



## Anti-brain Cancer Activity of New (N, O) Bidentate Schiff Base Ligand and its Metal Ion Complexes

Hayder Muneam A.M.\*, Mohammed H.A. Al-Amery

*Department of Chemistry, College of Sciences, University of Baghdad, Jadriyah, Baghdad, Iraq.*

\*Corresponding Author: Hayder Muneam A.M.

### Abstract

Anti-brain cancer activity was studied by treated it with new bidentate Schiff base ligand and its metal ion complexes. The ligand 2-(((Z)-1-(4-(((E)-4-(dimethyl amino) benzylidene) amino) phenyl) ethylidene) amino) phenol and its metal ion complexes have been characterized by using FT-IR, UV. visible,  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , mass spectroscopy, thermal analysis, (CHN) analysis, atomic absorption, magnetic susceptibility and molar conductivity. The octahedral geometry was suggested for all the synthesized complexes with the bidentate ligand in (1:2) mole ratio of metal: ligand. The M (II) complexes were having neutral nature while the Fe(III) was an electrical according to the magnetic susceptibility. Copper ion complex has been shown a good anti-brain cancer activity than other complexes and the ligand.

**Keywords:** Schiff base, Anti-brain cancer, Metal ion complexes, Bidentate ligand.

### Introduction

Antitumor chemotherapeutic agents, such as compound derivatives from 4-aminoacetophenon [1-3] have a good toxicity toward cancer cell and make it dysfunctional. Effective antitumor strategies require a selective response between normal and tumor tissue (i.e., therapeutic index). Replication component on colytic viruses have important factors contributing to the therapeutic index by differential destruction of tumor cells with low toxicity to normal cells[4]. Combination strategies involve attacking tumor cells through different mechanisms of action, which can prevent tumor cells from having the time to develop resistance to treatment[5].

It is also used in drug screening development and large scale manufacturing of biological compounds (e.g., vaccines, therapeutic proteins). The major advantage of using cell culture for any of the these applications is the consistency and reproducibility of results that can be obtained from using a batch of clonal cells[6]. Schiff bases which are effective as coordinating ligands and widely used in coordinating chemistry because of the relative easiness of preparation, synthetic flexibility and the special property of C=N group, Schiff bases are generally excellent chelating agents, especially when a functional group

like –OH or –SH is present close to the azomethine group so as to form a five or six membered ring with the metal ion. Several studies showed that the presence of a lone pair of electrons in a  $sp^2$  hybridised orbital of nitrogen atom of the azomethine group is considerable of chemical and biological importance[7, 8]. Schiff bases and their metal ion complexes have a wide range of application in many fields such as anticancer activity[9], antitumor[10], cytotoxicity activity [11, 12], dyes [13], anti-HIV activity [14], anticonvulsant [15], anti-corrosion activity [16], antiviral activity[17] and also as a catalyst[18].

### Apparatus

Fourier transform infrared (FT-IR) spectra were recorded by SHIMADZU 8400s ultraviolet-visible (UV-Vis) spectra for all the studied compound has been recorded on the SHIMADZU 1800.  $^1\text{H}$  and  $^{13}\text{C}$  nuclear magnetic resonance (NMR) spectra were measured by a BRUKER AV 400 Avance- III (400 MHz and 100 MHz). The metal content was determined by using (GBC Avanta Ver. 1.33). The atomic absorption analysis was used to determine the metal contents by Nova 350 spectrophotometer.

The percentage of carbon, hydrogen and nitrogen (CHN elemental analysis) were carried out by CHN recorded on a Euro EA Elemental Analyzer (Euro EA 3000/Italy). The melting points for all compounds have been carrying out by Gallenkamp melting point apparatus. The molar conductivity for metal ion complexes was carrying out in ethanol ( $10^{-3}$  M) which was determined in WTW conduct meter.

The magnetic susceptibility of the studied complexes was performed at room temperature by auto magnetic susceptibility balance model Sherwood Scientific. The mass spectra were recorded by using LC-MS (Perkin-Elmer, USA/Flexer SQ 300 M). Thermal analysis of the synthesized complexes and ligand were performed using (SHIMADZU 60-H Thermal Analyser) and Perkin Elmer STA6000thermal analyser.

### Reagents, Chemicals and Supplements

Chemicals and reagents used in this work were of inorganic and bio application grade.

### The Chemicals (Organic, Inorganic, and Solvents)

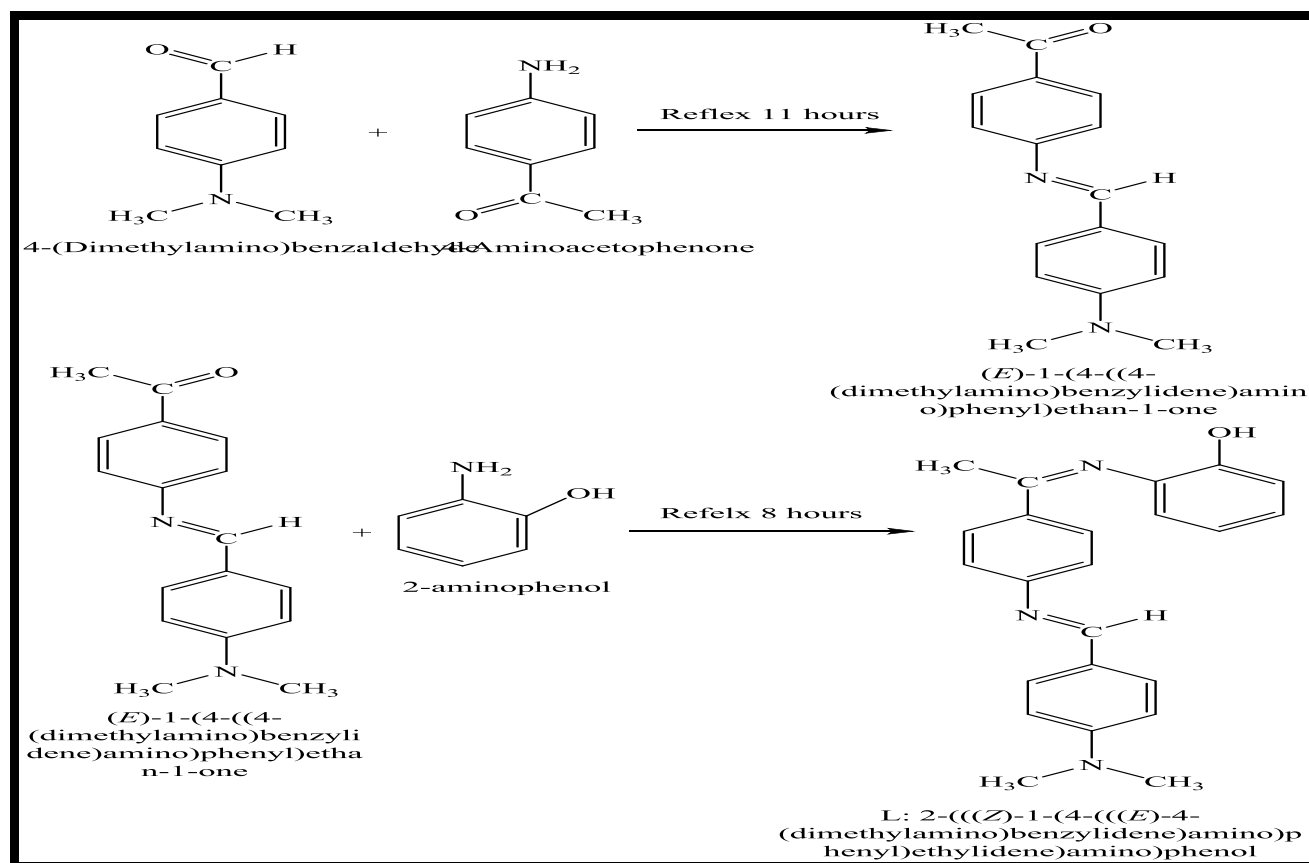
The chemicals used included 4-aminoacetophenone (alpha Acer), 2-amino phenol (merch), 4-N, N-Dimethyleamino benzaldehyde (Fluka),  $MnCl_2 \cdot 4H_2O$  (Fluka),

$FeCl_3 \cdot 6H_2O$  (Fluka),  $CoCl_2 \cdot 6H_2O$  (Fluka),  $NiCl_2 \cdot 4H_2O$  (Fluka) and  $CuCl_2 \cdot 2H_2O$  (BDH). The organic solvents which were used included ethanol 95% (BDH), DMSO (CDH), glacial acetic acid (BDH) and Petroleum ether (30–60°C) (Fluka).

### Synthesis the ligand

The preparation of 4-N,N-Dimethyleaminobenzylidene-4-amino acetophenone was carried out by refluxing an ethanolic solution (25 mL) of 4-aminoacetophenone (1 mmol, 0.135 gm) containing (2-3) drops of glacial acetic acid with an ethanolic solution (25 mL) of 4-N,N-Dimethyleamino benzaldehyde (1 mmol, 0.12 gm) for 8 hrs and then allowed to cool overnight at room temperature.

The yellow colored product was collected, washed thoroughly with ethanol and dried in air. Yield=0.1 gm (65%). An ethanolic solution of 4-N, N-Dimethyleaminobenzylidene -4-amino acetophenone (25 mL) of the (1 mmol, 0.266 gm) and an ethanolic solution (25 mL) of 2-aminophenol (1 mmol, 0.1gm) were mixed and refluxed for 8 hrs and allowed to cool over-night at room temperature. The product was filtered, washed successfully with water, ethanol and dried in air. Yield=0.28g (81%) Scheme (1).



Scheme 1: Synthesis of the ligand

## Synthesis of Complexes

The complexes had been synthesis by dissolving of (2mmole, 0.715 gm) of the ligand in (15mL) absolute ethanol and mixing with (10 ml, 1mmole) of hot absolute ethanol solution of chloride metals salts of Mn(II), Fe(III), Co(II), Ni(II) and Cu(II) each one of them separately have been added and left them under reflux for 3 hrs, after that allow to cool and added 10mL diethyl ether to precipitate the solid complexes. The crystals were filtered, washed with cold water, ethanol and dried it, then recrystallized with ethanol.

## Anticancer Activity

### Maintenance of Cell Cultures

Cell lines were obtained from the Iraq biotech Cell Bank Unit and maintained in RPMI-1640 supplemented with 10% Fetal bovine, 100 units/ mL penicillin, and 100 µg/mL streptomycin. Cells were passaged using Trypsin-EDTA reseeded at 50% confluence twice a week, and incubated at 37 °C[19].

### Cytotoxicity Assays

Cytotoxic effect is depends on the enzymetic phenomenon of MTT and gives information

about direct relationship between an absorbance and the viable cell. The MTT cell viability assay has been done by using 96-well plates. Cell lines were seeded at ( $1 \times 10^4$  cells / well). After 24 hr. at 37°C and 5% CO<sub>2</sub>, Stock solution of the ligand and its metal ion complexes have been prepared and diluted to desired concentrations (6.125 µM, 12.5 µM, 25 µM, 50µM and 100 µM) in culture medium. Cells were treated with synthesized compounds.

