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Synthesis, Characterization and Antioxidant Study of New 4-Methoxy-2-{(Z)-[(3-Phenyl-5-Sulfanyl-4H-1,2,4-Triazol-4-Yl)Imino]Methyl}Phenol and Their Transition Metal Complexes

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Abstract

The present study included synthesis a new 4-methoxy-2-{(E)-[(3-phenyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl}phenol and its complexeswith Ni(II) , Co(II), Cu(II) ions were synthesized.
,characterization by conductance measurements , magnetic susceptibility, mass spectra, 1HNMR , IR , and elemental analyses .Their conductance confirmed the nonelectrolytic behavior of them. data spectral study of transition metal complexes suggest octahedral geometry for Co^{+2} ion , square planer geometry for Ni^{+2} and 0.83 BM for Cu(II) suggesting tetrahedral geometry . The effective magnetic moment of cobalt complex is 3.8 BM , 0.51 BM for Ni^{+2} and 0.83 BM for Cu^{+2} . The ligand were tested antioxidant the prepared ligand showed good antioxidant activity.

Keywords: - Triazole , Transitions metal complexes, antioxidant activity

Introduction

The chemistry of heterocyclic compounds is the largest and one of the classical branches of organic chemistry is heterocycles , also it is one of the most complex divisions of organic chemistry. It is equally interesting for its theoretical implications, for the variety of its synthetic procedures, and for the industrial and physiological significance of heterocyclic compounds. The most of pharmaceutical products that mimic natural products with biological activity are heterocycles. There were about 20 million chemical compounds specified by the end of the last century, more than two thirds were partially or fully aromatic and about one-half were hetero aromatic. The heterocyclic chemistry providespermanentand aninexhaustible resource of novel compounds [(1)].

Triazole one class of a family of five-membered heterocycles contain from three nitrogen atoms and predominantly take place in different isomeric forms: 1,2,4-triazole and 1,2,3-triazoleexists in two tautomeric forms as shown in Figure (1).
Triazole was first time synthesed by Fischer in1878. Triazole derivatives have attracted fantastic attention because to their comprehensive properties [(2,3)].
1,2,4-triazole comprising derivatives exhibited wide range of bioactivities suchas anticonvulsant [(4)], antimicrobial [(5)], antitubercular [(6)], anticancer[(7)], anti-inflammatory [(8)], analgesic [(9)], antiviral [(10)], insecticidal , plant growth regulator [(11,12)] , antiasthmatics [(13)] and antidepressants [(14)].
Theyare stable to metabolic degradation and their efficient binding to biomolecular targets also high solubility due hydrogen bonding [(15)]. 1,2,4-triazoles are capable of preparing bifunctional drug by acting as a binder between two pharmacophores [(16,17)]. 1,2,4-Triazole is the core structure of many therapeutically Interesting drug candidate including CNS depressants such as etizolam**(1)** [(18)], triazolam (**2**) [(19)], alprazolam **(3)** [(20)], etc.; aromatase inhibitors such as letrozole (**4**) [(21)], anastrazole **(5)** [(22)], vorozole (**6**) and; antimycotic agents such as epoxiconazole **(7)**, voriconazole (**8**), anticonvulsants such as estazolam (**9**) [(23)]; tebuconazole **(10) ,**

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antiviral such as ribavirin **(11)** [24]and hexaconazole **(12)** [25].
In addition to their a significant biological activities, 1,2,4-triazoles have also played aninteresting role in synthetic chemistry. Theyare used in the synthesis of diverse bioactive heterocyclic compounds such as schiff bases [26], mannich bases [27], thioureas [28], thioethers , schiff bases[29],triazolothiazines, triazolothiazepines [30] , triazolothiadiazoles and triazolothiadiazines [31].

Figure (1)

2- Chemistry of 1,2,4-triazoles

The stability of 1,2,4-triazole nucleus is an ingrained property of itsaromatic nature. An aromatic sextet is created by contribution of one πelectron from each atom linked by double bonds and the residual twoelectrons from a nitrogen atom. This a system is stabilized by resonance andalthough the triazole ring may be represented by tautomeric forms, eachtautomer case is capable of extended resonance and its structure is more exactlyrepresented as a hybrid to which the following the original forms contribute[32], expression is to regard 1,2,4-triazoles as a true aromatic system, stabilized byresonance and represented belowFigure (2) .

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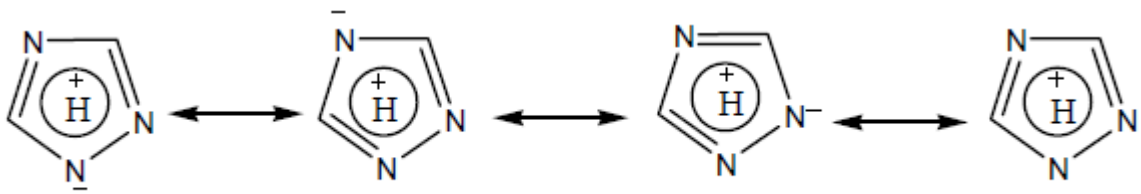


Figure (2)

3. Experimental

All chemicals used are supplied from PDH and Merck companies and utilized without any further purification. All metal salts were utilized as chloride .

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3.1. Physical Measurements

Melting point of the ligand and its metal complexes were recorded by an electro thermal melting point instrument model (Melting SMP31).
The FTIR spectra were checked as (KBr) disc for ligand and(CsI) for complexes utilized a Shimadzu FTIR spectrophotometer in the domain (400-4000 cm-1) (Model: IR- affinity, Shimadzu).
1H NMR Spectra were geted by using Bruker DXR System AL500 (500 MHz), TMS utilize as standard, DMSO-d6 used as solvent .
Molecular weights were recorded with Mass Spectra (MS) were listed in the range (0-800) were geted by (Network Mass Selective Detector 5973).

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The Elemental Analyzer device for the synthesis ligand were done on a LECO elemental analyzer/CHNS-932.

3.2. Synthesis of the ligand:

New ligand 4-methoxy-2-{(*E*)-[(3-phenyl-5-sulfanyl-4*H*-1,2,4-triazol-4-yl)imino]methyl}phenol (Scheme 1) was prepared as follows:-

3.2.1. Synthesis of benzohydrazide (A)

methyl benzoate (0.08 mol,10 ml) was added to hydrazine monohydrate (0.2 mol,10 ml) in ethanol absolute (100ml). The mixture was heated under reflux for (10 hours). The mixture was concentrated**,** The product was filtered and washed with ethanol to get the **product** (A) benzohydrazide(soild) , white color ,melting point 118 C°, yield 92%) [33].

