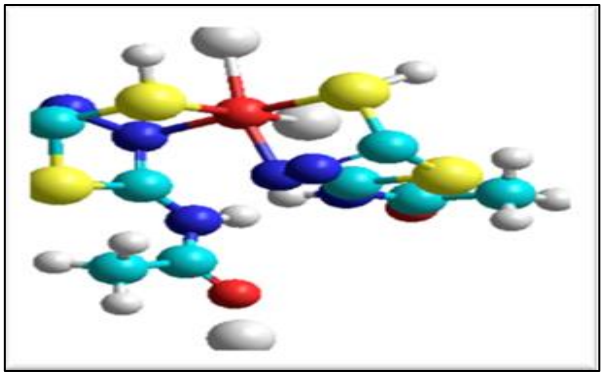


Figure5: [Fe(L)2Cl2]

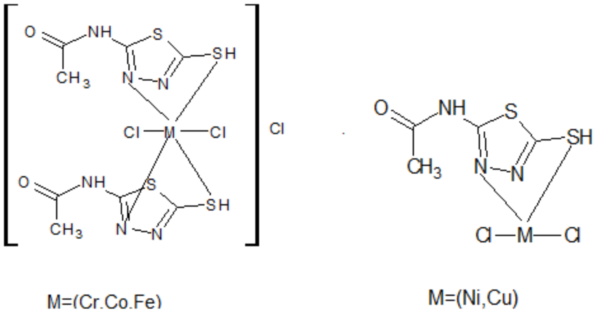


Figure 6:Analytical and spectral data (^{1}H NMR,IR, mass spectra) of all synthesized compounds were in full agreement with the proposed structure

3-١ –Biological Activity

The antibacterial activity of all the synthesized complexes were evaluated by using agar well diffusion method. All the microbial cultures were adjusted to 0.5 McFarland standard, which is visually comparable to a microbial suspension of approximately 1.5 × 108 cfu/mL. 20mL of Mueller Hinton agar medium was poured into each Petri plate and plates were swabbed with 100 μL inocula of the test microorganisms and kept for 15 min for adsorption. Using sterile cork borer of 8mm diameter, wells were bored into the seeded agar plates, and these were loaded with a 100 μL volume with concentration of 4.0mg/mL of each compound reconstituted in the dimethyl sulphoxide (DMSO). All the plates were incubated at 37◦C for 24 hrs. Antibacterial activity of each compound was evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (Hi Antibiotic zone scale). DMSO was used as a negative control whereas Ciprofloxacin was used as positive control. This procedure was performed in three replicate plates for each organism (12,13).

Table 4 . Antibacterial screening data of the ligand and its metal complexes

Compound	Escherichia coli Inhibition zone(mm)	Staphylococcus Aurens Inhibition zone(mm)
L1= $C_4H_5N_3S_2O$	21++	28++++
A= $[Cr(L1)_2Cl_2]Cl$	18+	20+++
B= $[Co(L1)_2Cl_2]Cl$	21++	30++++
C = [Cu(L1)CL2]	18+	18++
D= [Ni(L1)Cl2]	17+	18++
E= $[Fe(L1)_2Cl_2]Cl$	17+	30++++
Ciprofloxacin	35	25

**(+ = Weak Inhibition , ++ =Medium Inhibition , +++ = Good Inhibition ,++++ =Very good Inhibition)

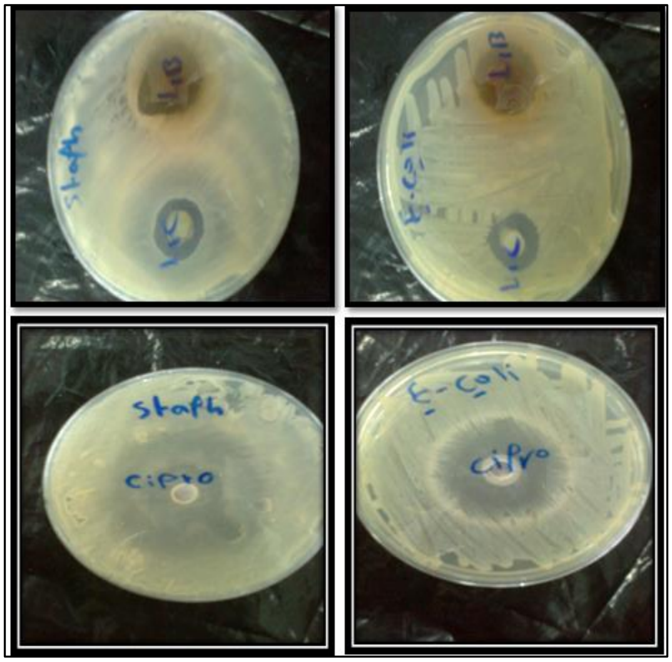


Figure (7)

4. Conclusion

The ligand [N-(5-sulfonyl-1,3,4,thiadiazol-2-yl) acetamide was successfully synthesized. The elemental analysis, , IR, ^{1}H NMR and mass spectral observations suggest the octahedral geometry for the Cr(III), Co(III),Fe(III). tetrahedral geometry was proposed for Ni(II),Cu(II) .

