

SYNTHESIS, CHARACTERIZATION AND ANTIOXID STUDY OF NEW 4-({2-[5-(2-Hydroxyphenyl)-1,3,4-Oxadiazol-2-Yl] Hydrazinylidene} Methyl)-2-Methoxy Phenol AND THEIR TRANSITION METAL COMPLEXES

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Abstract

New ligand 4-({2-[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] hydrazinylidene} methyl)-2-methoxy phenol. (L) and its transition metal ion complexes Ni (II), Fe (III), Co (II), Cr (III) Cu (II) were synthesized. The authenticity of the ligand and its transition metal complexes were established by mass spectra, conductance measurements ¹HNMR, FTIR, as well as elemental analyses, the program of Hyper chem 7.51 has been used up for theoretical accounts using the PM3 method to study the electrostatic potential that provided good information about the complexity site. We can suggest octahedral geometries for Cr³⁺ and Fe³⁺ complexes, tetrahedral geometry for Ni +2 and Co+2 complex, and square planer geometry for Cu+2 the complex The ligand was tested antioxidant. the synthesized ligand showed good antioxidant, activity.

Keywords

Oxadiazole ,Ligand, Transitions metal complexes, Antioxidant

in the early nineteenth century, the chemistry of heterocyclic compounds quickly took off with the help of methods for organic synthesis. The largest area of organic chemistry is heterocyclic molecules, which have a broad variety of therapeutic applications ⁽¹⁾. Oxadiazole is a heterocyclic chemical with two nitrogen atoms and one oxygen atom in the five-member ring. It is one of several groups of heterocyclic that are particularly significant. The Oxadiazoles are comprised of many isomeric forms, such as 1,2,5, 1,2,4, 1,2,3, and 1,3,4-oxadiazoles ⁽²⁾, as illustrated in the following Figure (1)

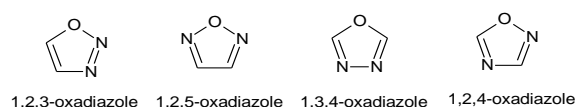


Figure (1)

The 1,3,4-oxadiazole heterocyclic compound has frequently been used as a privileged scaffold to produce a variety of novel pharmaceutical drugs, such as anti-inflammatory ⁽³⁾, antimicrobial ⁽⁴⁾, antiviral ⁽⁵⁾, antitumor ⁽⁶⁾, antidepressant ⁽⁷⁾, anthelmintic ⁽⁸⁾, analgesic ⁽⁹⁾, anti-hypoglycemic ⁽¹⁰⁾, anti-osteoporotic⁽¹¹⁾, anti-gastrocolic ⁽¹²⁾, anticancer ⁽¹³⁾, anti-HIV⁽¹⁴⁾, antioxidant⁽¹⁵⁾, analgesic⁽¹⁶⁾ antibacterial ^(17,18),

antifungal⁽¹⁹⁾ anticancer⁽²⁰⁾, anticonvulsant⁽²¹⁾ anti-tubercular⁽²²⁾, lipid peroxidation inhibitor⁽²³⁾ and anti-diabetic⁽²⁴⁾. 1,3,4-Oxadiazole has further uses as an insecticide⁽⁹⁾ as well as in fluorescent and colorimetric chemical sensors⁽²⁵⁾, polymers⁽²⁶⁾, and light-emitting diodes⁽²⁷⁾. In addition to their employment as beneficial corrosion inhibitors and metal chelating agents⁽²⁸⁾, 1,3,4-oxadiazoles also have essential structural motifs in cyanine dyes⁽²⁹⁾.

Experimental

All the chemicals and solvents utilized were readily available and chemically pure. all metal salts were employed as chlorides.

Physical Measurements

An electro-thermal melting point device model (Melting SMP31) was used to calculate the melting points of the ligand and metal complexes. Using a Shimadzu FTIR spectrophotometer (Model: IR- affinity, Shimadzu), the FTIR spectra were recorded as a potassium bromide (KBr) disc for the ligand and metal complex. Utilizing a Bruker DXR System AL500 (500 MHz), TMS was utilized as the standard, and DMSO-d⁶ was used as the solvent, ¹HNMR, Spectra. Mass Spectra (MS) were used to calculate molecular weights, which were registered in the range of 0 to 800. The results were acquired using the (Network Mass Selective Detector 5973).