3.2.2. Synthesis of potassium (2-benzoylhydrazinyl)disulfanide (B)

benzohydrazide (A) (0.1mol, 13.6 g) mix with solution of Potassium Hydroxide (KOH) (0.15mol, 8.4g)dissolved in(100 ml) absolute ethanol then added carbon disulfide(CS_2) (0.15 mol,9 ml) after mixture was cooled at 0 C°. The resulting mixture was shaken by stirrer at room temperature for (16-18 hours). It was then diluted with dry ether (200 mL) and the products were filtered off and vacuum dried at 60-65 ºC. The salts prepared as described above were got in nearly good yields and were used without recrystallize .The resultant was Yellowish white crystalsof salt potassium 2-benzoylhydrazine-1-carbodithioate (B).

3.2.3. Synthesis of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol (C)

A salt(B) (5 g , 0.02 mol) , water (2 ml was added to salt , than hydrazine monohydrate (0.04 mol ,2 ml), the mixture was putted under heating and reflux for 48 hr or until H2S gas was stopped , the mixture was cooled and water (100 ml) , and gently acidified with hydrochloric acid HCl (10%) This product was filtered, washed with cold water (30 mL) and recrystallized . It wss obtained white precipitate 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol (C) melting point 205 C°[34] .

3.2.4. Synthesis of 4-methoxy-2-{(Z)-[(3-phenyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl}phenol (L)

The Schiff bases have been prepared by condensation of precipitate (2,3 g , 0.012 mol) 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol (C) and (1.8 g , 0.012 mol) 2-hydroxy-5-methoxybenzaldehyde with ethanol absolute (100ml) for (3hours). The yellow precipitate of ligand formed were filtered, washed with cold ethanol and recrystallized from ethanol (solid, yellow , melting point 240 °C, yield 80%) [35].

3.3. Synthesis of complexes

A solution of $CoCl_2$.6H2O, $CrCl_2$.6H2O and $NiCl_2$.6H2O) (0.001 mol) was mixed with (L) (0.326 g , 0.001 mol) in ethanol absolute heating with and refluxed for 4 hrs. the resultant precipitated is complex was filtered, washed with ethanol absolute .

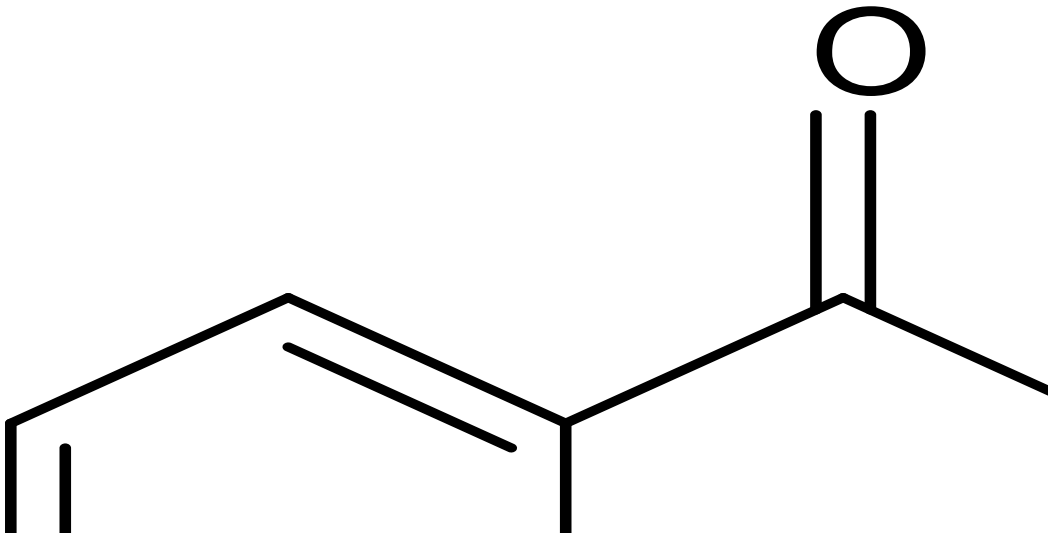
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Figure (3)

4. Result and discussion

4.1 Synthesis of ligand L

The ligand L was prepared by several steps which has been outlined in **Scheme 1**. First the key intermediate **(C)** was synthesized in four steps (**1-4**) starting from methyl benzoate. The compound **(C)**react with (2-hydroxy-5-methoxybenzaldehyde) afforded the desired ligand **L**.



scheme (1)

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Table (1) physical properties of the ligand and its complexes

No.	formula	colour	M(g/mol)	ʌ s cm^2 mol^{-1}	M.p ^{0} C	μeff. B.M
1	$C_{16}H_{14}N_4O_2S$	yellow	326	……	235	……
2	[Co(L_1) Cl_2 .2 H_2O]	white	492	9.74	193	3.8
3	[Ni(L_1) Cl_2] .2 H_2O	yellow	492	10.12	210	0.51
4	[Cu(L_1) Cl_2] .2 H_2O	green	495	13	245	0.83

4.2. FT-IR spectral

FT-IR spectroscopy is one of important tools which used characterization of functional group in of the prepared ligand and complexes were carried out using KBr disc and CsI for to ligand and complexes respectively.

The free ligand (L) exhibited nine major bands at (3297), (3189), (3104),(2933) ,(1633), (1533),(1529) , (1232) and (1068) cm^{-1}. Which are corresponding with (υO-H), (υN-H), (υC-H aro) , (υC-H Elaph) (υC=N)oxo , (υC=N)endo,(υC=C), (υC-N-C)sym, (υ C-N-C)asy structure movement bands respectively, as shown in table (2) and figure(5). New bands were formed corresponding with the coordinated (M- N), (M-S) and (M-Cl) bonds and shown at the region (680-690) cm^{-1}, (350-366)$cm^{-1}$and (265-324) cm^{-1}respectively.

Table (2) Infrared spectra of L and its metal complexes (υ cm-1)

Assign ment	**Wavenumber (cm^{-1})**			
	L1	Co	Ni	Cu
OH	3297	3348	3360	3313
NH	3189	2934	3360	3105
Ar(C-H)	3104	2927	2974	3052
Elf(C-H)	2933	2893	2893	2939
Azo(C=N)	1633	1627	1654	1627
Het(C=N)	1533	1573	1562	1573
(C=C)	1529	1543	1489	1543
Asy(C-O-O)	1232	1269	1265	1269
Sym(C-O-C)	1068	1161	1161	1188
M-N	-------	690	687	690
M-S	-------	366	358	366
M-Cl	--------	324	289	270

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4.3. Nuclear Magnetic Resonance

The 1HNMR spectra data of the **4-methoxy-2-{(Z)-[(3-phenyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl}phenol (L) ,** The H1-NMR spectral data gave other support for the suggested structure of the ligand , that showed signals at (2.51and3.35ppm) the first due to protons of the solvent
(DMSO) and the second for the D_2O , (3.71 ppm, 3 H) due to protons of methoxy group (6.94-8.04 ppm,m,8H) due to protons of aromatic rings,
, (9.95 ppm , 1 H) due to proton of azo methane group (-N=CH-), (10.06 ppm, s,1H) due to OH group and (14.2 ppm, s,1H)due to N-H proton [(36)],as shown in figure (9).

