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Synthesis , Characterization and biological activity of new derivatives of 1,3,4,thiadiazol with some transitions metal ion

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Abstract

In the present study we prepared derivatives of 2,5-dihydrazino-1,3,4 thiadiazole and its, Cd (ll) and Ni (ll) complexes, compound (**L_1**): 2-cyano-*N*'-(5-hydrazinyl-1,3,4-thiadiazol-2-yl)acetohydrazide, compound (**L_2**): 2,2'-[1,3,4-thiadiazole-2,5-diyldi(hydrazine-2,1-diyl)]bis(1,3- benzothiazole). all prepared compounds were diagnosed by spectra of H^1-NMR, mass, Fourier transform infrared (FTIR), as well as magnetic susceptibility, micro- elemental analysis(CHN) and molar electrical conductance measurements. The conductivity data of the complexes Confirmed their non-electrolytic.The magnetic studies suggest an tetrahedral and square planer geometry of the complexes, From results it was suggested square plainer geometry for Ni(II) complex and tetrahedral geometry for Cd (II) complexes. The derivatives and its complexes has shown moderate to good activity against gram-positive bacteria (*Staphylococcus aureus*), gram-negative bacteria (*Escherichia coli*) when compared with standard antibiotic gentamycin.

Keywords: thiadiazole, 1,3,4-thiadiazole, synthesis, biological activities

INTRODUCTION

Thiadiazoles are an important class of heterocyclic compounds that exhibit diverse applications in organic synthesis, pharmaceutical and biological applications. Thiadiazole is a five-membered unsaturated ring structure having molecular formula C2H2N2S[1], It is a clear to yellowish liquid with a pyridine like odor, It is soluble in alcohol and ether and slightly soluble in water. Thiadiazole moiety act as a "hydrogen binding domain" and "two-electron donor system", Thiadiazole is occur in four isomeric forms. Its dihydro derivative provides bulk of literature on thiadiazole [2]

1,3,4-thiadiazole is the most common isomer of the other thiazazole isomers, where it is used in various applications , as a ligand in Coordination Chemistry, In addition to its varied and high biological activity Which are due to e presence of N=C-S [3,4]. Also, the isomer is more thermally stable than other isomers, and it is the only one that does not contain sulfur-nitrogen bond [5] 1,3,4-thiadiazole is a polar symmetric molecule, the value of The dipole moment is equal 3.25D,its exhibiting pseudo aromatic character. Actually 1,3,4-thiadiazole molecule does not display a true aromatic behavior as do benzene, pyridine and thiophene [6]. 1,3,4-thiadiazole derivatives have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. They have known to exhibit diverse biological activities such as Analgesic and Anti-inflammatory Activity[7-9], antibacterial and Antifungal[10], Antitubercular[11], Anticancer[12], Antidiabetics[13], Acaricidal [14]. They are also useful as oxidation inhibitors[15], dyes[16], anti-corrosion agents[17]and Liquid crystalline[18].

EXPERIMENTAL

Synthesis of 1,3,4-thiadiazole-2,5-dithiol (A)

A mixture of (8 ml,0.1mol) of hydrazine and (11.2gm,0.2 mol) potassium hydroxide was dissolved in (50ml) absolute ethanol, to this solution (15.2 ml, 0.2mol) of carbon disulfide was added. The resulting mixture was heated under reflux for (15 hours).The resultant mixture was concentrated , and carefully acidified with hydrochloric acid HCl(10%) to give yellow precipitate. The crude product was filtered and washed and recrystallized by ethanol absolute to give the desired product (A) ,melting point 165 C^0 , yield 83% [19]

Synthesis of 2,5-dihydrazino-1,3,4-thiadiazole (B):

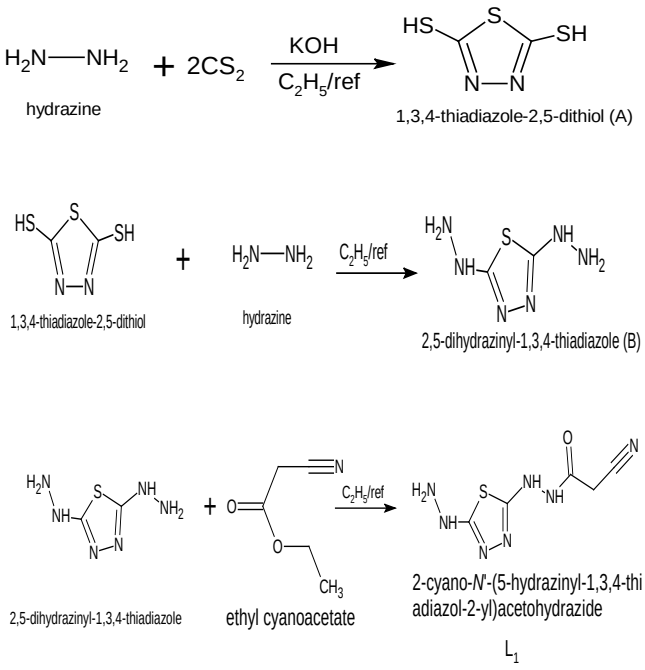
2,5-dimercapto-1,3,4-thiadiazole (A) (10 gm,0.06 mol) dissolved in ethanol, hydrazine hydrate (8ml,0.13 mol) was added , and the mixture was then refluxed for (20 h), the mixture was evaporated to half volume ,Filtered the resulting solid which was separated out on cooling and recrystallized from ethanol to give the desired product (B), the solid (B) was pale white , melting point 198 C^0 , yield 77% [19].

Synthesis of 2-cyano-N'-(5-hydrazinyl-1,3,4-thiadiazol-2-yl)acetohydrazide(L_1).

A mixture of (A) (5 gm, 0.03 mol) in absolute ethanol (50 mL) and (ethyl cyanoacetate) (3.6gm ,0.03 mol) was refluxed (18 h). The product was isolated and recrystallized from ethanol to get yellow ligand(**L_1**) melting point 128 C^0, yield 79%.