Cell viability has been measured after 72 hr of treatment by removing the medium, adding 28 µL of 2 mg/mL solution of MTT (and incubating the cells for 2.5 h at 37 °C) until the formazan blue crystal developed .After removing the MTT solution, the crystals remaining in the wells were solubilized by adding of 130 µL of DMSO at 37 °C incubation for 15 min with shaking[20]. The absorbance has been recorded at 492 nm by using a microplate reader, the assay was performed triplicate. The inhibition rate of cell growth (the percentage of cytotoxicity) was calculated as the following equation:-

$$\text{Cytotoxicity} = A-B/A * 100$$

Where A and B are the optical density of control and the optical density of test.

## Results and Discussion

### Physical Properties and Elemental Analysis

The data of atomic absorption, CHN and chloride analysis as well as the physical properties of the ligand and its metal ion complexes are show in Table (1). The molecular formulae of the studied compounds were suggested depending on CHN, chloride content, atomic absorption analysis, spectral data and conductivity measurements.

Table 1: Physical properties and analytical data for the ligand and its metal ion complexes

symbol	color	m.p °C	Yield %	M.Wt g.mol <sup>-1</sup>	Micro Elemental Analysis Found (calc.)			Metal content % Found (calc.)	Chloride content % Found (calc.)
					C%	H%	N%		
L	Yellow	120-123	60	357.46	25.90 (77.28)	2.05 (6.49)	15.90 (11.76)	—	—
C <sub>1</sub>	Brown	155-158	65	840.75	65.30 (65.72)	5.97 (5.52)	10.51 (10.00)	6.89 (6.53)	8.89 (8.43)
C <sub>2</sub>	Brown	142-144	75	841.66	65.20 (65.64)	5.60 (5.51)	10.29 (9.99)	6.48 (6.64)	8.38 (8.42)
C <sub>3</sub>	Dark brown	148-151	66	898.79	61.70 (61.47)	5.95 (5.83)	9.81 (9.35)	6.62 (6.56)	7.20 (7.89)
C <sub>4</sub>	Yellow	200/dec.	71	844.51	65.69 (65.42)	5.60 (5.49)	9.46 (9.95)	6.89 (6.95)	8.78 (8.40)
C <sub>5</sub>	Back	50	75	921.42	59.69 (59.96)	7.30 (5.91)	9.61 (9.12)	7.20 (6.90)	7.88 (7.69)

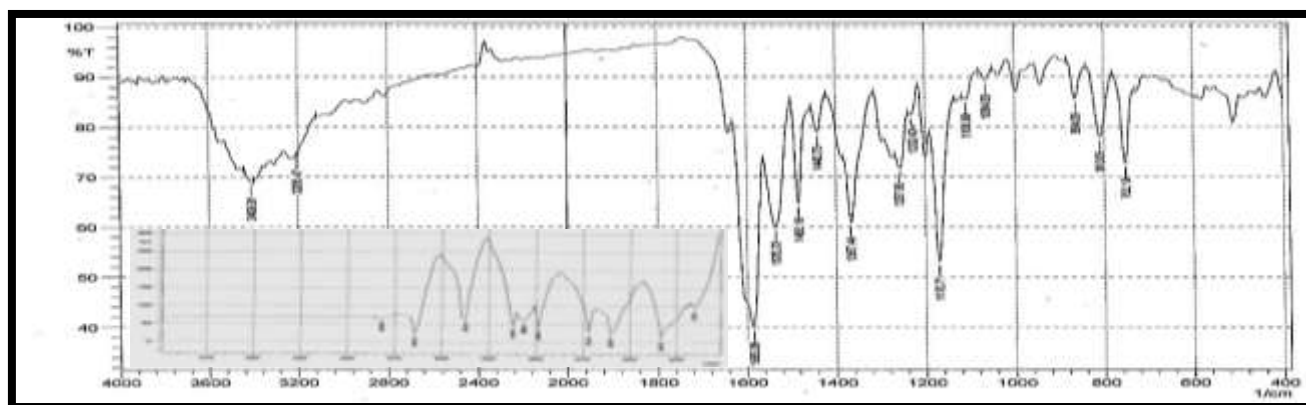
## FT-IR Spectra of ligand and their Metal ion Complexes

The FT-IR spectrum of the ligand (L) shows broad absorption bands at (2292 to 3483)  $\text{cm}^{-1}$  weak absorption for phenolic group, in some complexes the water entered in lattice or coordinated with the metal ion and exhibited broad band (3100-3500)  $\text{cm}^{-1}$ [21].  $\nu$  (C=N) imine group was appeared as sharp band at (1535)  $\text{cm}^{-1}$  [22, 23], while  $\nu$  (C-N) exhibited as a medium band at (1373)  $\text{cm}^{-1}$ ,  $\nu$  (C-O) exhibited absorption band at (1245)  $\text{cm}^{-1}$ [24]. The shift of  $\nu$  (C-O) and  $\nu$  (C=N) imine in

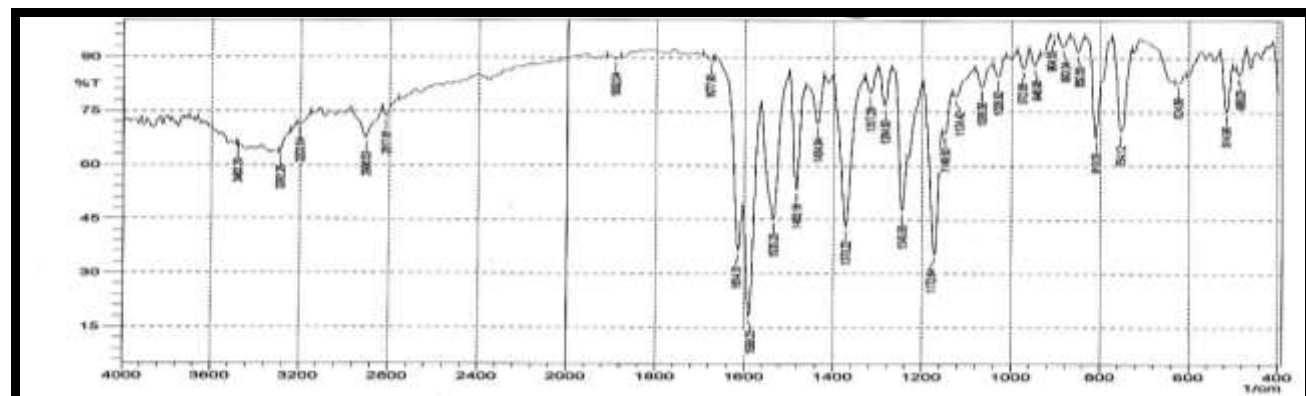
their positions and change the shape or intensity of band compared with the ligand (L) attributable to the coordination of this ligand with the metal ions and gave an indication that the complexes were formed, (1587)  $\text{cm}^{-1}$  with a sharp strong intensity attributable to the stretching bands of  $\nu$  (C=C) aromatic and (2918)  $\text{cm}^{-1}$  weak absorption band for H-aliphatic [25]. The range (200-600)  $\text{cm}^{-1}$  appeared stretching band for  $\nu$  (M-O),  $\nu$  (M-N) [26] and  $\nu$  (M-Cl)[27] in complexes. FT-IR spectra of the ligand (L) and its complexes were shown in Table (2) and in Figures (1-6).

**Table 2: FT-IR data of the functional groups of the ligand and its metal ion complexes**

Functional group $\nu$ $\text{cm}^{-1}$	(O-H), (H <sub>2</sub> O) $\nu$ $\text{cm}^{-1}$	(C-O) $\nu$ $\text{cm}^{-1}$	(C=N), (C-N) $\nu$ $\text{cm}^{-1}$	(M-N) $\nu$ $\text{cm}^{-1}$	(M-O) $\nu$ $\text{cm}^{-1}$	(M-Cl) $\nu$ $\text{cm}^{-1}$
L	2292-3483	1245	1535, 1373	----	----	----
C <sub>1</sub>	3205-3600	1274	1539, 1365	440	364.52	337.52
C <sub>2</sub>	3300-3600	1278	1546, 1365	420	362.59	297.02
C <sub>3</sub>	3100-3600	1257	1527, 1369	410	318.23	281.59
C <sub>4</sub>	3200-3600	1261	1548, 1369	437.81	420	325.95
C <sub>5</sub>	3350-3550	1240	1544, 1365	480.24	420	312.45