4.4. Mass spectra

The mass spectra of 4-methoxy-2-{(Z)-[(3-phenyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl}phenolappeared molecular ion peak at 326 m/z which is in conformity with the molecular formula $C16H14N4O_2S$. Other peaks are due to the subsequent fragments like $[C14H12N4OS]^{\cdot+}$=283 m/z, $[C8H7N3S]^{\cdot+}$=177 m/z , $[C8H8NO2]^{\cdot+}$=149 m/z,
$[C_8H_8O_2]^{\cdot+}$=136 m/z .
The mass spectral of the Co(II) complex showed molecular ion peaks at 492 m/z corresponding to [Co(L) Cl2].$2H_2O$ $^{\cdot+}$stoichiometry . This complex shows another a fragmentation peaks at 439 m/z due to loss one chlorine atom and one water molecule , 422 m/z due to loss one water molecule . The mass spectral of the Ni(II) complex showed molecular ion peaks at 492 m/zcorresponding to [Ni(L)Cl2].$2H_2O^{\cdot+}$stoichiometry . This complex shows another a fragmentation peak at 326 m/z due to loss tow water molcules and two chlorine atoms. The mass spectral of the Cu(II) complex showed molecular ion peaks at 495 m/z corresponding to [Cu (L)Cl2].$2H_2O^{\cdot+}$stoichiometry . This complex shows another a fragmentation peaks at 479 m/z due to loss one water molecule ,326 m/z due to loss two chlorine atoms and one water molecule as shown in figure (10-13).

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3.5. Magnetic susceptibility

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. The observed magnetic momentum value of Co(II) complex was 3.8 BM , expected for octahedralgeometry, 0.51 BM for Ni(II) , expected for square, geometry , and 0.83 BMfor Cu(II) suggestingfor tetrahedral geometry.

4.6. Evaluation of Antioxidant Activity

DPPH scavenger was used for estimation of antioxidant activity of 4-methoxy-2-{(Z)-[(3-phenyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl}phenol. The ethanol solution of each DPPH scavenger and the ligand was synthesized inconcentration 1 mM and then 1 ml of DPPH solution was mixed with (0.5, 1, 2) ml of the ligand solution tobecome the new concentration (100, 200, 400)µM and then absorption measuring for each solution at 516 nm after (1, 2,3) hr , the ligand gave high antioxidant activity because NH and OH group donate the hydrogen atom to the freeradical to become more a stable free radical by HAT mechanism . This stability enhances with the extent of delocalization and the IC50 (ligand concentration required to decrease the absorbance of the DPPH control solution by 50%)[(37)] was identified. The IC50 is reduce with the increasing of a concentration of solution and the time. As shown in table (3) and figure (4)

Activity inhibition = (AC-ACS/AC) *100(1)

Where, AC= the absorbance of control DPPH, ACS= the absorbance of control and sample

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Table (3) antioxidant data

Comp.	Conc. µM	Time (1h)		Time (2h)		Time (3h)	
		inh	IC50	inh	IC50	inh	IC50
L1	100	57	88	73	69	91	56
	200	60		81		94	
	400	65		88		97	

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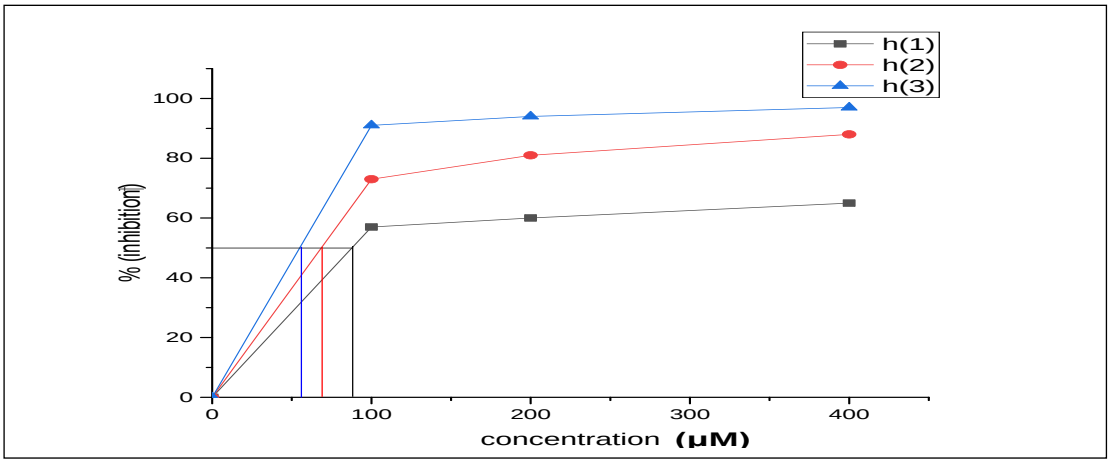


Figure (4) antioxidant activity for ligand

Conclusion:

The ligand acts as a bidentate ligand. The spectroscopic data display the involvement of CH=N groups in coordination to the central transition metal ion. The molar conductance confirms that all the complexes are inelectrolyte. According to a magnetic susceptibility to characterization of transition metal complexes shown that a tetrahedral geometry for Co (II), Ni(II) and Cu(II).