Synthesis 2,2'-[1,3,4-thiadiazole-2,5-diyldi(hydrazine-2,1-diyl)]bis(1,3- benzothiazole)(L_2).

The ligand(L_2) was synthesized by condensation of 2,5-dihydrazino-1,3,4-thiadiazole (B) and 2-Mercaptobenzothiazole in ethanol absolute (50ml) , the product was isolated and recrystallized from tetrahydrofuran (THF), the solid (L_2) was light orange crystals, melting point 137 C^0, yield 66%.



Preparation of Complexes

preparation of L_1complexes

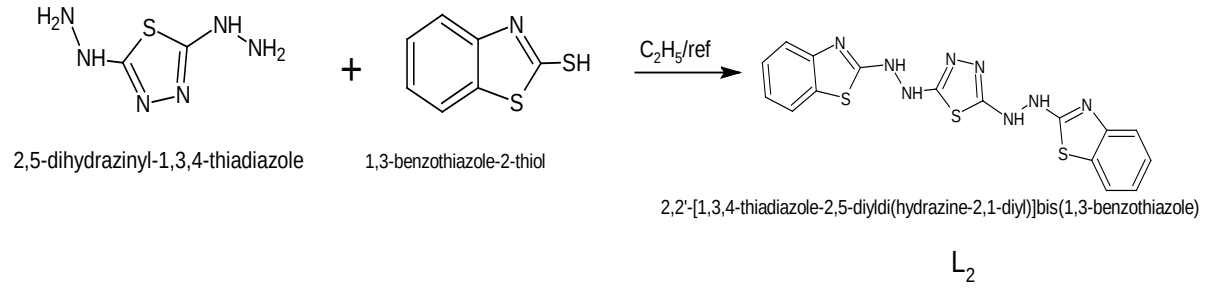
The Ni(II), Cd(II) complexes were prepared by refluxing the respective hydrated metal chloride(0.14 gm,9 mmol) and (0. 21 gm,9 mmol) in 15 ml ethanol with 50 ml of an ethanolic solution of the[L_1](0.2g, 9 mmol) for 3 hr. The resultant solids which separated were filtered, washed with ethanol and dried.

Preparation of L_2complexes

The Ni(II), Cd(II) complexes were prepared by refluxing the respective hydrated metal chloride (0.214 gm,9 mmol) and (0. 21 gm,9 mmol) in 15 ml ethanol with 50 ml of an ethanolic solution of the [L_2](3.22g,0.01mol) for 3 hr. The resultant solids which separated were filtered, washed with ethanol and dried .

RESULTS & DISCUSSION

The physical properties of ligands and its complexes are presented, magnetic susptibility, and molar electrical conductivity in table 1 . The Elemental microanalysis CHN shown in table 2.



Scheme 1. Synthesis of ligands (L_1,L_2)

Table 1. conductance ,magnetic susptibility, physical properties data of the ligands and its complexes

No	Compound	Molecular formula	M.wt	Color	ΛScm^2 mol^{-1}	Mel.Point °C	μ_{eff} B.M.
1	L_1	$C_5H_7N_7OS$	213	Black	-----	130-132	-----
2	[Ni(L_1) Cl_2]	Ni($C_5H_7N_7OS$)Cl_2	342	Brown	16	292-290	0.5
3	[Cd(L_1)Cl_2]	$C_5H_7N_7OS$)Cl_2(Cd	396	light Brown	14	360 d*	0.83
4	L_2	$C_{16}H_{12}N_8S_3$)(	412	light orange	-----	136-137	----
5	[Ni(L_2)Cl_2]	$C_{16}H_{12}N_8S_3$)Cl_2(Ni	541	light Yellow	8	120-122	0.61
6	[Cd(L_2)Cl_2]	$C_{16}H_{12}N_8S_3$)Cl_2(Cd	596	Brown light	18	150-152	0.8

Table 2. Elemental microanalysis CHN for the ligands

	Theoretical			Experimental		
Compound	C%	H%	N%	C%	H%	N%
L_1	28.16 %	3.28 %	5.9 %4	28.3 %	%2.9	%45.2
L_2	46.59%	2.9%	27.16%	46.88%	2.6%	27.4 %

Table 3: Infrared spectra of L and its metal complexes (υ cm-1)

No	υ(N-H)	υ(C=N)	Asy(C-S-C)	Sy (C-S-C)	Stru. Move.	*Other bands*	M-N	M-Cl
1	3474	1624	1457	1280	1010	C=O 1651 CN 2300 C-H 2965	----	----
2	3348	1496	1427	1300	1049	C=O 1608 CN 2106 C-H 2900	470	227
3	3379	1604	1419	1237	1056	C=O 1651 CN 2206 C-H 2954	432	378
4	3259	1701	1427	1238	1006	C=C 1558	-----	-----
5	3113	1611	1427	1242	1005	C=C 1558	667	289
6	3417	1666	1427	1234	1000	1620	**532**	310

FT-IR Spectral

The FTIR spectrum for L_1 shows a characteristic stretching absorption bands at 3474 cm^{-1}, 2300 ,1651 cm^{-1}, 1624 cm^{-1},1457,1280 cm^{-1}assigned to υ(N-H) ,υ(CN**)**, υ(C=N**)**, υ(C=O**)**, asymmetrical and symmetrical C-S-C stretching respectively [21].

The FTIR spectrum for L_2 shows a characteristic stretching absorption bands at 3259cm^{-1}, 3059 cm^{-1}, 1465 cm^{-1},1701 cm^{-1}, 1558 cm^{-1}, 1427 cm^{-1},1238 cm^{-1} assigned to υ(N-H), υ (C-H), υ(C=N) of benzothiazole, υ(C=N) of thiadiazole, υ (C=C) , asymmetrical (C-S-C, **)**, symmetrical C-S-C stretching respectively[[20-25].]. The C=N and N-H stretching vibrations are important to predict the bonding mode of the ligand ,these bands were shifted to the high or low frequencies in the spectra of complexes compare with ligand, observed changes are the evidences of complexion had happened . New bands were formed Attributed to the coordinated (M- N) and (M-Cl) bonds and appeared at the region (524-560) cm^{-1} ,(331-278) cm^{-1} respectively. The IR data of the complexes are shown in Table (3) and figure(1-6). lists the stretching frequency(υ) for some of the characteristics groups exhibited by the (L_1,L_2) and complexes.