**Figure 1: FT-IR spectrum of the ligand**



**Figure 2: FT-IR spectrum of C1**

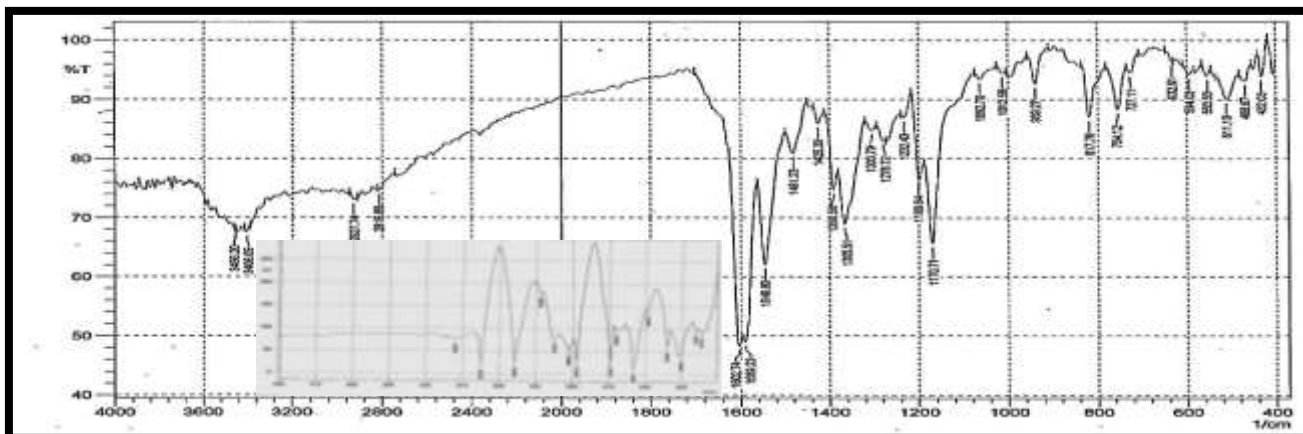


Figure 3: FT-IR spectrum of C2

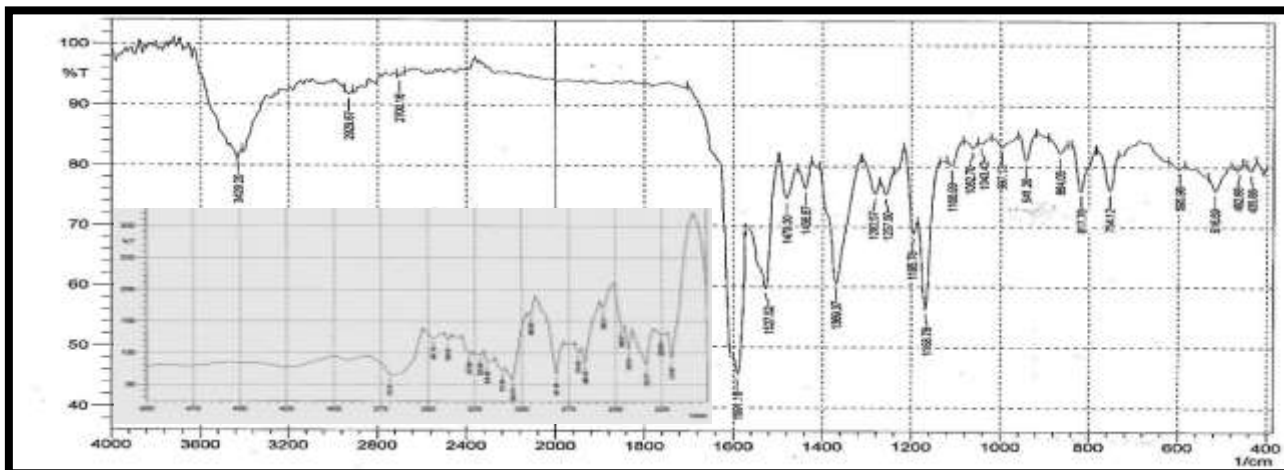


Figure 4: FT-IR spectrum of C3

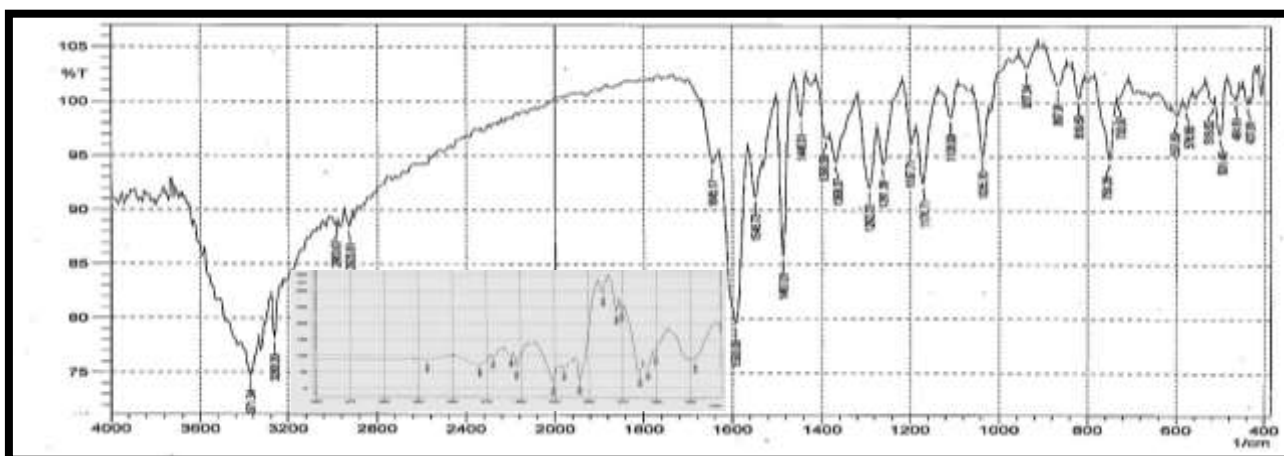


Figure 5: FT-IR spectrum of C4

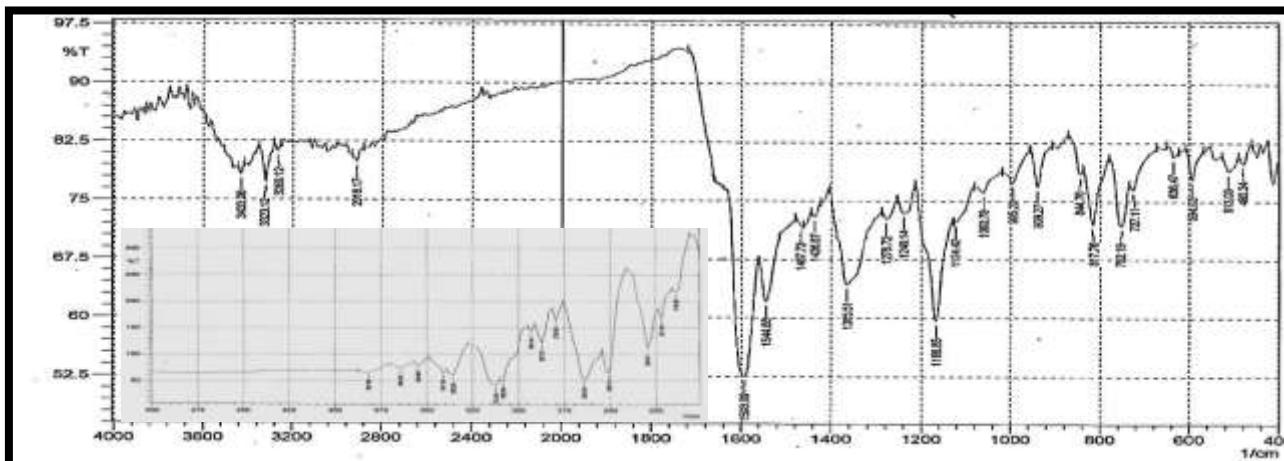


Figure 6: FT-IR spectrum of C5

### <sup>1</sup>H-NMR and <sup>13</sup>C-NMR Spectra of the ligand

The <sup>1</sup>H-NMR spectrum of the ligand in DMSO-d<sub>6</sub> is shown in Figure (6). Chemical shifts of methyl protons were observed as a single peak around (2.08 ppm). The peak around (2.5) ppm was attributed to DMSO[28]. A multiplets peaks were observed around (6.58-7.64) ppm assigned to aromatic protons[29, 30]. Chemical shifts of the OH proton appeared around (11.99)

ppm[31, 32]. Chemical shift of imines proton were observed at (8.33- 8.83)[33-35]. The <sup>13</sup>C-NMR spectrum of the ligand in DMSO is shown in Figure (7). The spectrum showed a signal at (24.42) ppm which was assigned to methyl group. The peaks observed at (112.12-133.79) ppm were attributed to aromatic carbons[36, 37]. The azomethine carbon atom showed a peak at (143.77-156.56) ppm[38, 39]. Carbon atom of phenyl group exhibited a peak at (156.21) ppm.