Synthesis of the ligand (L)

Step I: "Synthesis of 2-hydroxy benzo hydrazide" (A) Methyl 2-hydroxybenzoate (13 ml, 0.1 mol), hydrazine hydrate (10 ml, 0.2 mol), and 100 ml of 100% ethanol were gently combined and heated under reflux for 6 hours. The product was filtered, then 2-hydroxybenzohydrazide (A) was produced by washing it with ethyl alcohol and drying it. (m.p:111- 120 C) .

Step II: "Synthesis of 2-(5-sulfanyl-1,3,4-oxadiazol-2-yl) phenyl (B)"

Potassium hydroxide (4.5 g, 0.08 mol) was heated with compound (A) (12.5 g, 0.08 mol) in 100 ml of 100% ethanol until the potassium hydroxide was entirely dissolved. The mixture was placed in ice until it reached a

temperature of 0°C, at this point carbon di sulfide (5 ml, 0.08 mol) was added. For 36 hours, the mixture was heated under reflux. The product mixture was cautiously acidified with hydrochloric acid HCl (10%) and concentrated to half volume to white crystals⁽³⁰⁾ (B).

Step III: "Synthesis of 2-(5-hydrazinyl-1,3,4-oxadiazol-2-yl) phenol (C)"

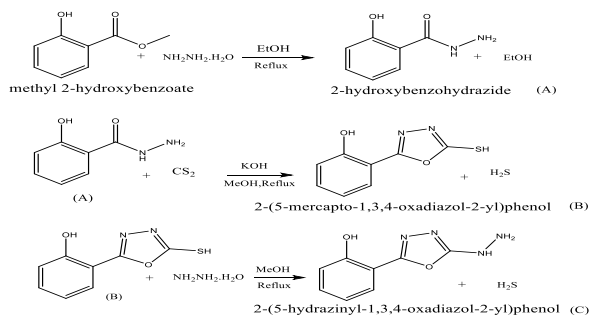
Compound B (9.7 g, 0.05 mol) and hydrazine hydrate (5 ml, 0.1 mol) are combined with 50 ml of ethanol and then allowed to reflux for 42 hours. The raw material was compressed to half its original volume, then cooled^(31,35-49). The product (2-(5-hydrazinyl-1,3,4-oxadiazol-2-yl) phenol) (C) was produced by recrystallizing the crude product with ethanol. It has a yield of 64% and a melting point of 220 C⁰.

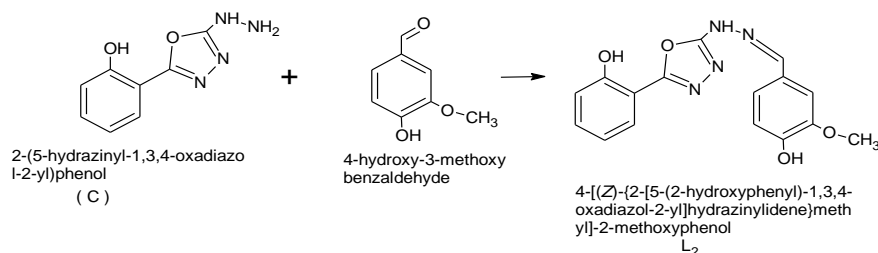
Step IV: "4-({2-[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] hydrazinylidene} methyl)-2-methoxyphenol"

L) (1.92 g, 0.01 mol) of compound (C) and (1.52 g, 0.01 mol) of (4-hydroxy-3-methoxybenzaldehyde) were combined, and they were dissolved in 50 ml of 100% ethanol. also had a four-hour reflux the solution is reduced to half its original volume, and the ligand is precipitated, filtered, and recrystallized with ethyl alcohol to provide use white ligand with a melting point of 222-226 C⁰ and a yield of 75%. the scheme (1)