Nuclear magnetic resonance

The H^1- NMR spectral data for the L_1 exhibit a singlet signals at (12.06 ppm, 1H), (5.29 ppm,4H) and (2.54 ppm, 2H) due to N-H amide protons N-H protons and C-H protons respectively.[26-28] as showed in the Figure(7).

The 1H-NMR spectra of the ligand L_2 showed signals at (7.4 -8.05 ppm, 8H) due to protons of aromatic rings, spectra of the ligand showed signals at (7.8ppm, 4H) due to N-H protons [25,29]. as showed in the Figure(8).

mass spectra

The mass spectra of ligand(L_1) appeared molecular ion peak at 213m/z which is in conformity with the molecular formula $C_5H_7N_7OS$, other peaks m/z(211,185 ,83,69 ,55,44) are due to the subsequent fragments $[C_5H_3N_9S_2]^{\cdot+}$, $[C_5H_7N_5OS]^{\cdot+}$, $[C_2N_2S]^{\cdot+}$, $[C_3H_2NO]^{\cdot+}$ $[CHN_3]^{\cdot+}$, $[C_2H_2O]^{\cdot+}$ respectively as shown in Figure (9). The mass spectrum of the complex [Ni(L_1) Cl_2] shows a molecular ion peak at m/z (342) which is equivalent to molecular mass of the complex the complex spectrum shows fragment ion peak with loss two chlorine atom at m/z (306,271) due to[Ni(L_1) Cl] $^{\cdot+}$and [Ni(L_1)] $^{\cdot+}$ respectively. The mass spectrum of the complex [Cd(L_1) Cl_2] shows a molecular ion peak at m/z (396) which is equivalent to molecular mass of the complex. the complex spectrum shows fragment ion peak with loss two chlorine atom at m/z (361,324) due to[Cd(L_1) Cl] $^{\cdot+}$and [Cd(L_1)] $^{\cdot+}$ respectively as shown in Figure (10,11).

The mass spectra of ligand(L_2) appeared molecular ion peak(parent peak) at 412 m/z which is in conformity structure(L_2) other peaks m/z (336,332,290,122,108,95,82) are due to the subsequent fragments $[C_{10}H_8N_8S_3]^{\cdot+}$, $[C_{11}H_6N_7S_3]^{\cdot+}$, $[C_{10}H_9N_7S_2]^{\cdot+}$, $[C_6H_4NS]^{\cdot+}$, $[C_6H_5S]^{\cdot+}$, $[C_5H_3S]^{\cdot+}$, $[C_4H_3S]^{\cdot+}$ respectively as shown in Figure (12). The mass spectrum of the complexes [Ni(L_2) Cl_2], [Cd(L_2) Cl_2] shows a molecular ion peak at m/z (541,595) respectively. which is equivalent to molecular mass of the complexes. This complexes shows another a fragment ion peak with loss of chlorine atom at m/z (505,470) for Ni(II) complex and m/z(559,524) for Cd(II) complex as shown in Figure (13,14).

Magnetic Susptibility

The magnetic momentum for each metal complex is listed in table 1 .these magnetic measurements give an idea about the electronic state of the transition metal ion of the complexes and type of ligand. The observed magnetic momentum value of L1Ni (II) complex was 0.5 BM, expected for square plainer geometry. The magnetic momentum value was 0.83 BM for L1Cd (II) complex expected for tetrahedral geometry, the value 0.61 BM for L_2Ni (II) suggesting square plainer geometry while the value 0.8 BM for L2Cd suggesting tetrahedral geometry.[25] we conclude that the ligand works as strong ligand (strong field).

Molecular Electrostatic Potential (MEP)

Electrostatic potential is very important in finding the active site in the molecule system with a positive point charge. The species that have positive charge tend to attack a molecule where the electrostatic potential is strongly negative (electrophilic attack) Electrostatic potential of free

ligands were measured and plotted as 2D contour to find the active site of molecule as shown in figures(15-22)

Biological Activity

The ligand and its transition metal ions complexes were evaluated for antimicrobial activity against gram positive bacteria such as Staphylococcus aureus and gram negative bacteria Escherichia coli, by using agar well diffusion method. All the microbial cultures were adjusted to 0.5 McFarland standard, dimethyl sulphoxide (DMSO) were used to prepared all the test solution .The area of inhibition was measured in millimeter. nutrient agar used as culture medium.

Table 4: Anti-bacterial data of ligand and its complexes

Compound	Escherichia coli Inhibition zone(mm)	Staphylococcus Aurens Inhibition zone(mm)
Gentamycin	20	23
L_1	12	10
$[Cr(L_1)\ Cl_2]Cl$	25	25
$[Cd(L_1)Cl_2]$	18	20
L_2	20	18
$[Ni(L_2)Cl_2]$	20	25
$[Cd(L_2)Cl_2]$	20	20