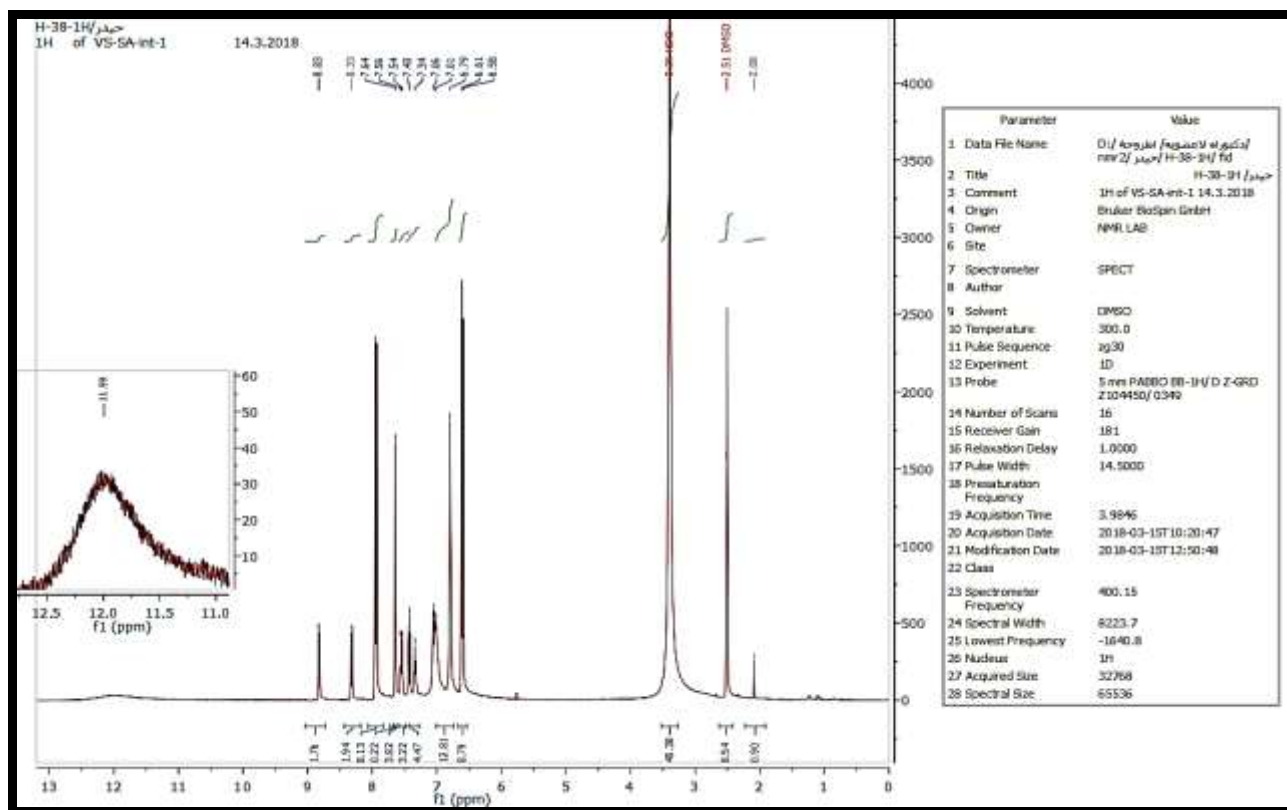


Figure 7: 1H-NMR spectrum of the ligand

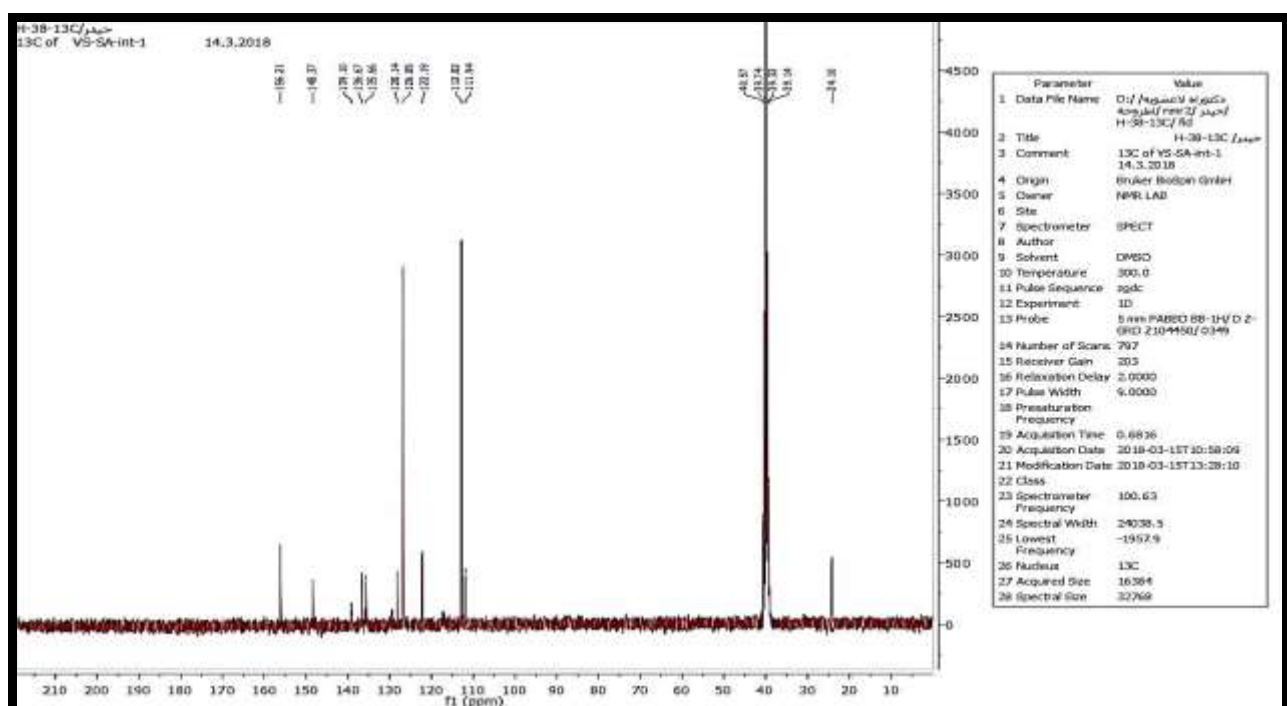


Figure 8: 13C-NMR spectrum of the ligand

### Electronic Spectra (UV-Visible)

The electronic spectrum of the ligand was shown three main bands appeared at (404nm, 24752 cm<sup>-1</sup>) due to intraligand charge transfer, (331nm, 30211 cm<sup>-1</sup>) for ( $\pi-\pi^*$ ) transition and (260nm, 38461 cm<sup>-1</sup>) for ( $\pi-\pi^*$ )[40]. Electronic spectrum of the complex (C<sub>1</sub>) exhibited three main bands observed at (419 nm, 23866 cm<sup>-1</sup>) for LMCT,(335 nm, 29850 cm<sup>-1</sup>) and (234 nm, 42735 cm<sup>-1</sup>) bands may be assigned to the transitions of intra ligand charge transfer[41, 42]. The electronic spectrum of the complex (C<sub>2</sub>) has been shown four bands observed at (436 nm, 22935 cm<sup>-1</sup>) due to ( ${}^6A_{1g} \rightarrow {}^4T_{2g}(G)$ ) and (415nm, 24096 cm<sup>-1</sup>) for ( ${}^6A_{1g} \rightarrow {}^4E_g$ ). (339nm, 29498 cm<sup>-1</sup>) for LMCT and (236 nm, 42372 cm<sup>-1</sup>) bands may be assigned to the transitions of intra ligand charge transfer[43, 44].

The spectrum of the complex (C<sub>3</sub>) was displayed four bands observed at (680 nm, 14705 cm<sup>-1</sup>) assigned to the transitions of ( ${}^4T_{1g} \rightarrow {}^4T_{1g}(P)$ ). At (430 nm, 23255 cm<sup>-1</sup>) due to MLCT and (339 nm, 29498 cm<sup>-1</sup>), (236 nm, 42372cm<sup>-1</sup>) bands may be assigned to the transitions of intra ligand charge transfer[45]. Electronic spectrum of the complex (C<sub>4</sub>) exhibited five bands observed at (1062 nm, 9416 cm<sup>-1</sup>) due to ( ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ ) and (662 nm, 15105 cm<sup>-1</sup>) for ( ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ ) and (401 nm, 24937 cm<sup>-1</sup>) band assigned to the transitions of MLCT. (329nm, 30395 cm<sup>-1</sup>) and (229nm, 43668 cm<sup>-1</sup>) bands may be assigned to the transitions of intra ligand charge transfer[46].

The electronic spectrum of the complex (C<sub>5</sub>) has been shown five bands observed at (947

nm, 10559 cm<sup>-1</sup>) due to ( ${}^2B_{1g} \rightarrow {}^2A_{1g}$ ), (680 nm, 14705 cm<sup>-1</sup>) for ( ${}^2B_{1g} \rightarrow {}^2B_{2g}$ ) and at (495 nm, 20202 cm<sup>-1</sup>) for ( ${}^2B_{1g} \rightarrow {}^2E_g$ ).The bands appeared at (432 nm, 23148 cm<sup>-1</sup>) for MLCT and (345 nm, 28985 cm<sup>-1</sup>) assigned for intra ligand charge transfer[47, 48].

### Thermal Analysis of the Ligand and its Metal ion Complexes

Thermal analysis (TGA-DTA) of the synthesized ligand and its metal ion complexes have been carried out under nitrogen gas with heating range (25-800) °C and ramp rate of heating (10°C/min). The thermal analysis was suggested the structures of the ligand and its complexes.

The thermal decomposition data for the ligand and its metal ion complexes were shown in Table (3) and their thermographs were given in Figures (9-13) respectively. The following results were obtained: The first stage which took place at temperature range of (25-180) °C include leaving of water molecules (lattice water) or any lattice molecules such as ethanol in addition of some fragments[49].

The next stages include the decompose of organic part of the ligand and its complexes may occurs in one or more steps [50]. The final stages involved the residual fragments of the ligand and the metal ion still coordinated to the remaining part of the ligand[51]. The average percentages of fragments were exhibited a good agreement between calculated and suggested values in addition of compatibility with elemental analyses.

**Table 3: Thermal decomposition data of the ligand and its metal ions complexes**

Comp	Molecular formula	Step	Temp. rang of the Decompositi on C°	Suggested Formula of loss	Mass loss%	
					Cal.	Found
L	C <sub>21</sub> H <sub>17</sub> BrN <sub>2</sub> O 393.28	1	200-800 > 800	C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> O Residue (Br)	79.65 20.3	79.46 20.53
C <sub>1</sub>	[Mn(L) <sub>2</sub> Cl <sub>2</sub> ].2H <sub>2</sub> O 948.44	1	25-195	2H <sub>2</sub> O	3.79	3.07
		2	195-360	2Cl,CH <sub>3</sub> ,BrC <sub>6</sub> H <sub>4</sub> CHN	28.36	28.52
		3	360-495	CH <sub>3</sub> ,BrC <sub>6</sub> H <sub>4</sub> CHN	20.87	20.24
		4	495-790 > 790	C <sub>6</sub> H <sub>4</sub> CN,OH Residue (C <sub>6</sub> H <sub>4</sub> MNC <sub>6</sub> H <sub>4</sub> CNCC <sub>6</sub> H <sub>4</sub> OH)	12.54 35.62	11.97 36.20
C <sub>3</sub>	[Co(L) <sub>2</sub> Cl <sub>2</sub> ] 916.40	1	175-256	2(BrC <sub>6</sub> H <sub>4</sub> )	34.04	32.92
		2	256-700 > 700	2Cl,2(CHNC <sub>6</sub> H <sub>4</sub> CCH <sub>3</sub> N) Residue(Co(C <sub>6</sub> H <sub>4</sub> OH) <sub>2</sub> )	39.17 26.72	38.72 28.36
C <sub>4</sub>	[Ni(L) <sub>2</sub> Cl <sub>2</sub> ].4H <sub>2</sub> O 988.22	1	25-248	2Cl,4H <sub>2</sub> O	14.47	15.12
		2	248-354 > 354	Br,2CH <sub>3</sub> Residue (Ni(C <sub>6</sub> H <sub>4</sub> CHNC <sub>6</sub> H <sub>4</sub> CNC <sub>6</sub> H <sub>4</sub> OH) <sub>2</sub> Br)	11.13 74.34	12.12 72.75

C <sub>5</sub>	[Cu(L) <sub>2</sub> Cl <sub>2</sub> ].2H <sub>2</sub> O	1	25-155	CH <sub>3</sub> , 2H <sub>2</sub> O	5.33	4.93
	957.04	2	155-145	BrC <sub>6</sub> H <sub>4</sub> CHNC <sub>6</sub> H <sub>4</sub> C	28.31	28.09
		3	145-790	CH <sub>3</sub> , BrC <sub>6</sub> H <sub>4</sub> CHNC <sub>6</sub> H <sub>4</sub>	28.63	28.34
			> 790	Residue (CNC <sub>6</sub> H <sub>4</sub> OHCuNC <sub>6</sub> H <sub>4</sub> OH, 2Cl)	37.77	38.70