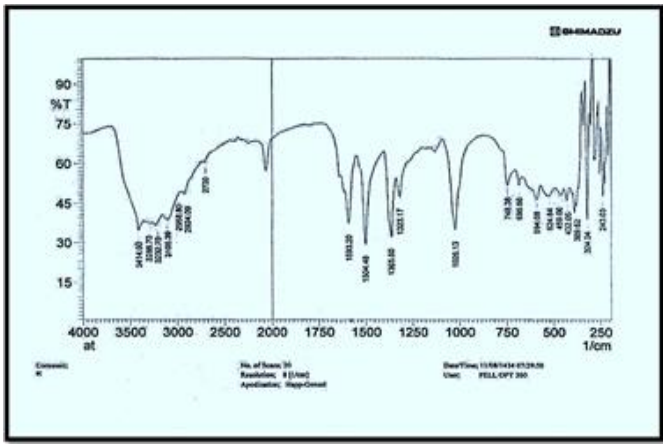


Figure 8: IR spectra of Ligand ($C_4H_5N_3S_2O$)

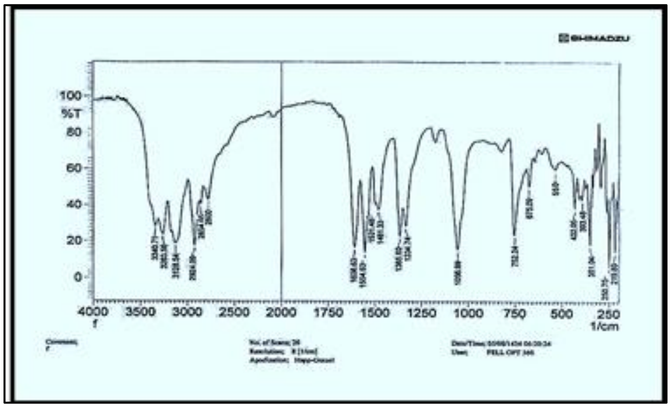


Figure 9: IR spectra of [Cr(L)$_2$Cl$_2$]

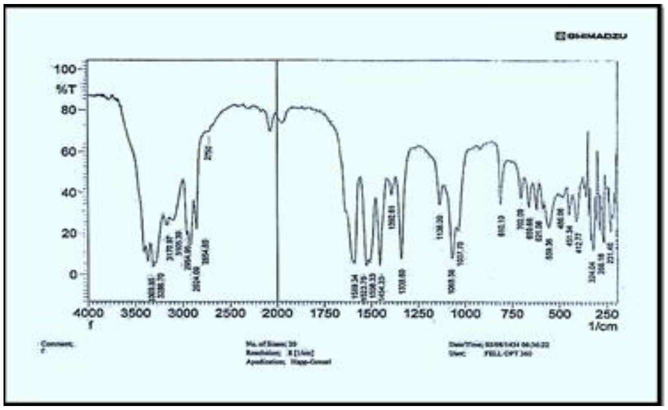


Figure 10: IR spectra of [Co(L)2Cl2]

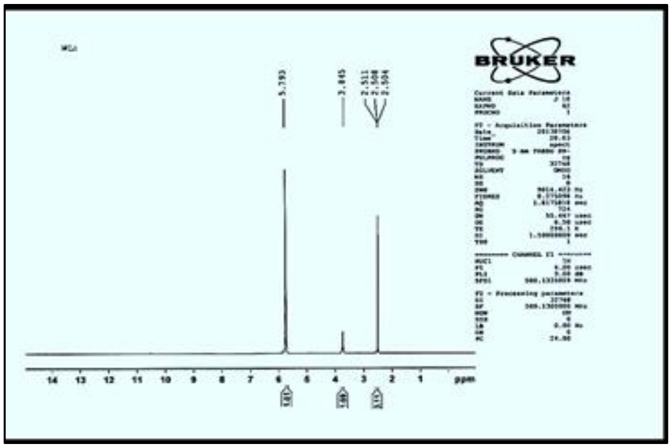


Figure 11 :H1-NMR spectra of the ligand(C4H5N3S2O)