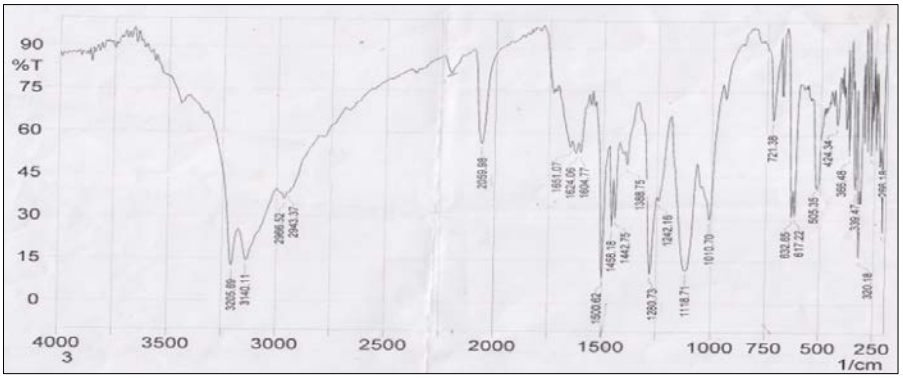


Figure 1: IR spectra of L_1

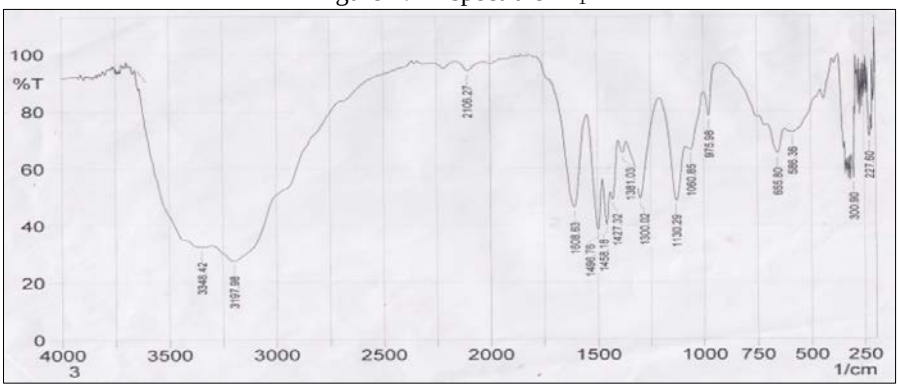


Figure 2: IR spectra of $[Ni(L_1)Cl_2]$

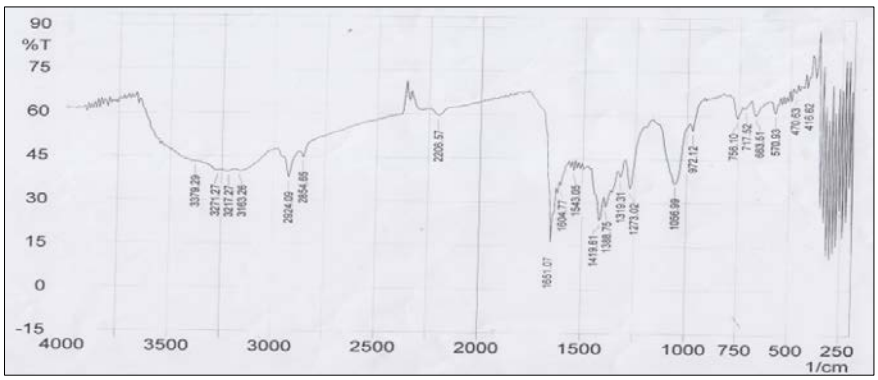


Figure 3: IR spectra of $[Cd(L_1)Cl_2]$

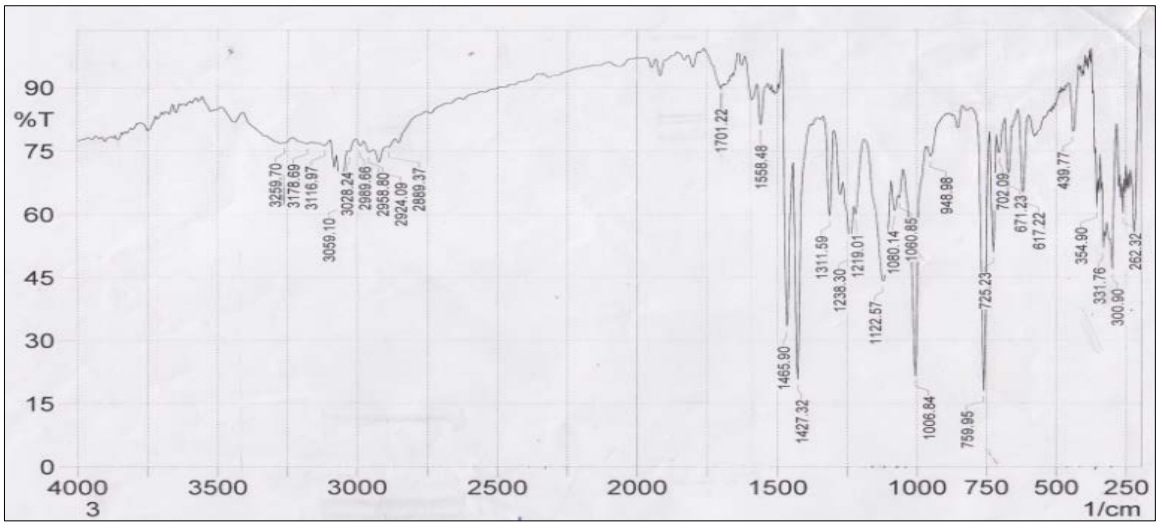


Figure 4: IR spectra of L_2

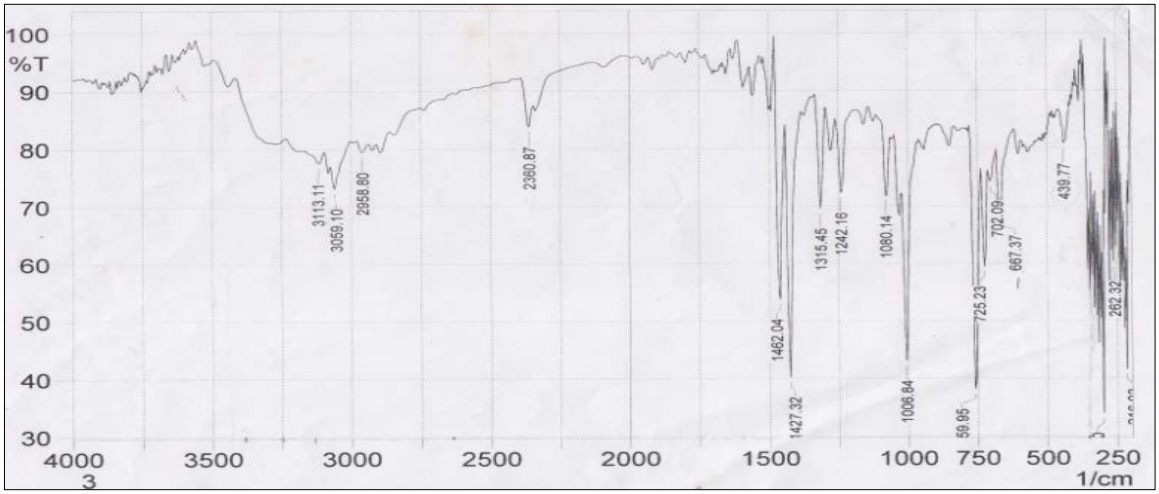


Figure 5: IR spectra of $[Ni(L_2)Cl_2]$