Figure 9: Thermogram of the ligand

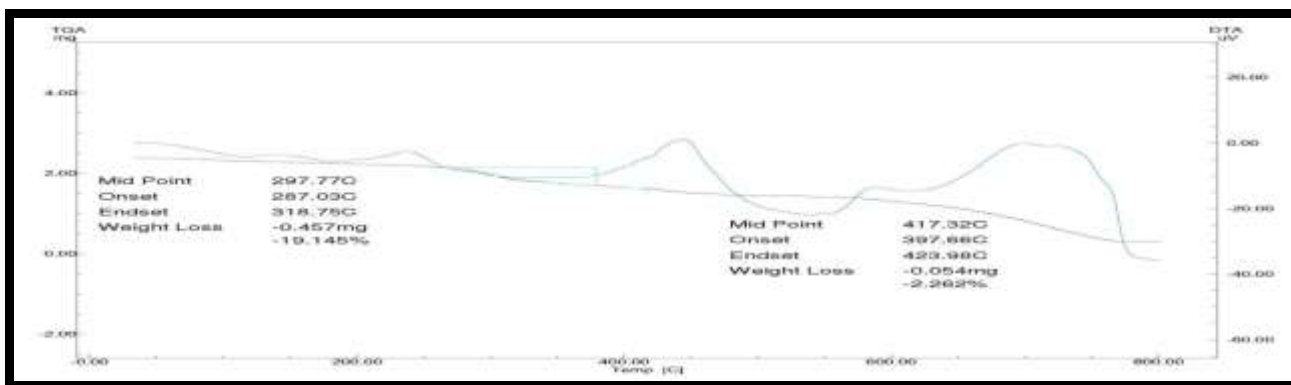


Figure 10: Thermogram of C1

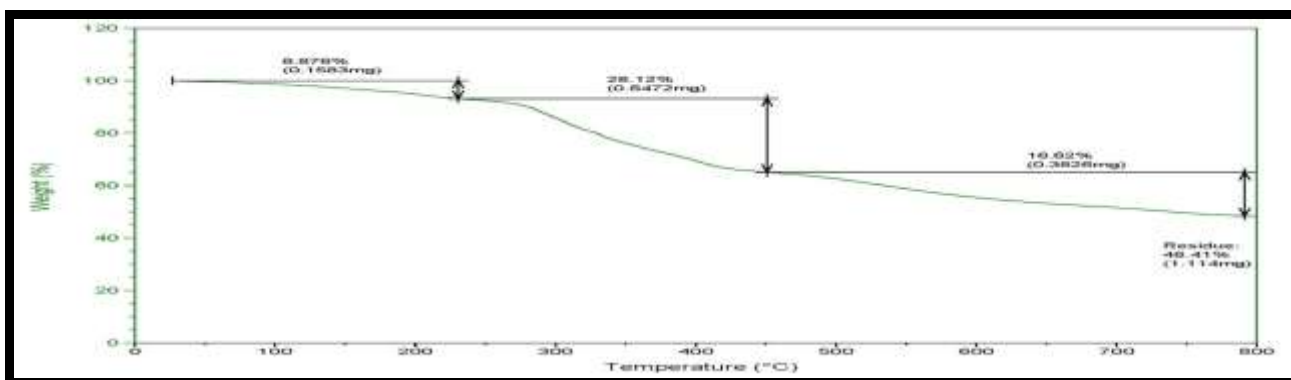


Figure 11: Thermogram of C

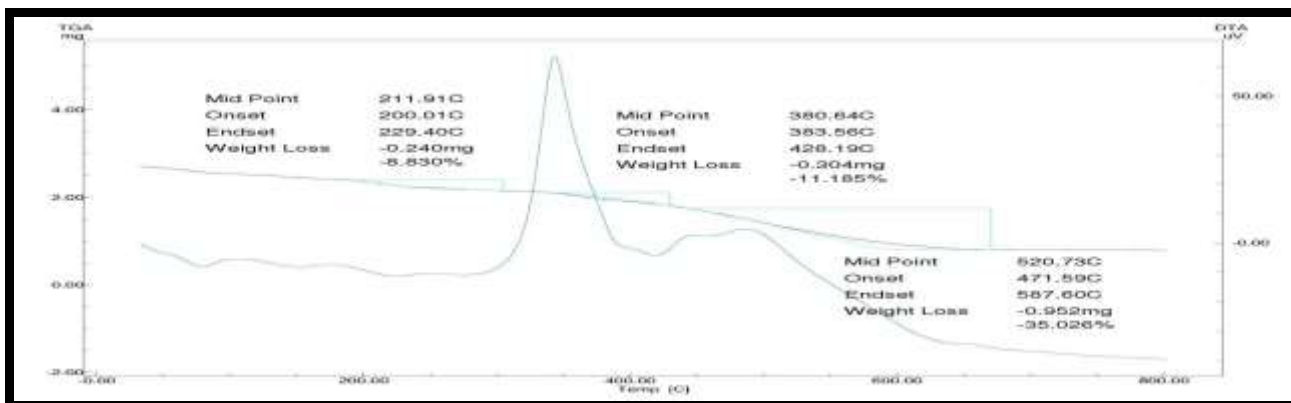


Figure 12: Thermogram of C4



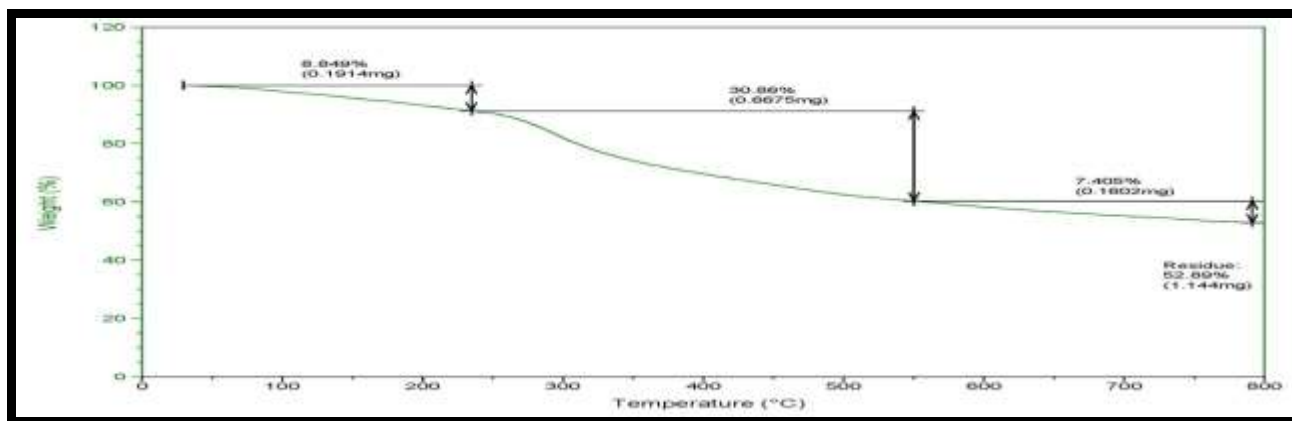


Figure 13: Thermogram of C5

### Mass Spectroscopy

Mass spectrometry has been used to investigate the molecular ion[52]. The ligand has been identified by mass spectrum and compared with the suggested molecular

computability with the mass spectrum and shown a molecular ion at  $m/z = 357.46$  as shown in Figure (14).

weight that obtained from TGA-DTA and CHN techniques and shown a good

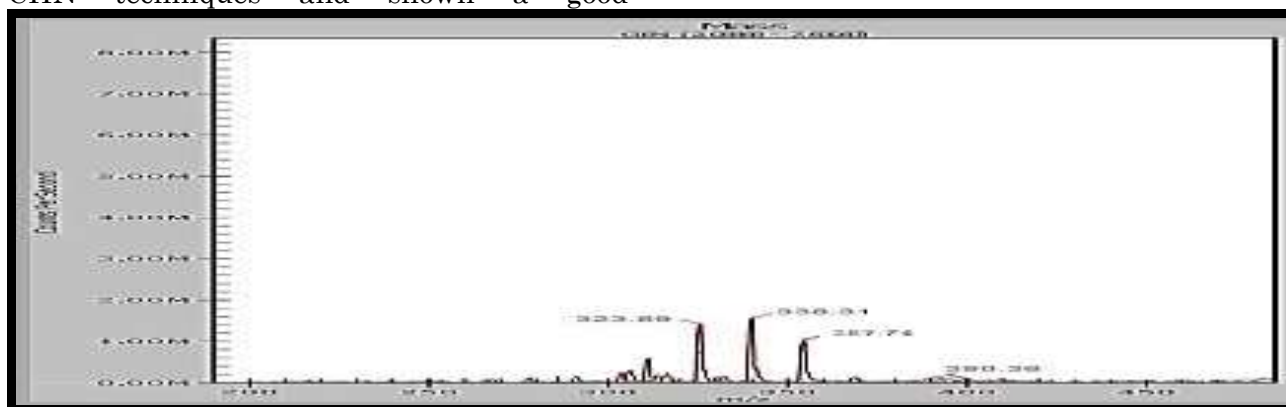


Figure 14: Mass spectra of the ligand

### Molar Conductance and Magnetic Susceptibility Measurements

The molar conductance values of the complexes carried out in ethanol as a solvent at room temperature [53] and the results which are given in Table (4). The magnetic susceptibility measurements were contributed to determine the suggested

structures of the complexes. These measurements were provided important information about the ligand field of complexes and also give information about the number of unpaired electrons. The effective magnetic spin of the complexes have been measured by using only a spin magnetic moment[54, 55].

Table 4: Molar conductance values and the values of magnetic moment of the synthesized metal ion complexes

Compound	Molar Cond. $S.cm^2 mol^{-1}$	$\mu_{eff.} (B.M)$	
		Cal.	Found
C <sub>1</sub>	22.16	5.91	6.04
C <sub>2</sub>	45.32	6.92	7.21
C <sub>3</sub>	11.88	3.87	3.90
C <sub>4</sub>	14.6	2.82	2.89
C <sub>5</sub>	7.04	1.73	1.89

### The Nomenclature and Suggested Structures of the Complexes

The suggested structures of the synthesized complexes have been investigated and confirmed by using infrared (FTIR), elemental analysis (CHN), UV-Visible

spectroscopy, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR spectroscopy, thermal analysis, mass spectroscopy, molar conductance, atomic absorption and also by magnetic susceptibility measurements. According to the observations obtained the structures of

the complexes were suggested as in Figures (15 - 19).

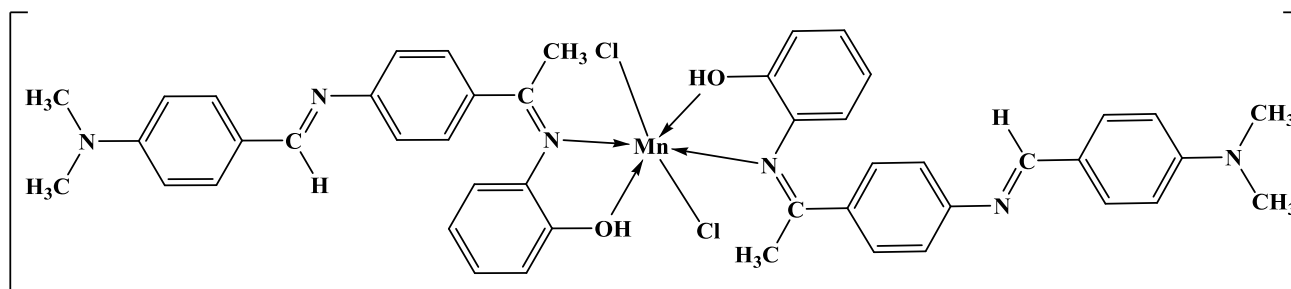


Figure 15: Structure and name of C1: [Dichloro bis (2-(((Z)-1-(4-(((E)-4-(dimethyl amino)benzylidene)amino)phenyl) ethylidene)amino)phenol) manganese(II)]

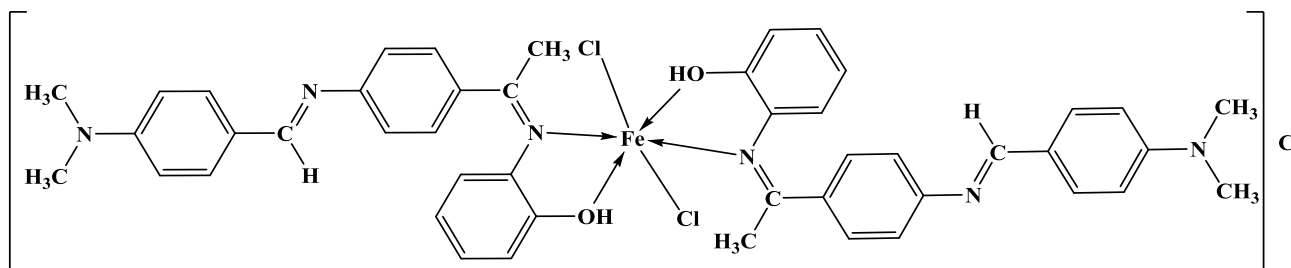


Figure 16: Structure and name of C2: [Dichloro bis (2-(((Z)-1-(4-(((E)-4-(dimethyl amino)benzylidene)amino)phenyl) ethylidene)amino)phenol) iron(III)]Chloride