2.3 "Synthesis of complexes"

The complexes were made by mixing (0.66 g,0.002 mol)of the ligand and (0.002 mol) of each of the salts (CrCl₃.6H₂O, eCl₃.6H₂O CoCl₂.6H₂O, NiCl₂.6H₂O, and CuCl₂.6H₂O) in 15 ml of ethanol and refluxing for 2 hours The resulting crystals were then filtered and occasionally washed with ethyl alcohol to remove unreacted salts or the ligand and precipitated complexes were dried at room temperature(32).





scheme (1) "Synthesis of the ligand (L)"

Table (1) Physical features of the ligand and its complexes

Num.	formula	color	M(g/mol)	M.P °C	Λ s cm ² mol ⁻¹
1	C ₁₆ H ₁₄ N ₄ O ₄	white	326	222-224	-----
2	C ₁₆ H ₁₄ N ₄ O ₄ Cl ₂ Cu	black	460	220	14.3
3	C ₁₆ H ₁₄ N ₄ O ₄ C ₂ Ni	Gray	455	208-210	15.7
4	C ₃₂ H ₂₈ Cl ₃ N ₈ O ₈ Cr	yellow	811	202-204	36.2
5	C ₁₆ H ₁₄ N ₄ O ₄ Cl ₃ Fe	white	488	204-206	17.6
6	C ₃₂ H ₂₈ Cl ₂ O ₈ N ₈ Co	Browne	782	210-2012	19.4

Result and Discussion

The prepared ligand and its metal complexes were characterized based on the infrared spectrum (FTIR), H1 NMR, CHN, and mass spectrum results.

3.1 Mass spectra: Mass spectra of the prepared ligand and its transition metal complex were recorded at a temperature of the room, the mass spectra of the ligand showed a molecular ion peak at 326 m/z which is by the molecular formula [C₁₆H₁₄N₄O₄]⁺, other peaks are due to the subsequent fragments such as (193 m/z, 165 m/z, 135 m/z, 120 m/z, 106 m/z, 77 m/z) respectively [C₉H₁₁N₃O₂]⁺, [C₈H₁₀N₂O₂]⁺, [C₇H₇NO₂]⁺, [C₇H₈N₂]⁺, [C₇H₇O]⁺, [C₆H₆]⁺.

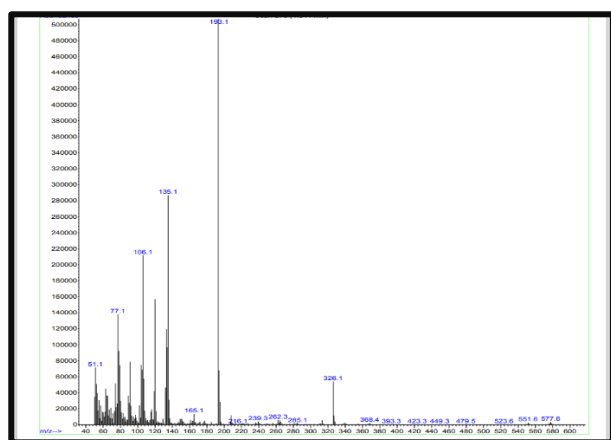


Figure (2) MS spectra of ligand

3.1.1 The MS of the complex [Ni (L) Cl₂] shows a molecular ion peak [M⁰] at 455 m/z that is equivalent to the molecular mass of the complex. The other peaks are shown as

follows.

1- [Ni (L) Cl]⁺ = 420 m/z

2- [Ni (L)]⁺ = 385 m/

3- [L]⁺ = 326 m/z

3.1.2 The MS of the complex [Cu(L) Cl₂] shows a molecular ion peak at 460 m/z, The other peaks are shown as follows

4- [Cu (L) Cl]⁺ = 425 m/z

5- [Cu (L)]⁺ = 389 m/z

6- [L]⁺ = 326 m/z

3.1.3 The complex [Co(L)₂ Cl₂] showed a molecular ion peak at [M⁰] = 782 m/z which is equivalent to the molecular mass of the complex The other peaks are shown as follows

7- [Co (L)₂Cl]⁺ = 747 m/z

8- [Co (L)₂]⁺ = 711 m/z

9- [Co (L)]⁺ = 385 m/z

10- [L]⁺ = 326 m/z

3.1.4 The complex [Fe(L) Cl₃] showed a molecular ion peak at [M⁰] = 488 m/z which is equivalent to molecular mass of the complex. The other peaks are shown as follows.