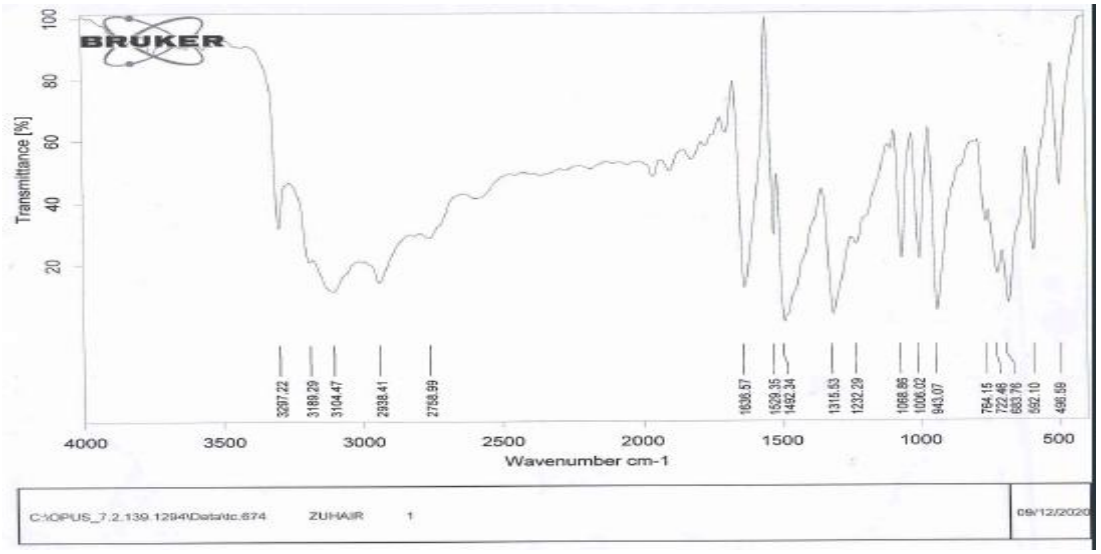


Figure (5) . IR spectra of legand

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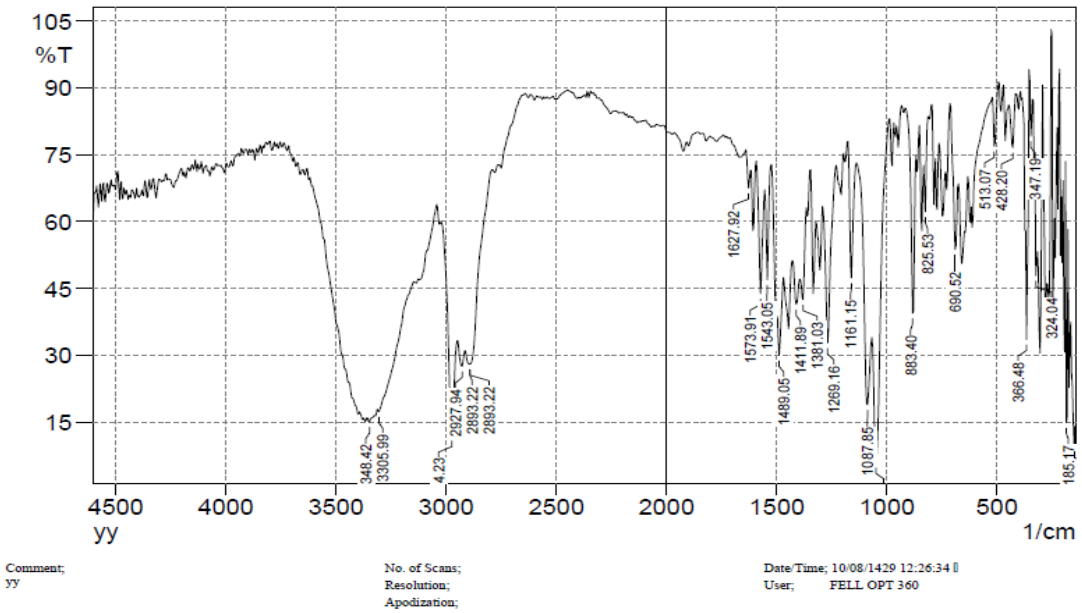


Figure (6) . IR spectra of $[Co(L)Cl_2] . 2H_2O$

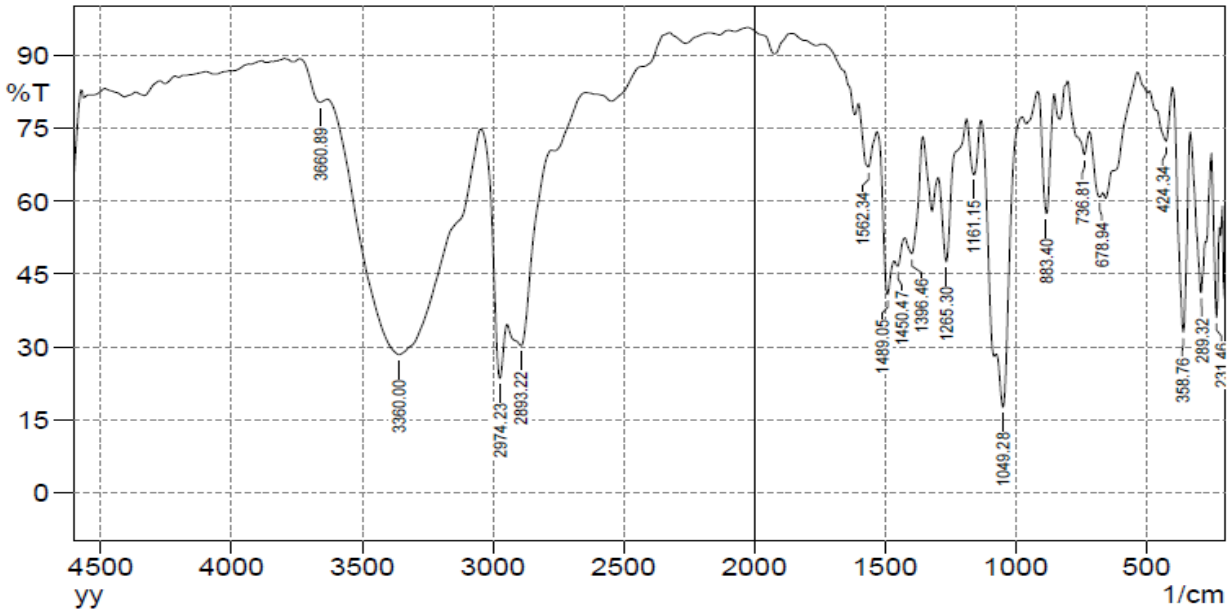


Figure (7) . IR spectra of $[Ni(L)Cl_2] . 2H_2O$

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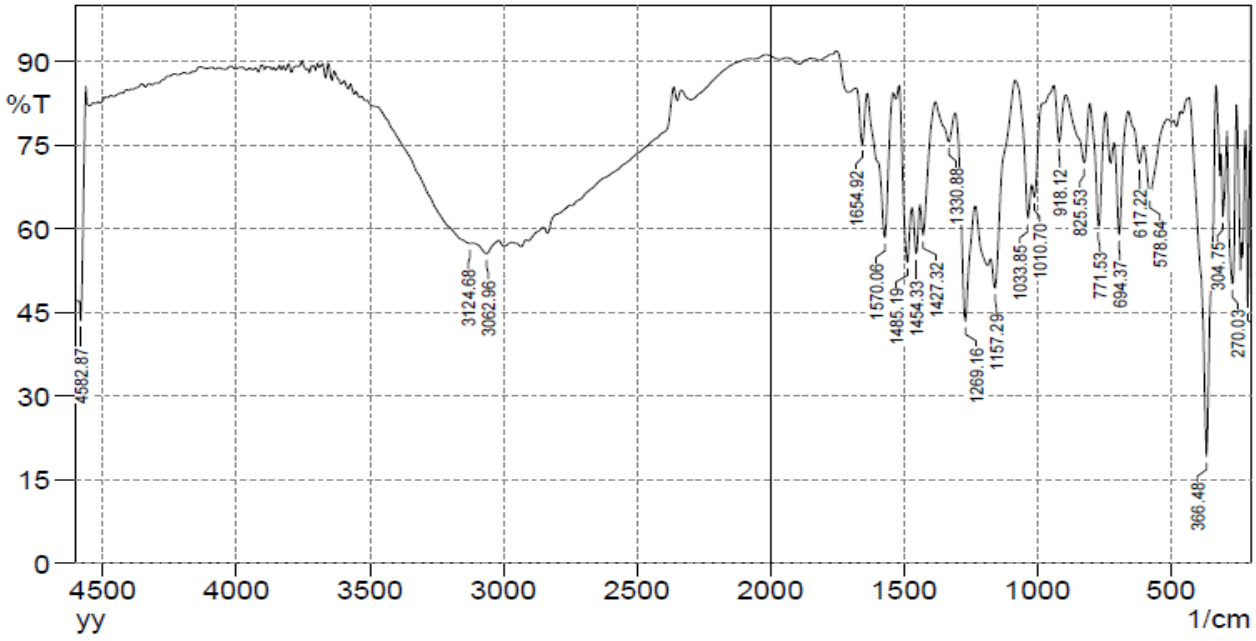