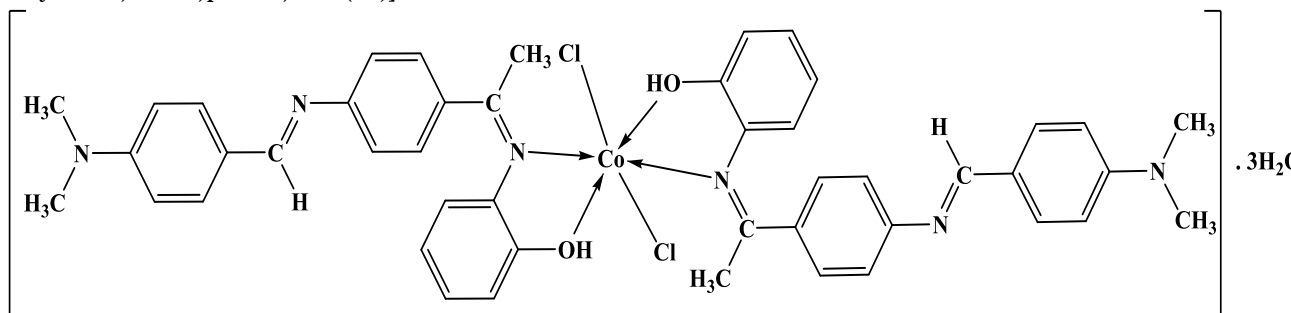


Figure 17: Structure and name of C3: [Dichloro bis (2-(((Z)-1-(4-(((E)-4-(dimethyl amino)benzylidene)amino)phenyl) ethylidene)amino)phenol) cobalt(II)]Trihydrate

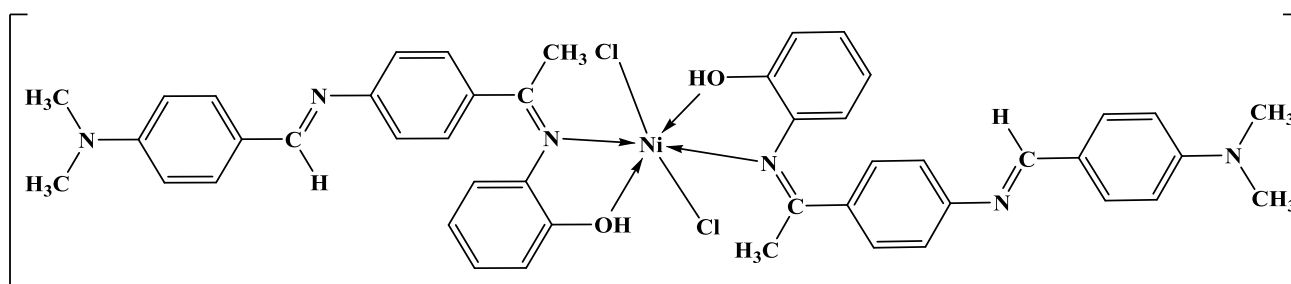


Figure 18: Structure and name of C4: [Dichloro bis (2-(((Z)-1-(4-(((E)-4-(dimethyl amino)benzylidene)amino)phenyl) ethylidene)amino)phenol) nickel(II)]

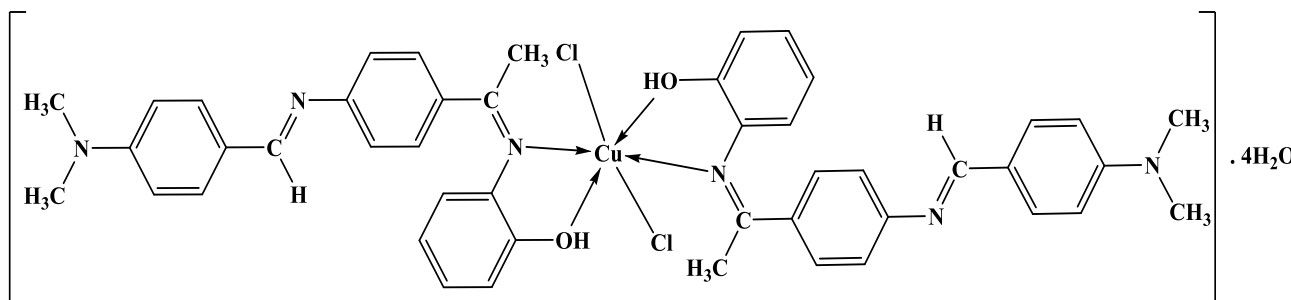


Figure 19: Structure and name of C5: [Dichloro bis (2-(((Z)-1-(4-(((E)-4-(dimethyl amino)benzylidene)amino)phenyl) ethylidene)amino)phenol) copper(II)] Tetrahydrate

### Inhibition of Proliferation of Human Brain Cancer (AMJM) Cells by the Ligand and its Complexes

Many anticancer agents have partial toxicity against normal and tumour cells as not have the ability to distinguish between the cells.

In this study the compounds were selected for their primary anticancer assay. It is necessary to identify some specific properties of cancer cells that different from the normal cells in order to reduce or elimination of toxicity[56], metal ion complexes were synthesized and screened for their anticancer properties[57, 58]. In order to study the ability of the ligand and complexes to cancer cells, by measuring the anti-proliferation

activity of the synthesized compounds by the MTT assay and find appropriate concentration that have the ability to kill human brain cancer cells in a concentration-dependent manner as in Figures (20-25). Schiff base metal ion complexes were exhibited a good improves to the anticancer properties[59, 60]. Figure (26) shown was the control and treated cells under microscope.