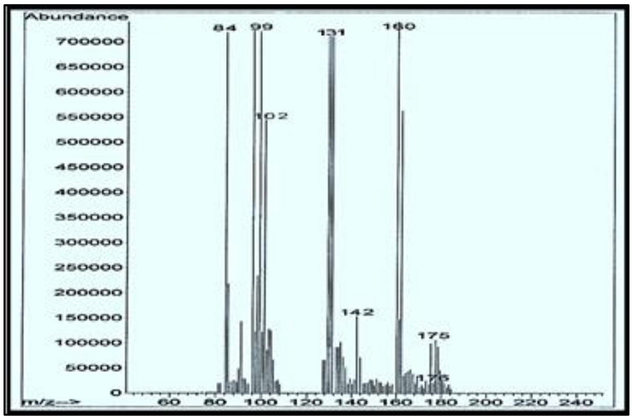


Figure 12: mass spectra of ligand

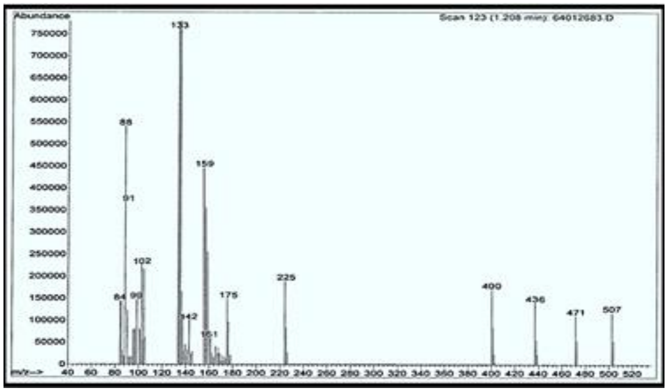


Figure 13: mass spectra of [Cr(L)2Cl2]Cl

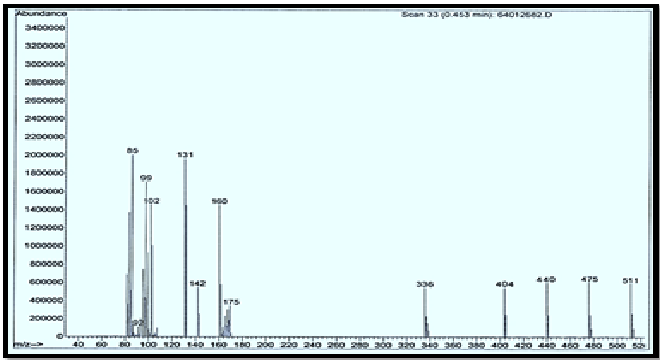


Figure 14: mass spectra of $[Fe(L)_2Cl_2]Cl$

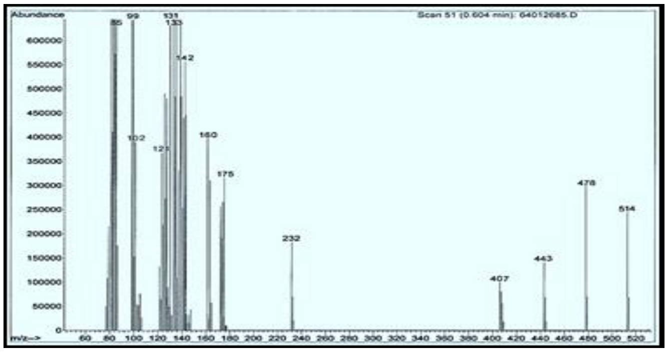


Figure 15: mass spectra of $[Co(L)_2Cl_2]Cl$

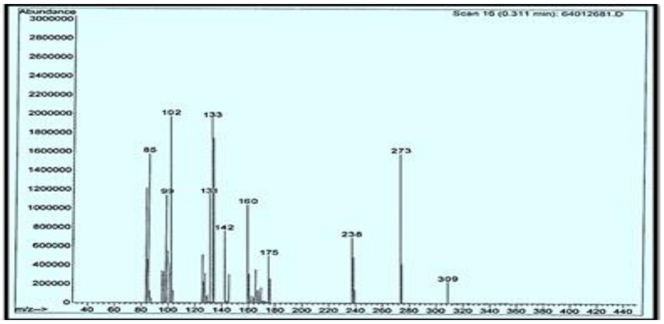


Figure 16: mass spectra of $[Cu LCl_2]$

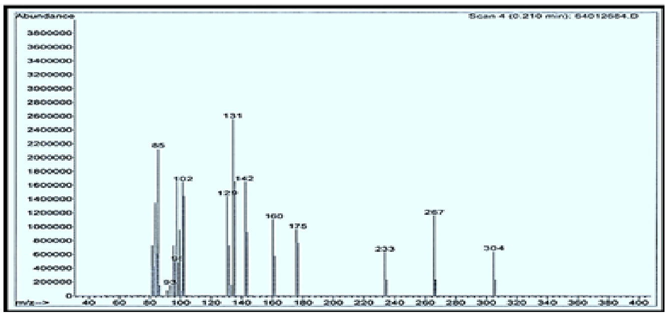


Figure 17: mass spectra of [Ni L Cl2]

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