Figure (8) . IR spectra of $[Cu(L)Cl_2] . 2H_2O$

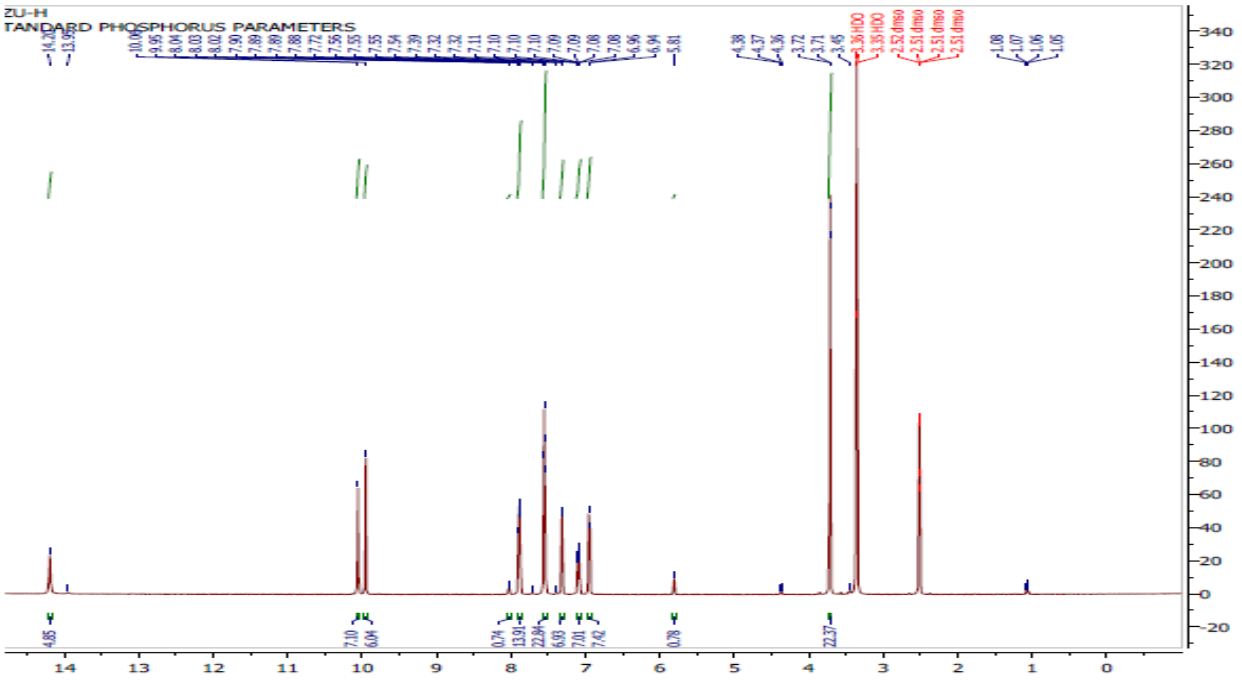


Figure (9). H1 NMR spectra of the ligand

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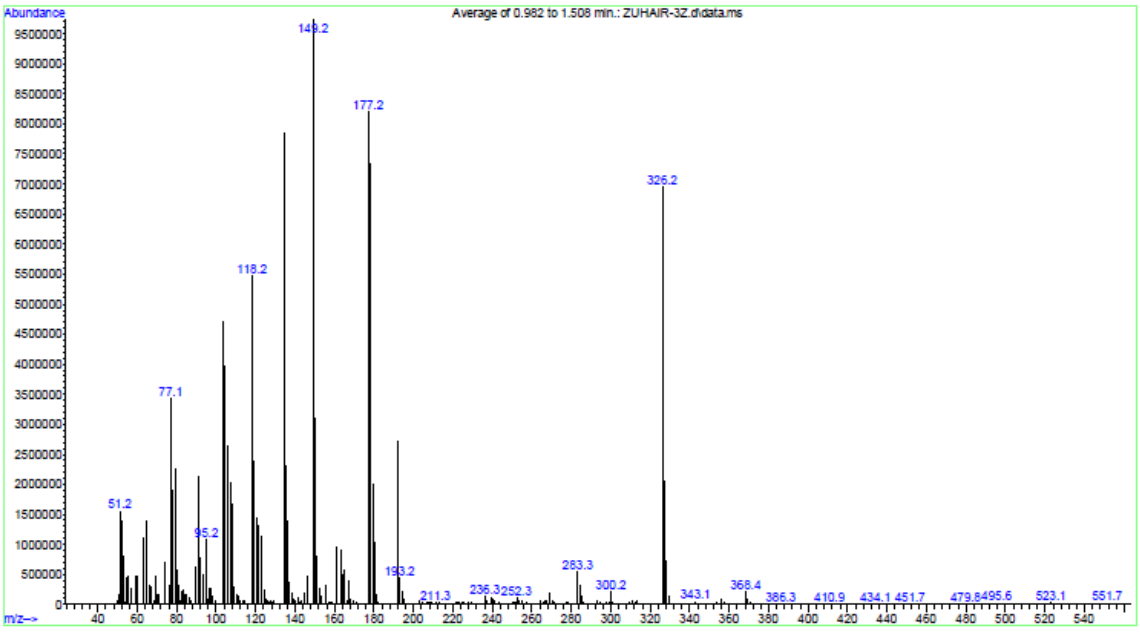