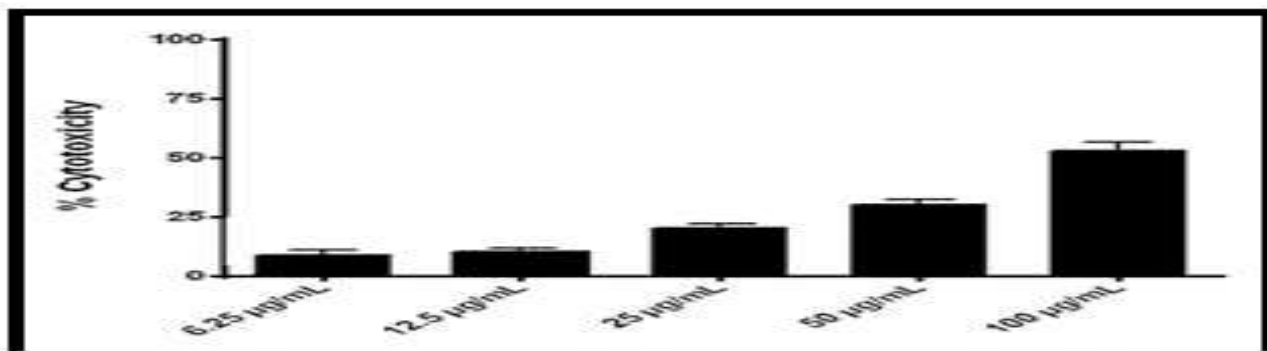


Figure 20: Cytotoxicity effect of L in AMJM cells

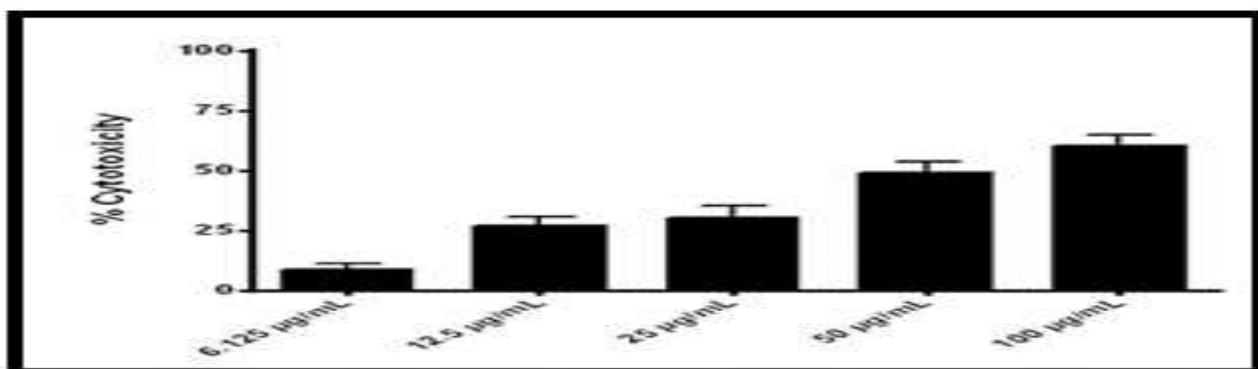


Figure 21: Cytotoxicity effect of C1 in AMJM cells

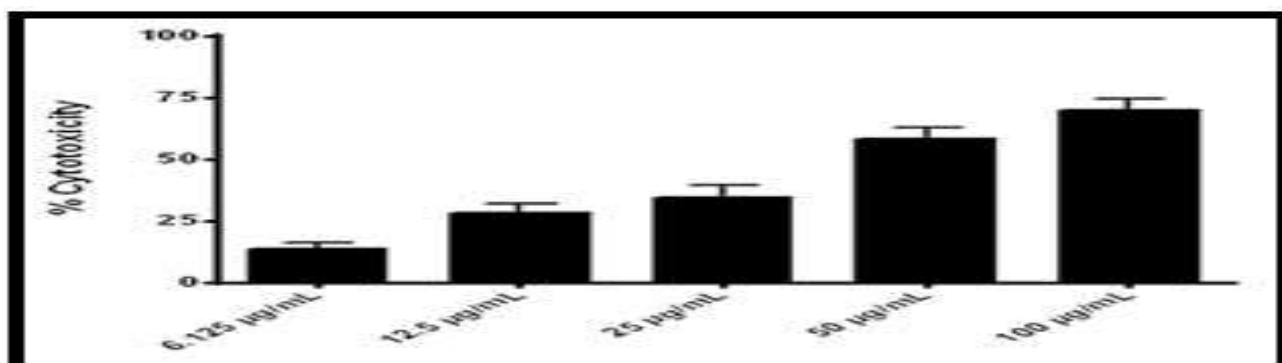


Figure 22: Cytotoxicity effect of C2 in AMJM cells

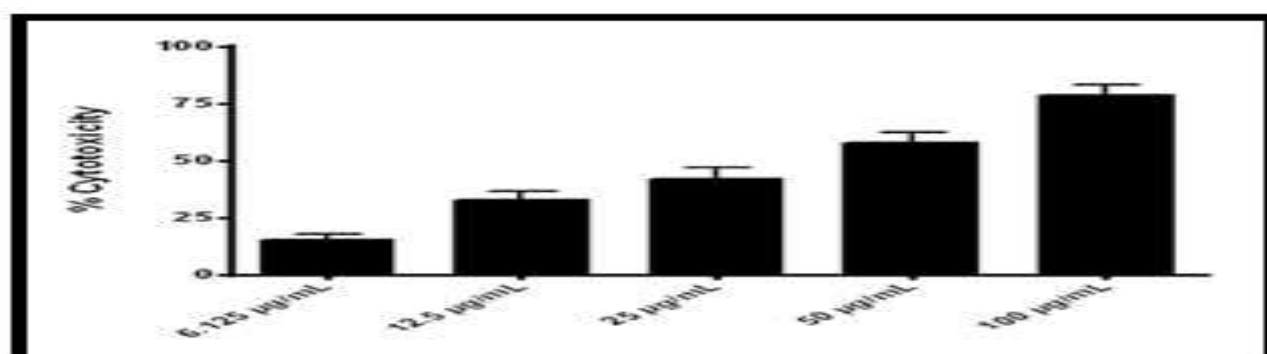


Figure 23: Cytotoxicity effect of C3 in AMJM cells

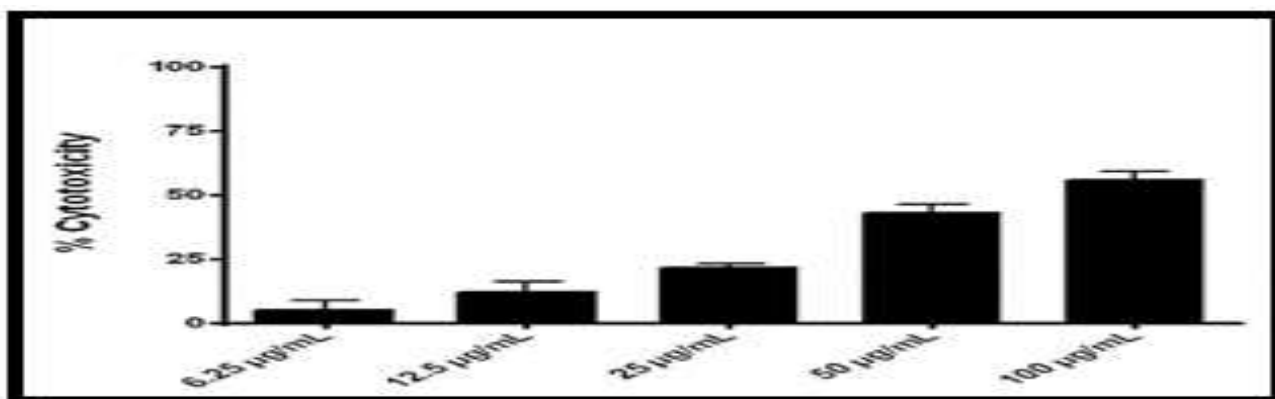


Figure 24: Cytotoxicity effect of C4 in AMJM cells

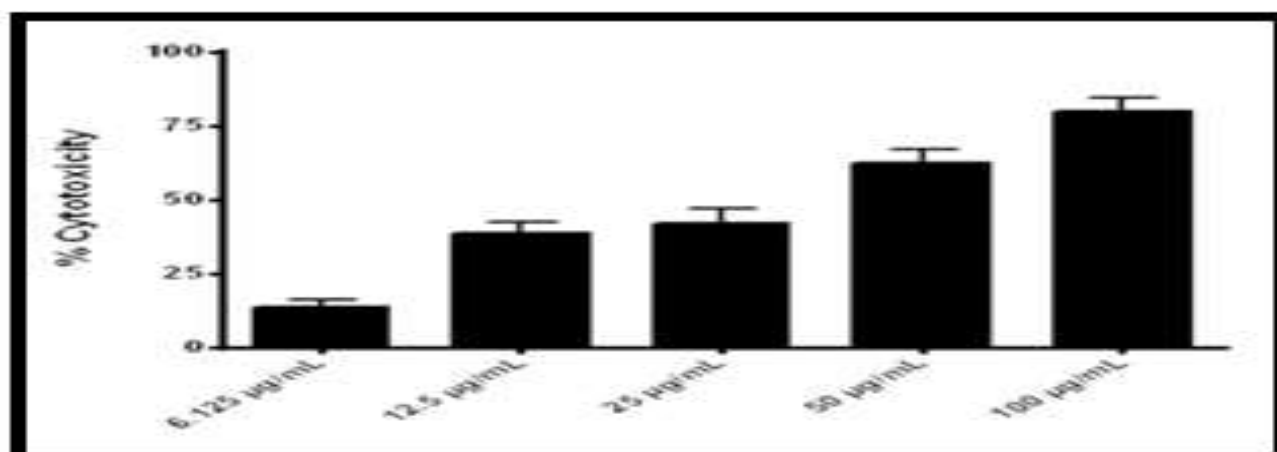


Figure 25: Cytotoxicity effect of C5 in AMJM cells

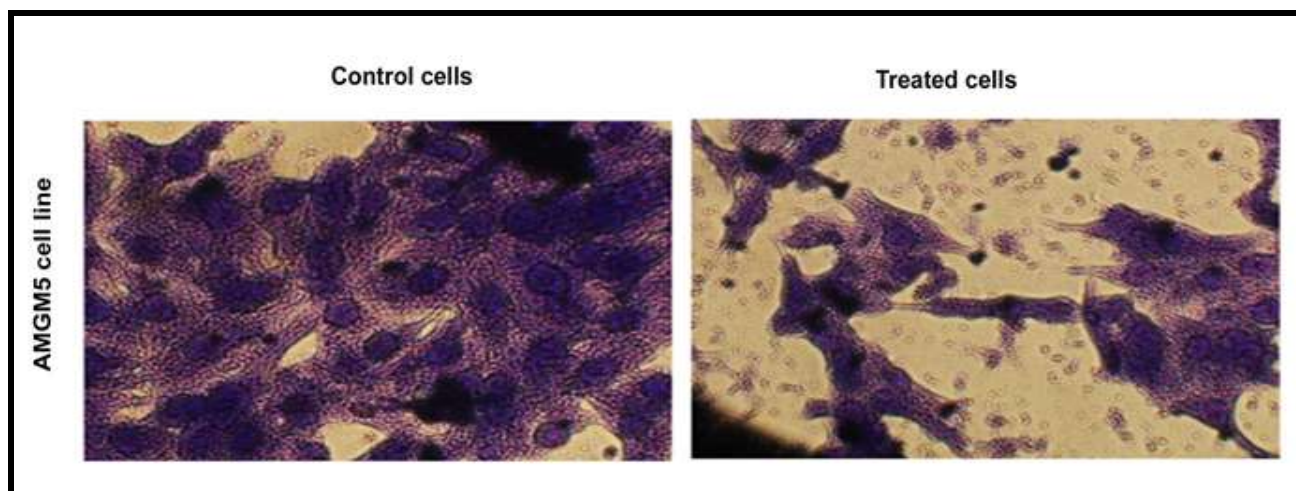


Figure 26: Control and treated cells line

## Conclusions

Mononuclear of (N,O) bidentate ligand has been synthesized as a new ligand derived from 4-aminoacetophenone, 4-N,N-dimethylaminobenzaldehyde, and 2-aminophenol. All synthesized complexes were taken the octahedral structure in (1:2) mole ratio and coordinated to the metal ion through N and

O atoms. Magnetic susceptibility proved the paramagnetic behaviour for the synthesized complexes. The M(II) complexes were non-electrical behaviour while M(III) was electrical according to the molar conductance. The anti-brain cancer studies were shown the copper complex was the higher activity than other complexes and the ligand.

## References

- Chen Y-L, Chen I-L, Wang T-C, Han C-H, Tzeng C-C (2005) "Synthesis and anticancer evaluation of certain 4-anilino-furo [2, 3-b] quinoline and 4-

anilino-furo [3, 2-c] quinoline derivatives". *European journal of Medicinal Chemistry*, 40 (9): 928-934.

2. Suresh S, Bhuvanesh N, Prabhu J, Thamilselvan A, Kannan K, Nandhakumar R(2018)"Pyrene based chalcone as a reversible fluorescent chemosensor for Al<sup>3+</sup> ion and its biological applications".*Journal of Photochemistry and Photobiology A: Chemistry*, 359: 172-182.
3. Vannocci T, Manzano RN, Beccalli O, Bettégazzi B, Grohovaz F, Cinque G, de Riso A, Quaroni L, Codazzi F, Pastore A(2018)"Adding a temporal dimension to the study of Friedreich's ataxia: the effect of frataxin overexpression in a human cell model".*Disease Models and Mechanisms*, 11 (6): (dmm. 032706).
4. Rogulski KR, Freytag SO, Zhang K, Gilbert JD, Paielli DL, Kim JH, Heise CC, Kirn DH(2000)"In vivo antitumor activity of ONYX-015 is influenced by p53 status and is augmented by radiotherapy".*Cancer Research*, 60 (5): 1193-1196.
5. Al-Shammari AM, Salman MI, Saihood YD, Yaseen NY, Raed K, Shaker HK, Ahmed A, Khalid A, Duiach A(2016)"In vitro synergistic enhancement of Newcastle Disease Virus to 5-fluorouracil cytotoxicity against tumor cells".*Biomedicines*, 4 (1): 1-10.
6. Scientific TF (2015) "Cell Culture Basics Handbook".UK: Gibco.
7. Hernández-Molina R, Mederos A (2003) 1.19 - Acyclic and Macrocyclic Schiff Base Ligands A2 - McCleverty, Jon A, in Book Titll, T.J. Meyer, Editor., Pergamon: Oxford, 411-446.
8. Kabak M, Elmali A, Elerman Y(1999)"Keto-enol tautomerism, conformations and structure of N-(2-hydroxy-5-methylphenyl), 2-hydroxybenzaldehydeimine".*Journal of molecular structure*, 477 (1): 151-158.
9. Zhao F, Wang W, Lu W, Xu L, Yang S, Cai X-M, Zhou M, Lei M, Ma M, Xu H-J, Cao F(2018)"High anticancer potency on tumor cells of dehydroabietylamine Schiff-base derivatives and a copper(II) complex".*European Journal of Medicinal Chemistry*, 146: 451-459.
10. Shebl M, Adly OMI, Abdelrhman EM, El-Shetary BA(2017)"Binary and ternary copper(II) complexes of a new Schiff base ligand derived from 4-acetyl-5,6-diphenyl-3(2H)-pyridazinone: Synthesis, spectral, thermal, antimicrobial and antitumor studies".*Journal of Molecular Structure*, 1145: 329-338.
11. Andiappan K, Sanmugam A (2018) Deivanayagam E., Karuppasamy K., Kim H.-S. and Vikraman D."In vitro cytotoxicity activity of novel Schiff base ligand-lanthanide complexes".*Scientific reports*, 8 (1): 3054.
12. Matesanz AI, Tapia S, Souza P (2016) "First 3,5-diacetyl-1,2,4-triazol derived mono(thiosemicarbazone) and its palladium and platinum complexes: Synthesis, structure and biological properties".*Inorganica Chimica Acta*, 445: 62-69.
13. Tao T, Xu F, Chen X-C, Liu Q-Q, Huang W, You X-Z (2012) "Comparisons between azo dyes and Schiff bases having the same benzothiazole/phenol skeleton: Syntheses, crystal structures and spectroscopic properties".*Dyes and Pigments*, 92 (3): 916-922.
14. Al-Masoudi NA, Aziz NM, Mohammed AT (2009) "Synthesis and In Vitro Anti-HIV Activity of Some New Schiff Base Ligands Derived from 5-Amino-4-phenyl-4 H-1, 2, 4-triazole-3-thiol and Their Metal Complexes".*Phosphorus, Sulfur, and Silicon*, 184 (11): 2891-2901.
15. Sridhar SK, Pandeya SN, Stables JP, Ramesh A (2002)"Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin derivatives".*European Journal of Pharmaceutical Sciences*, 16 (3): 129-132.
16. Prajila M, Ammal PR, Joseph A(2017)"Comparative studies on the corrosion inhibition characteristics of three different triazine based Schiff's bases, HMMT, DHMMT and MHMMT, for mild steel exposed in sulfuric acid".*Egyptian Journal of Petroleum*.
17. Kumar KS, Ganguly S, Veerasamy R, De Clercq E(2010)"Synthesis, antiviral activity and cytotoxicity evaluation of Schiff bases of some 2-phenyl quinazoline-4(3H)-ones".*European Journal of Medicinal Chemistry*, 45 (11): 5474-5479.
18. Vahdat SM, Mardani HR, Golchoubian H, Khavarpour M, Baghery S, Roshankouhi Z(2013)"Cu (II) Schiff base as catalyst in the synthesis of 1, 8-dioxodecahydroacridine".*Combinatorial chemistry & high throughput screening*, 16 (1): 2-6.