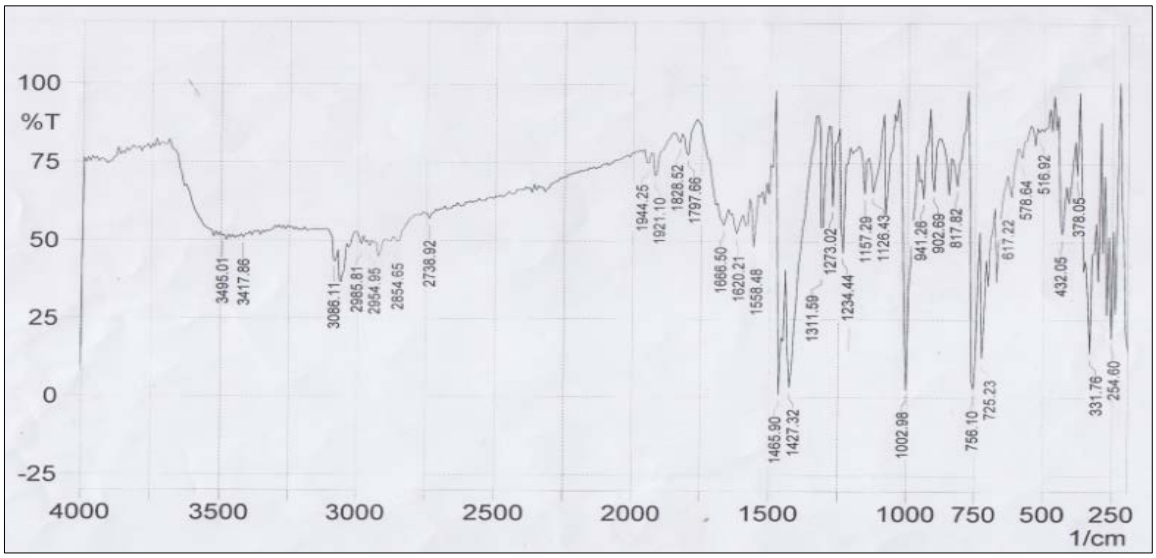


Figure 6: IR spectra of $[Cd(L_2)Cl_2]$

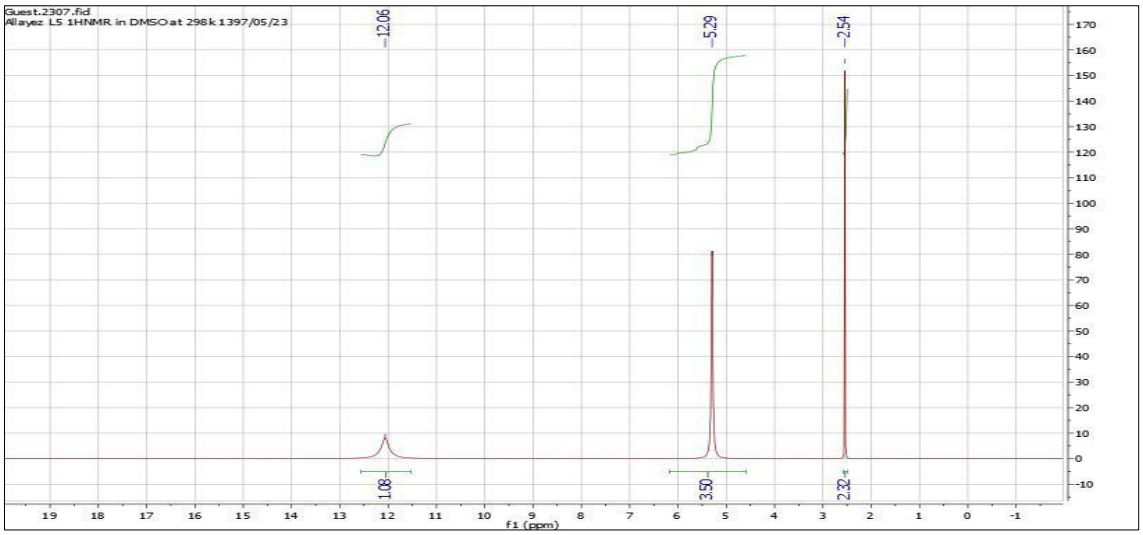


Figure 7 .H^1- NMR spectra of the ligand L_1

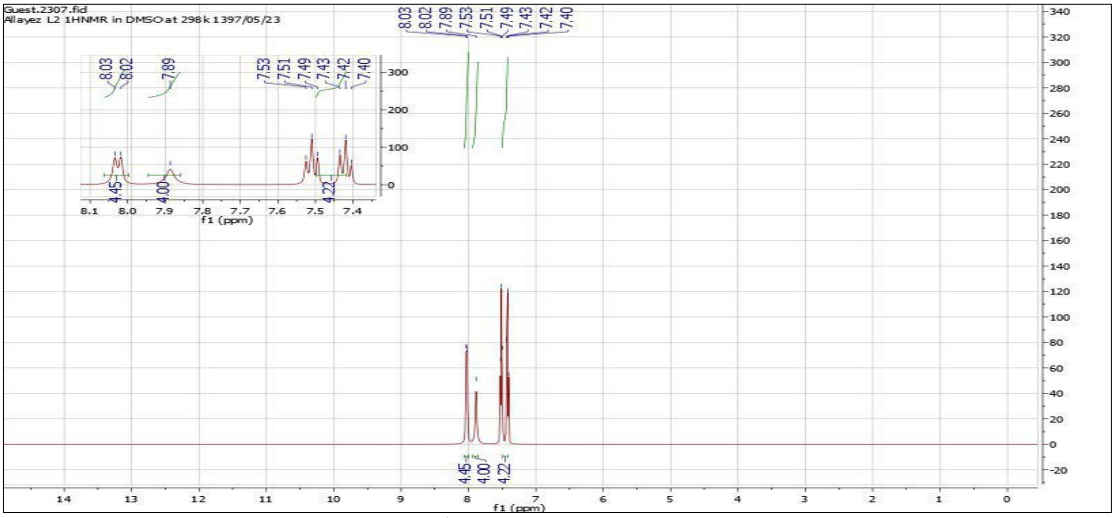


Figure 8 .H^1- NMR spectra of the ligand L_2

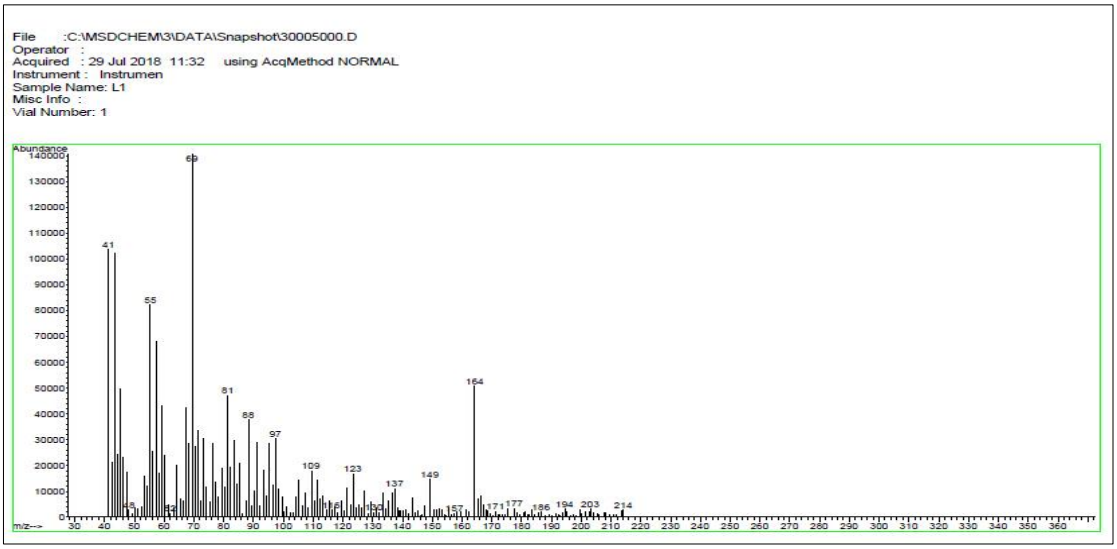


Figure 9 . mass spectra of ligand L_1

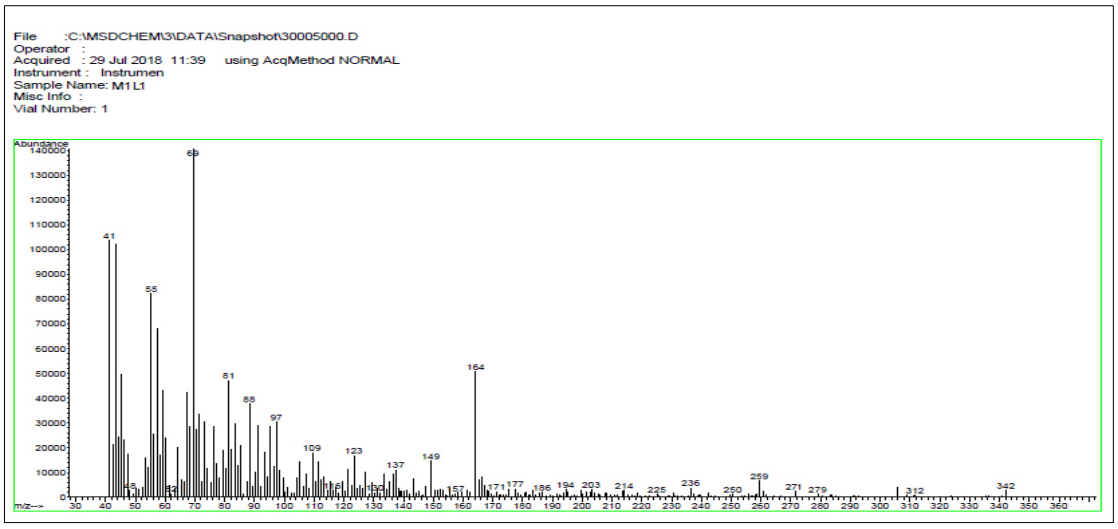


Figure 10 .mass spectra of $[Ni(L_1)Cl_2]$