Figure (10). Mass spectra of the ligand

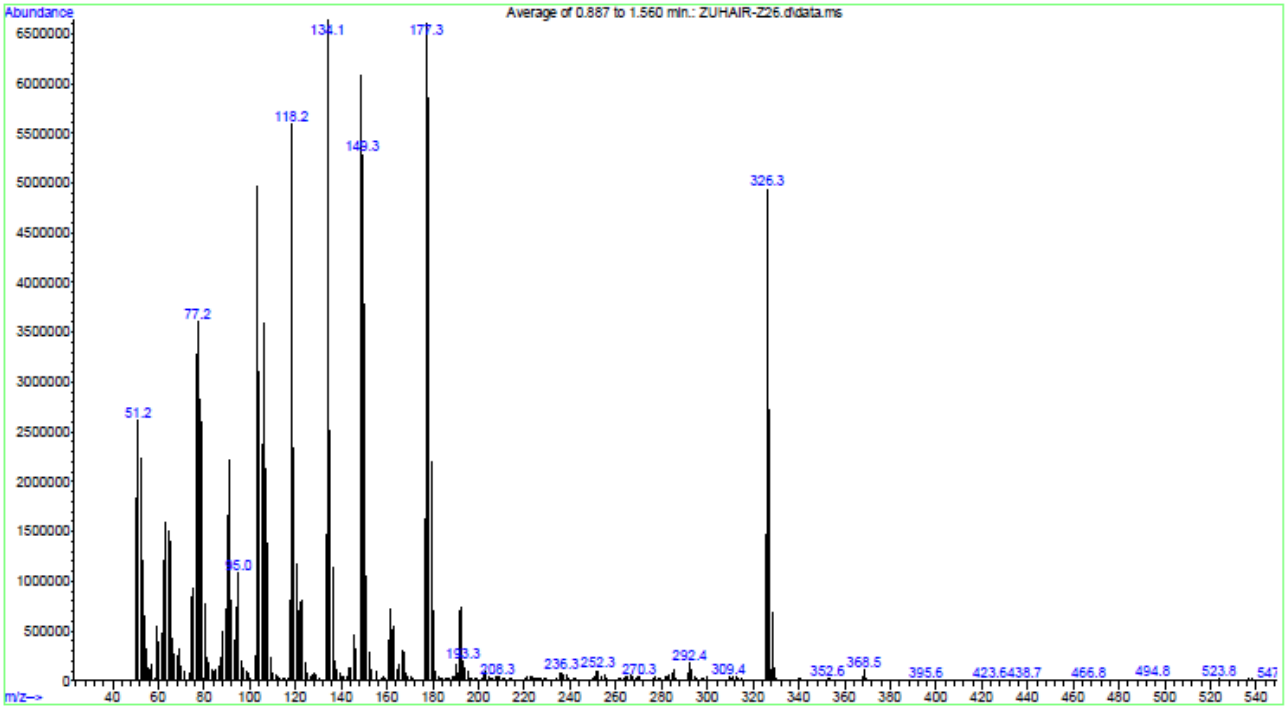
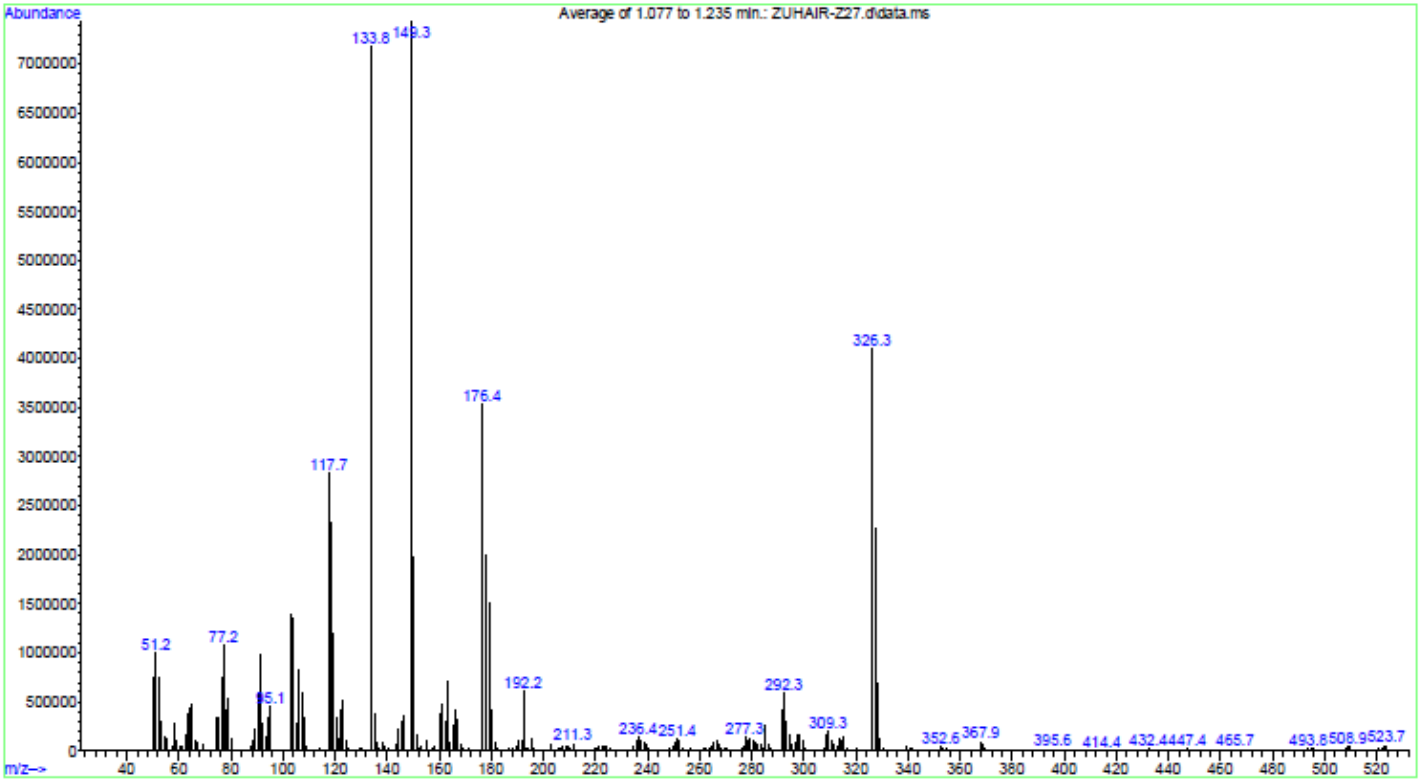


Figure (11). Mass spectra of the complex [Co(L)Cl2]. $2H_2O$

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Figure(12). Mass spectra of the complex [Ni(L)Cl2]. $2H_2O$