11- [Fe (L) Cl₂]⁺ = 453 m/z

12- [Fe (L) Cl]⁺ = 417 m/z

13- [Fe (L)]⁺ = 382 m/z

14- [L]⁺ = 326 m/z

3.1.5 The complex [Cr (L)₂ Cl₂] Cl showed a molecular ion peak at [M⁰] = 810 m/z which is equivalent to molecular mass of the complex. The other peaks are shown as follows.

15- [Cr (L)₂ Cl₂]⁺ = 775 m/z

16- [Cr (L)₂ Cl]⁺ = 740 m/z

17- [Cr (L)₂]⁺ = 704 m/z

18- [Cr (L)]⁺ = 364 m/z

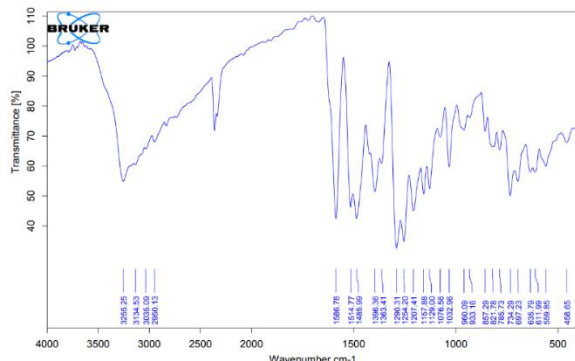


Figure (6) IR spectra of Fe Complex

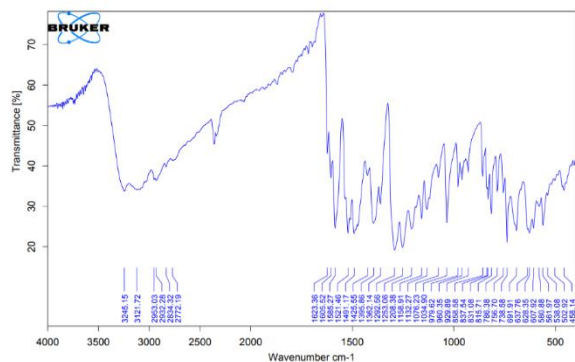


Figure (7) IR spectra of Co complex

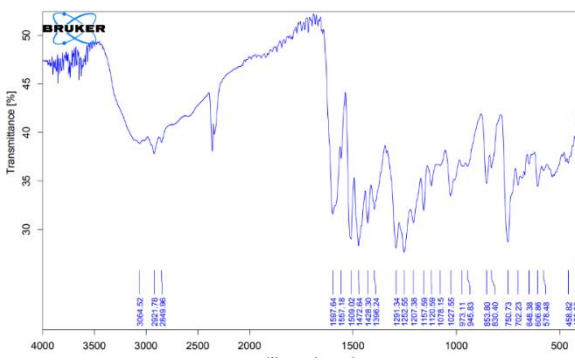


Figure (8) IR spectra of Cu Complex

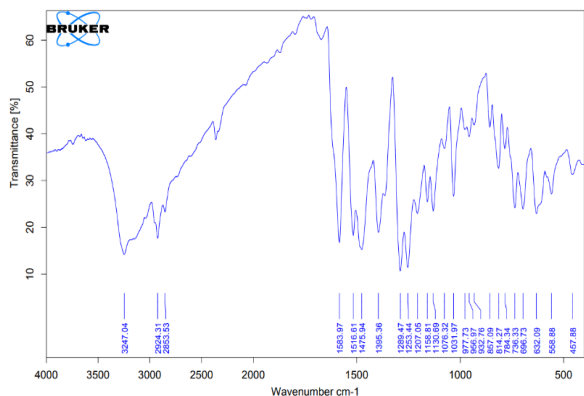


Figure (9) IR spectra of Ni Complex

CHN Analysis

Measurements of element analyses appear according to the following table:

Table (3) CHN measurement

Num.	The Elements	theoretical measurements	Practical measurements
1	carbon	58.89 %	54.82 %
2	hydrogen	4.32 %	4.18 %
3	oxygen	17.17 %	15.87 %

Electrostatic potential (MEP) Molecular

The optimization structure of the ligand was drawn by the hyper-chem program and found the electrostatic potential which is considered important to find the active site in the free ligand as shown in the figure.

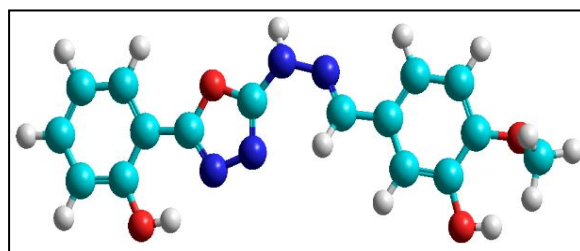


Figure (10). Graphical presentation of the stereochemistry of the Ligand (C16H14N4O4)

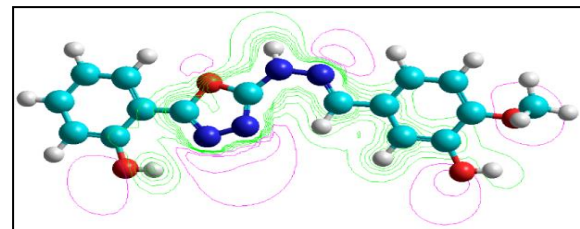


Figure (11). Electrostatic potential 2D counter of ligand

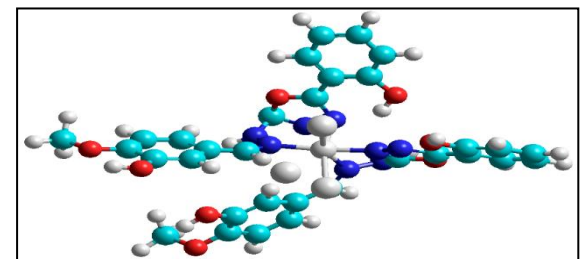


Figure (12). Graphical presentation of the stereochemistry of the [Cr(L2)Cl2]

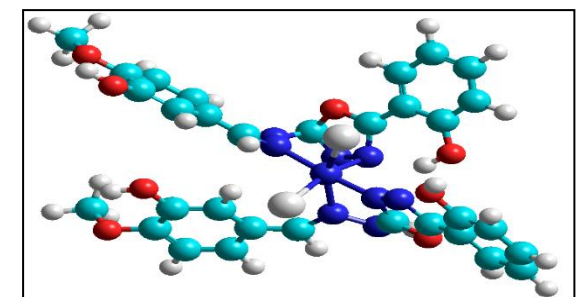


Figure (13). Graphical presentation of the stereochemistry of the [Co(L) Cl2]

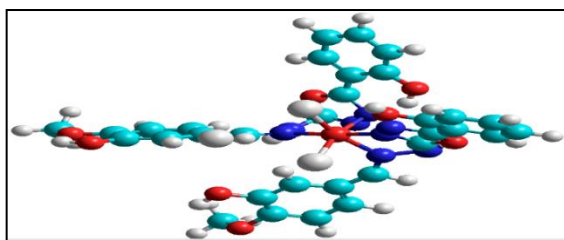


Figure (14). Graphical presentation of the stereochemistry of the [Fe (L) Cl2]

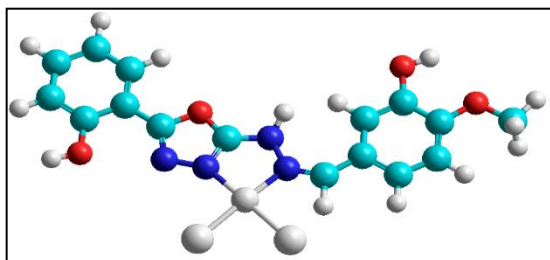


Figure (15). Graphical presentation of the stereochemistry of the [Ni (L) Cl2]