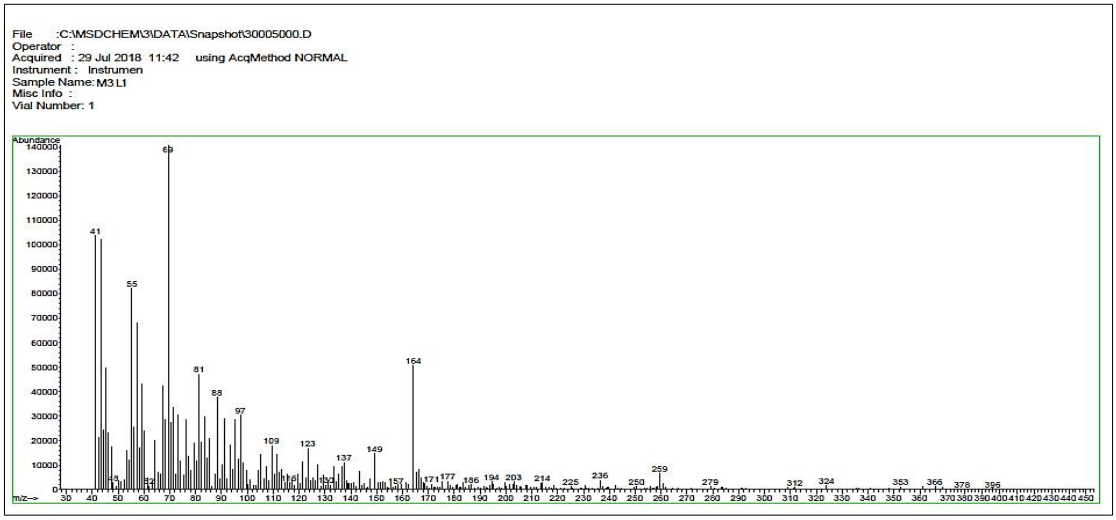


Figure 11 .mass spectra of $[Cd(L_1)Cl_2]$

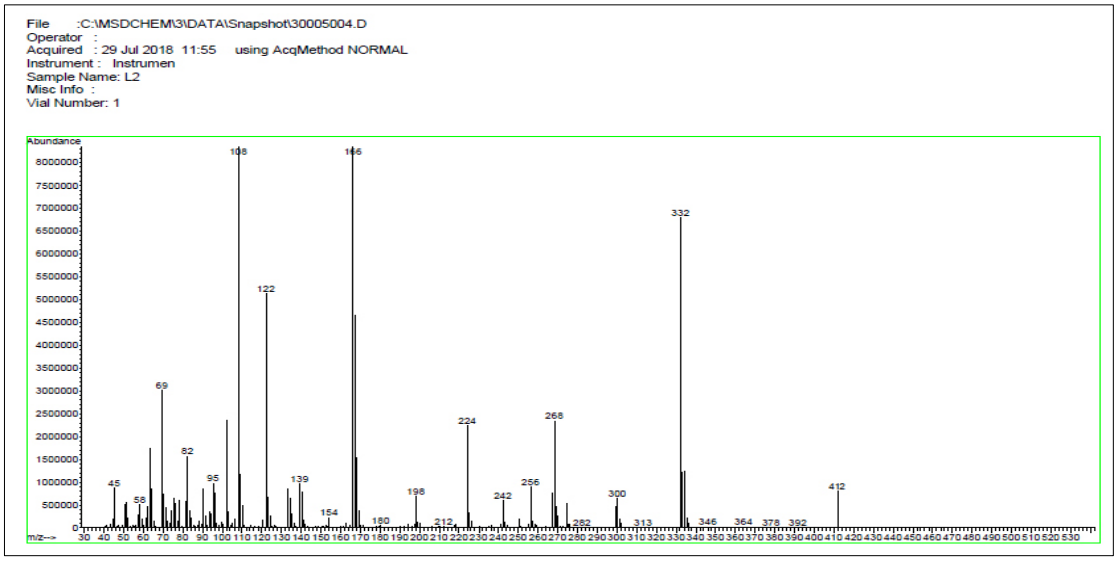


Figure 12 . mass spectra of ligand L_2

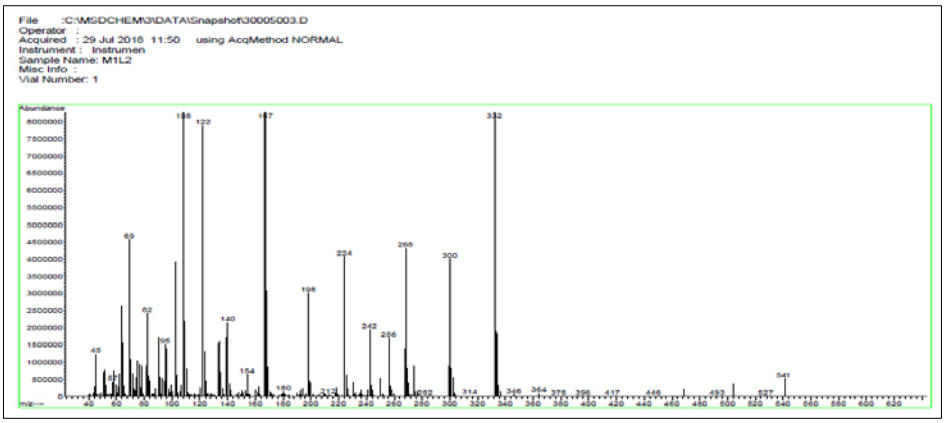


Figure 13 .mass spectra of $[Ni(L_2)Cl_2]$

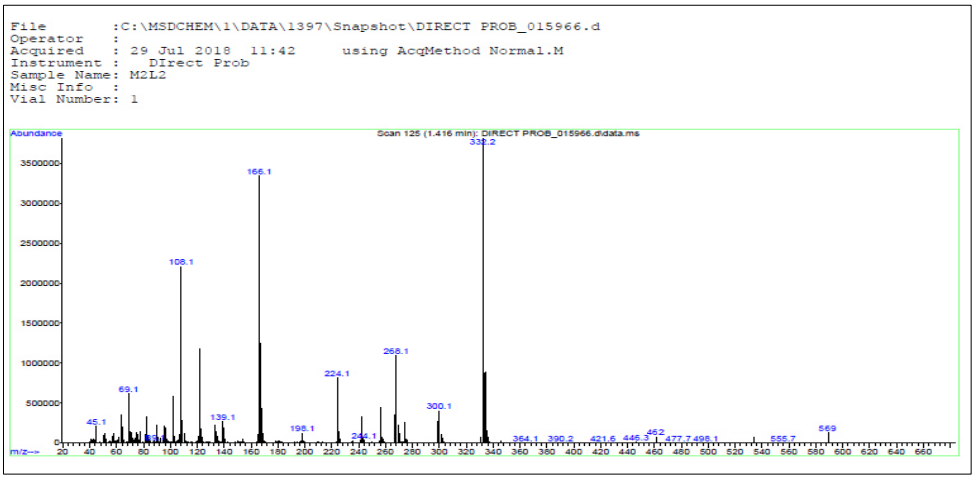


Figure 14 .mass spectra of $[Cd(L_1)Cl_2]$

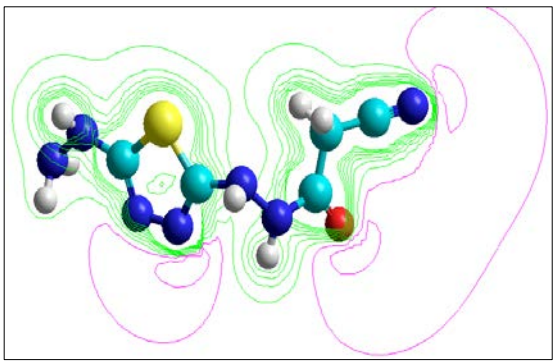


Figure 16:Electrostatic potential 2D of L_1