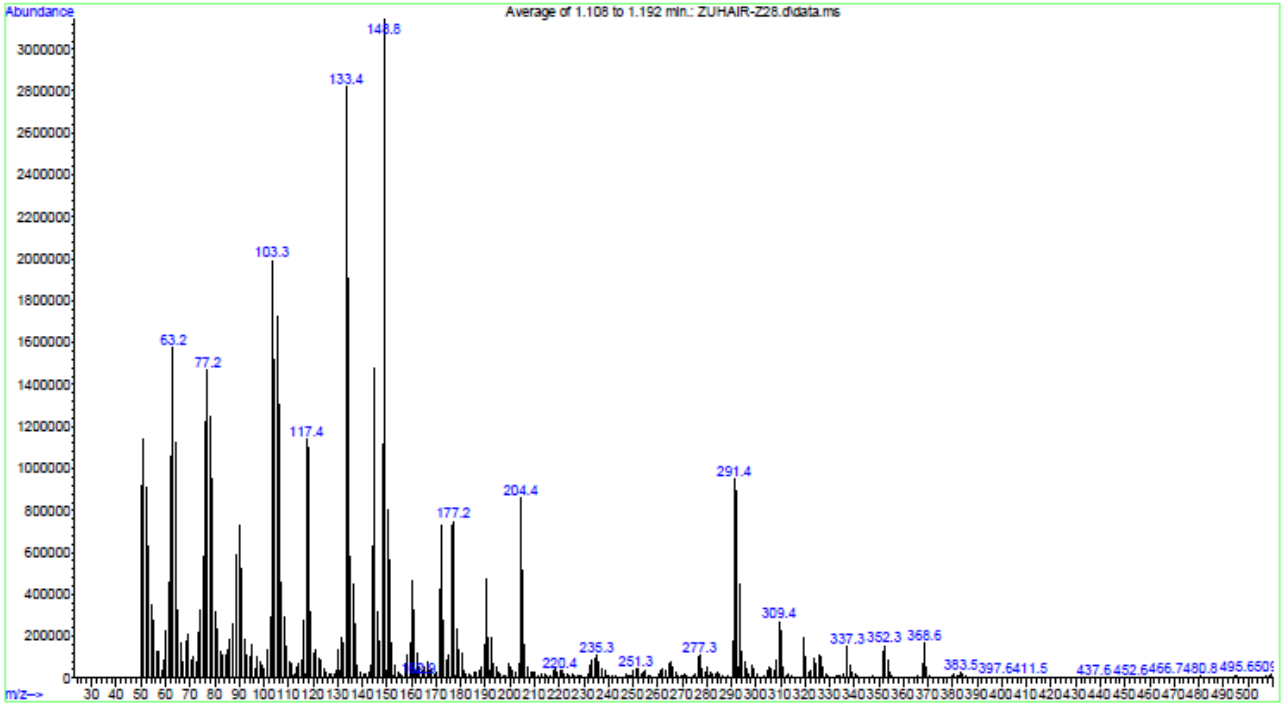
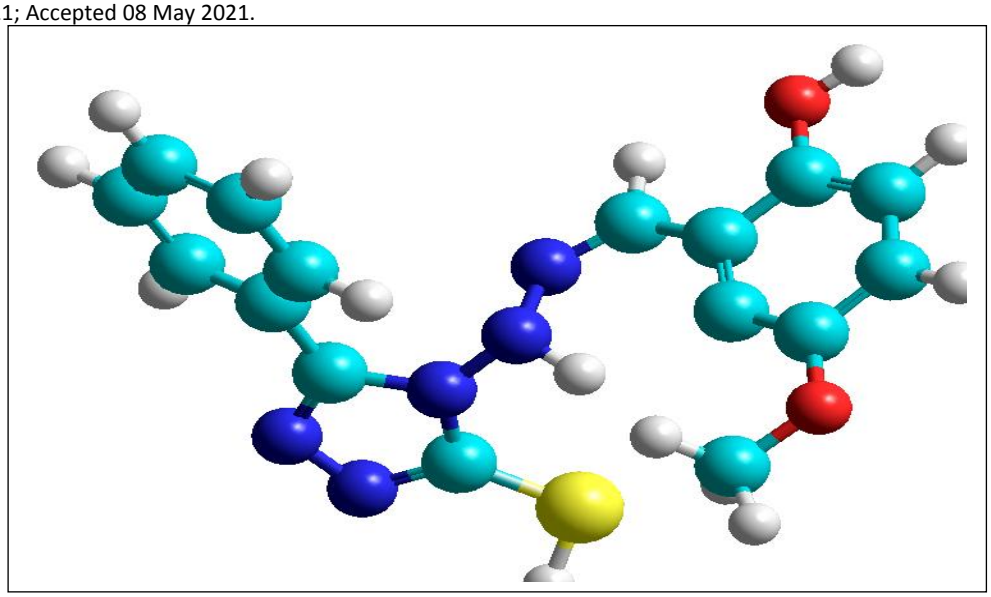


Figure (13). Mass spectra of the complex [Cu(L)Cl2]. $2H_2O$

Electrostatic potential (MEP). Molecular

Optimization structure of the ligand wasdraw by hyperchem program and find the electrostatic potential which is considered important to finding the active site in the free ligand as shown in figure (1)

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Figure(14) . Graphical presentation of stereochemistry of the Ligand ($C_{16}H_{14}N_4O_2S$)