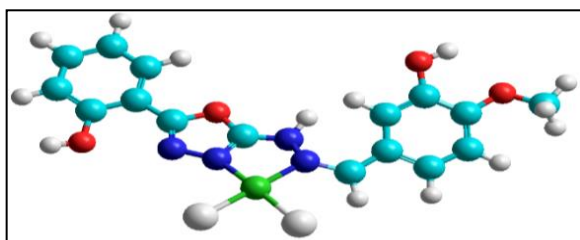


Figure (16). Graphical presentation of the stereochemistry of the [Cu (L) Cl2]

Evaluation of Antioxidant Activity

The antioxidant activity of 4-({2-[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]

hydrazinylidene) methyl)-2-methoxy phenol (L) A spectrophotometric approach was used to measure the antioxidant activity of 4-(2-[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] hydrazinylidene methyl)-2-methoxy phenol (L) based on a decrease in DPPH radicals at room temperature. The outcomes were contrasted with vitamin C results (Table 3). Each DPPH scavenger's ethanol solution and prepared ligand were in a concentration of 1 mM. Then, 1 ml of the DPPH solution was mixed with (0.5, 1, 2) ml of the purity ligand solution to create a new concentration of (12.5 ,25, 50,100, 200, 400) M. After (0, 1, 2) hours, absorption was measured for each solution at 516 nm. The NH and OH group transfer the hydrogen atom to the free radical to make it a stable free radical by the HAT process, which results in the ligand having high antioxidant activity. The degree of delocalization increases this stability, and the IC50 (ligand concentration needed to reduce the absorbance of the DPPH control solution by 50%) was found. The IC50 decreases as the duration and solution concentration are increased (34). Figure (17) and Table (4). Free oxadiazole ligand antioxidant activity and IC50 values when used with DPPH radicals (standard deviation (Sd) obtained from studies performed in triplicate).

Table (4) Antioxidant activity of the ligand

Compare each cell mean with the other cell mean in that row						
Number of families	1					
Number of comparisons per family	5					
Alpha	0.05					
Sadik's multiple comparisons tests	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value	
ascorbic acid - L2						
200	4.398	-6.526 to 15.32	No	ns	0.7884	
100	8.758	-2.166 to 19.68	No	ns	0.1595	
50	0.000	-10.92 to 10.92	No	ns	>0.9999	
25	3.472	-7.452 to 14.40	No	ns	0.9069	
12.5	0.2317	-10.69 to 11.16	No	ns	>0.9999	
Test details	Mean one	Mean two	Mean Diff.	SE of diff.	N1	N2
ascorbic acid - L2						
200	79.98	75.58	4.398	3.852	3	3
100	72.18	63.43	8.758	3.852	3	3
50	54.48	54.48	0.000	3.852	3	3
25	40.43	36.96	3.472	3.852	3	3
12.5	17.63	17.40	0.2317	3.852	3	3

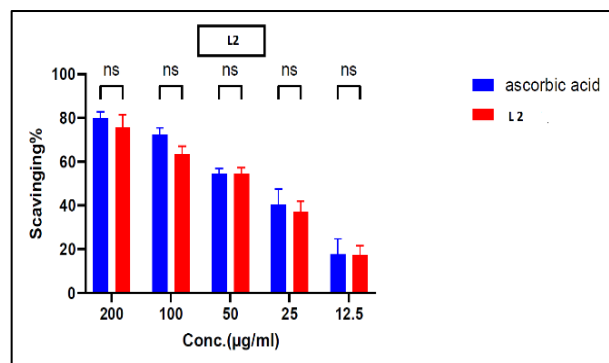


Figure (17) Antioxidant activity

Conclusion

The ligand 4-((2-[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl] hydrazinylidene) methyl)-2-methoxy phenol 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 non-electrolytes, just the Cr complex is the electrolyte. According to hyperchem characterization of transition metal complexes shown that octahedral geometry for Fe (III), Cr (III), tetrahedral geometry for Cu (II), Co (II), and square planar geometry was suggested for Ni (II). (L) was successfully synthesized. It acts like a bidentate ligand.