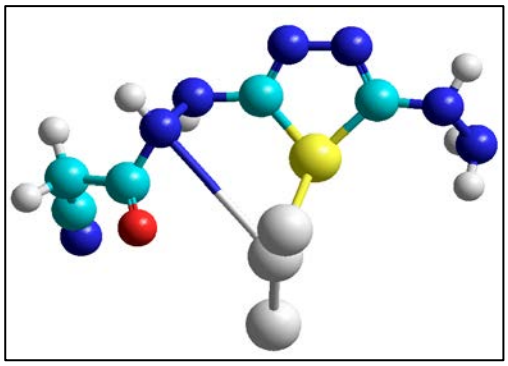


Figure 18: Graphical presentation of stereochemistry of $[CdL_1Cl_2]$

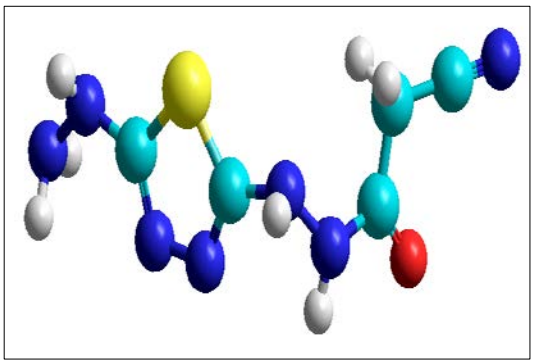


Figure 15: Graphical presentation of stereochemistry of L_1

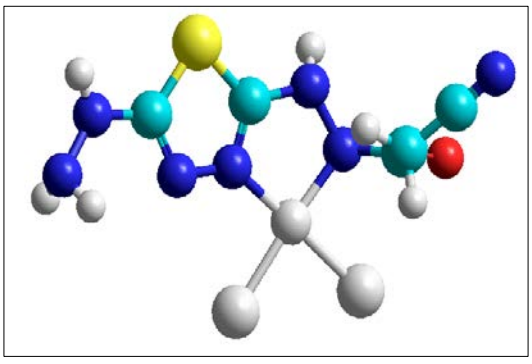


Figure 17: Graphical presentation of stereochemistry of $[NiL_1Cl_2]$

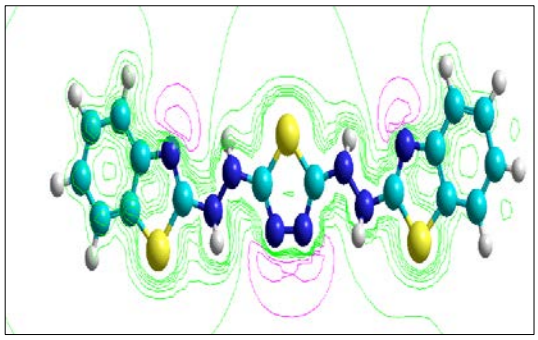