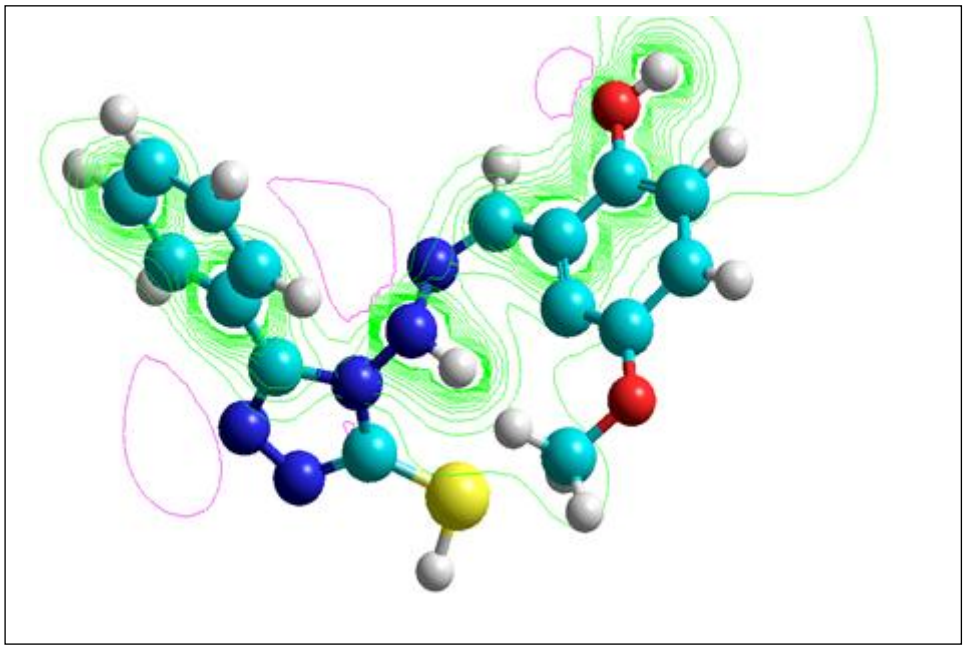


Figure (15). Electrostatic potential 2D counter of L1

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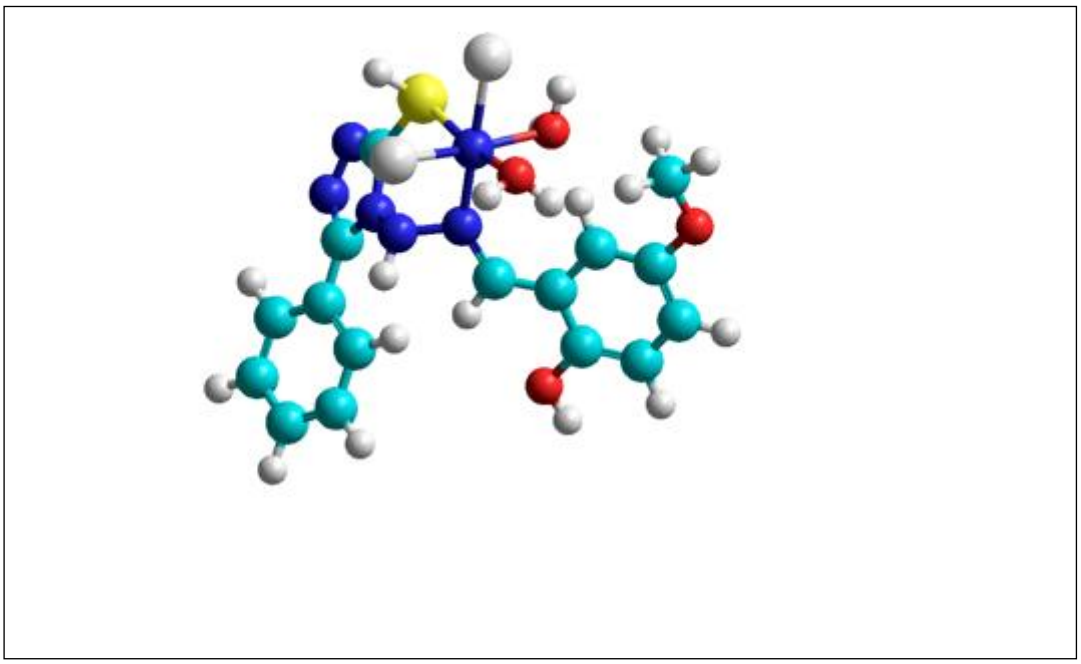


Figure (16). Graphical presentation of stereochemistry of the [Co(L) Cl_2 .$2H_2O$]

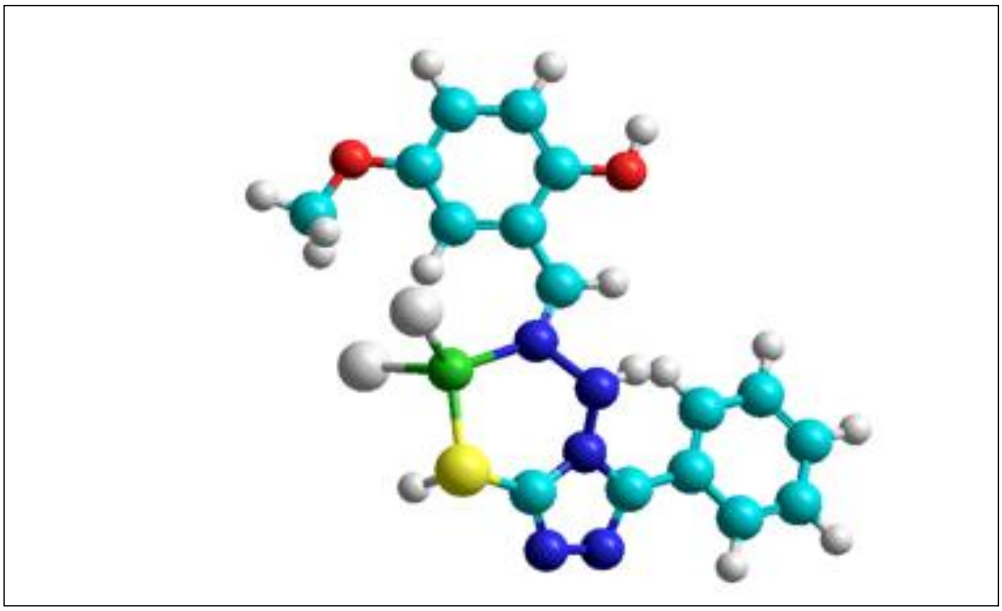


Figure (17) . Graphical presentation of stereochemistry of the [Ni(L) Cl_2] .$2H_2O$

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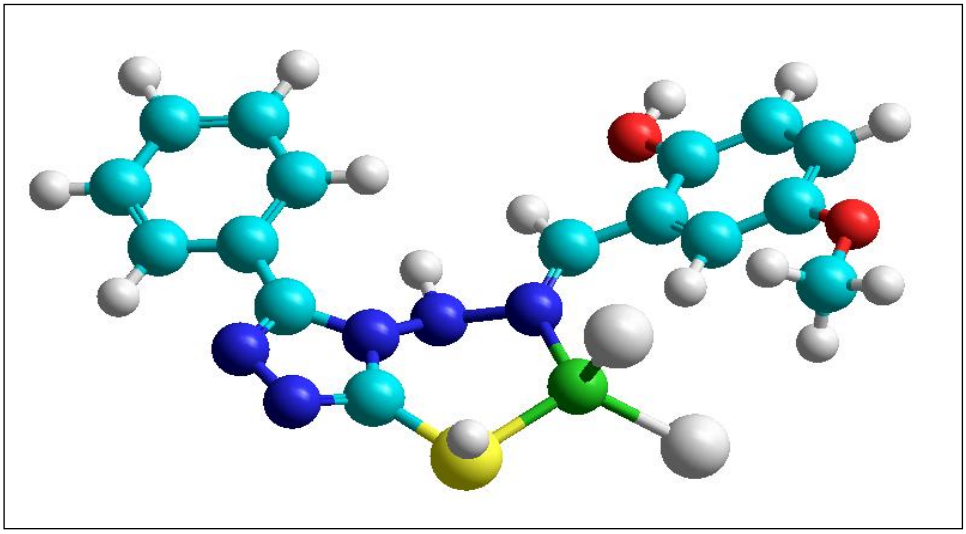


Figure (18). Graphical presentation of stereochemistry of the [Cu(L) Cl_2] .2H_2O

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