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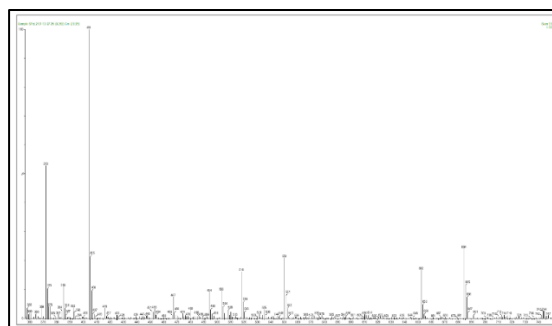


Figure (20) MS of Fe complex

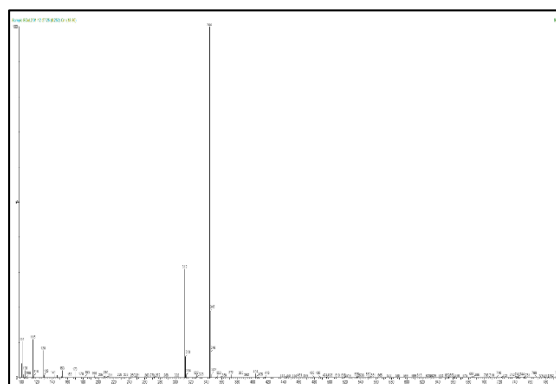


Figure (21) MS of Co complex

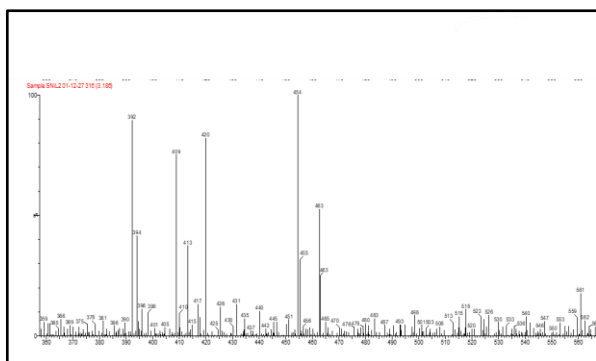


Figure (18) MS of Ni complex

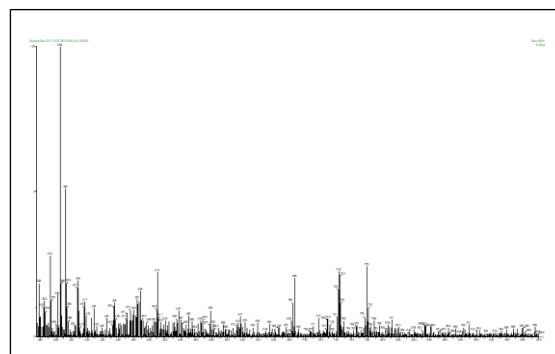


Figure (22) MS of Cr complex

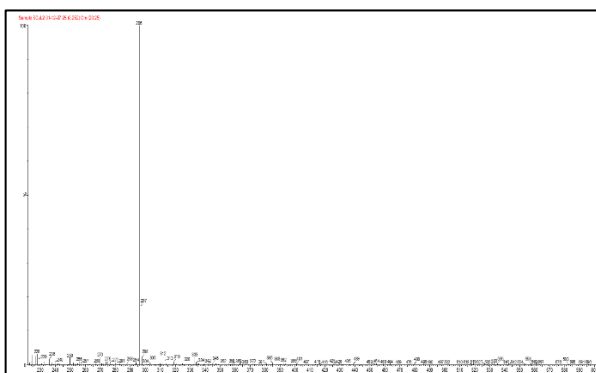


Figure (19) MS of Cu complex