Figure 20:Electrostatic potential 2D of L_2

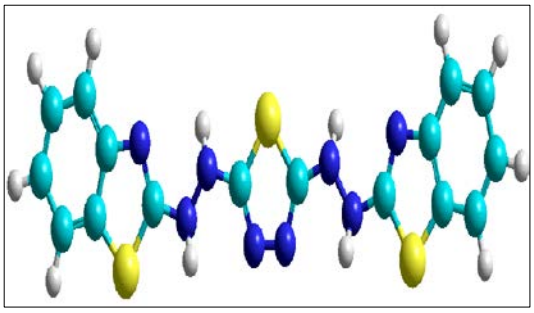


Figure 19: Graphical presentation of stereochemistry of L_2

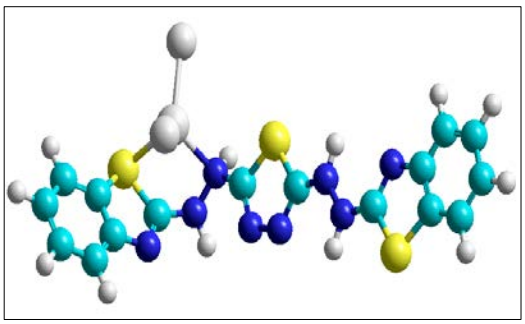


Figure 22: Graphical presentation of stereochemistry of $[CdL_1Cl_2]$

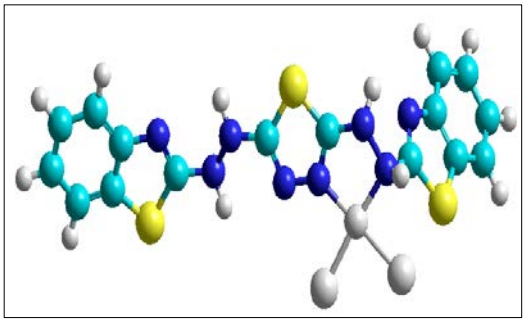


Figure 21: Graphical presentation of stereochemistry of $[NiL_2Cl_2]$

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