19. Sulaiman GM, Jabir MS, Hameed AH (2018) "Nanoscale modification of chrysin for improved of therapeutic efficiency and cytotoxicity". *Artificial cells, nanomedicine, and biotechnology*, 1-13.
20. Al-Shammari AM, Salman MI, Saihood YD, Yaseen NY, Raed K, Shaker HK, Ahmed A, Khalid A, Duiach A (2016) "In vitro synergistic enhancement of Newcastle Disease Virus to 5-fluorouracil cytotoxicity against tumor cells". *Biomedicines*, 4 (1): 3.
21. González-García C, Mata A, Zani F, Mendiola MA, López-Torres E (2016) "Synthesis and antimicrobial activity of tetradentate ligands bearing hydrazone and/or thiosemicarbazone motifs and their diorganotin (IV) complexes". *Journal of inorganic biochemistry*, 163: 118-130.
22. Hosseinpour S, Hosseini-Yazdi SA, White J (2017) "Binuclear zinc(II) complexes of N(4)-substituted bis(thiosemicarbazone) ligands incorporating hydroxyl group and their non-hydroxyl analogues". *Inorganica Chimica Acta*, 461: 150-160.
23. Nakamoto K (1997) "Infrared and Raman Spectra of Inorganic and Coordination Chemistry". Part B: Theory and Applications in Inorganic Chemistry, 6th edn., Wiley, New York. 218.
24. Mathan Kumar S, Kesavan MP, Vinoth Kumar GG, Sankarganesh M, Chakkaravarthi G, Rajagopal G, Rajesh J (2018) "New heteroleptic Zn(II) complexes of thiosemicarbazone and diimine Co-Ligands: Structural analysis and their biological impacts". *Journal of Molecular Structure*, 1153: 1-11.
25. Donald L Pavia, Gary M Lampman Kriz GS (2001) "Introduction to Spectroscopy". third ed., 3: 26.
26. Nakamoto K (1997) "Infrared and Raman Spectra of Inorganic and Coordination Chemistry". Part B: Theory and Applications in Inorganic Chemistry, 6th edn., Wiley, New York, 16 (12):8.
27. Nakamoto K (1997) "Infrared and Raman Spectra of Inorganic and Coordination Chemistry". Part B: Theory and Applications in Inorganic Chemistry, 6th edn., Wiley, New York, 285.
28. Gottlieb HE, Kotlyar V, Nudelman A (1997) "NMR chemical shifts of common laboratory solvents as trace impurities". *The Journal of organic chemistry*, 62 (21): 7512-7515.
29. Hosseini-Yazdi SA, Mirzaahmadi A, Khandar AA, Mahdavi M, Rahimian A, Eigner V, Dušek M, Zarrini G (2017) "Copper, nickel and zinc complexes of a new water-soluble thiosemicarbazone ligand: Synthesis, characterization, stability and biological evaluation". *Journal of Molecular Liquids*, 248: 658-667.
30. Khan SA, Asiri AM (2018) "Multi-step synthesis, spectroscopic studies of biological active steroidal thiosemicarbazones and their palladium (II) complex as macromolecules". *International journal of biological macromolecules*, 107: 105-111.
31. Kumar SM, Kesavan MP, Kumar GGV, Sankarganesh M, Chakkaravarthi G, Rajagopal G, Rajesh J (2018) "New heteroleptic Zn (II) complexes of thiosemicarbazone and diimine Co-Ligands: Structural analysis and their biological impacts". *Journal of Molecular Structure*, 1153: 1-11.
32. Sinniah SK, Sim KS, Ng SW, Tan KW (2017) "Structural and cytotoxic studies of cationic thiosemicarbazones". *Journal of Molecular Structure*, 1137: 253-259.
33. Stringer T, Hendricks DT, Guzgay H, Smith GS (2012) "Synthesis and characterization of multimeric salicylaldimine thiosemicarbazones and their Pd (II) and Pt (II) complexes". *Polyhedron*, 31 (1): 486-493.
34. de Araújo Neto LN, do Carmo Alves de Lima M, de Oliveira JF, de Souza ER, Buonafina MDS, Vitor Anjos MN, Brayner FA, Alves LC, Neves RP, Mendonça-Junior FJB (2017) "Synthesis, cytotoxicity and antifungal activity of 5-nitro-thiophene-thiosemicarbazones derivatives". *Chemico-Biological Interactions*, 272: 172-181.
35. Yaman PK, Şen B, Karagöz CS, Subaşı E (2017) "Half-sandwich ruthenium-arene complexes with thiophen containing thiosemicarbazones: Synthesis and structural characterization". *Journal of Organometallic Chemistry*, 832: 27-35.
36. Małecki J, Maroń A, Serda M, Polański J (2013) "Ruthenium (II) carbonyl complexes with thiosemicarbazone ligands". *Polyhedron*, 56: 44-54.

37. Moorthy N, Prabakar PJ, Ramalingam S, Periandy S, Parasuraman K (2016) "Vibrational, NMR and UV-Visible spectroscopic investigation, VCD and NLO studies on Benzophenone thiosemicarbazone using computational calculations". *Journal of Molecular Structure*, 1110: 162-179.
38. Arce ER, Machado I, Rodríguez B, Lapier M, Zúñiga MC, Maya JD, Azar CO, Otero L, Gambino D (2017) "Rhenium (I) tricarbonyl compounds of bioactive thiosemicarbazones: Synthesis, characterization and activity against *Trypanosoma cruzi*". *Journal of inorganic biochemistry*, 170: 125-133.
39. Tenchiu A-C, Ventouri I-K, Ntasi G, Palles D, Kokotos G, Kovala-Demertzi D, Kostas ID (2015) "Synthesis of a palladium complex with a  $\beta$ -d-glucopyranosyl-thiosemicarbazone and its application in the Suzuki-Miyaura coupling of aryl bromides with phenylboronic acid". *Inorganica Chimica Acta*, 435: 142-146.
40. Rasheed RT (2012) "Synthesis of new metal complexes derived from 5-nitroso 8-hydroxy quinoline and Salicylidene P-imino acetophenone with Fe (II), Co (II), Ni (II) and Cu (II) ions". *Journal of Al-Nahrain University-Science*, 15 (4): 68-73.
41. Arun TR, Raman N (2014) "Antimicrobial efficacy of phenanthrenequinone based Schiff base complexes incorporating methionine amino acid: structural elucidation and in vitro bio assay". *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 127: 292-302.
42. Raman N, Sakthivel A, Selvaganapathy M, Mitu L (2014) "Effect of DNA interaction involving antioxidative 4-aminoantipyrine incorporating mixed ligand complexes having alpha-amino acid as co-ligand". *Journal of Molecular Structure*, 1060: 63-74.
43. Gopalan R, Ramalingam V (2001) "Concise Coordination Chemistry". 1 ed. : Vikas Publishing House Pvt Ltd., 107.
44. Shebl M, Khalil SM, Al-Gohani FS (2010) "Preparation, spectral characterization and antimicrobial activity of binary and ternary Fe (III), Co (II), Ni (II), Cu (II), Zn (II), Ce (III) and UO<sub>2</sub> (VI) complexes of a thiocarbohydrazone ligand". *Journal of Molecular Structure*. 980 (1-3): 78-87.
45. Subbaraj P, Ramu A, Raman N, Dharmaraja J (2014) "Novel mixed ligand complexes of bioactive Schiff base (E)-4-(phenyl (phenylimino) methyl) benzene-1, 3-diol and 2-aminophenol/2-aminobenzoic acid: Synthesis, spectral characterization, antimicrobial and nuclease studies". *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 117: 65-71.
46. AL-Adilee KJ, Fanfon DY (2012) "Preparation, Spectral Identification and Analytical Studies of Some Transition Metal Complexes with New Thiazolylazo Ligand and Their Biological Activity Study". *Journal of Chemistry and Chemical Engineering*, 6 (11): 1016.
47. Sharma A, Shah M (2013) "Synthesis and characterization of some transition metal complexes derived from bidentate Schiff base ligand". *Journal of Applied Chemistry*, 3: 62-66.
48. Sherif OE, Abdel-Kader NS (2014) "Spectroscopic and biological activities studies of bivalent transition metal complexes of Schiff bases derived from condensation of 1, 4-phenylenediamine and benzopyrone derivatives". *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 117: 519-526.
49. Yin C-ML, Zi-Ru Kong, Yang-Hui Wu, Cheng-Yun Ren, De-Hou Lü, Yu-Gang Xue, Hong-Fu (1992) "Studies on the thermal behaviour and decomposition mechanism of complexes of rare earth (III) nitrates with 18-crown-6". *Thermochimica acta*, 204 (2): 251-260.
50. Abdel-Latif S, Hassib H, Issa Y (2007) "Studies on some salicylaldehyde Schiff base derivatives and their complexes with Cr (III), Mn (II), Fe (III), Ni (II) and Cu (II)". *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 67 (3-4): 950-957.
51. Macdonald A, Sirichanya P (1969) "The determination of metals in organic compounds by oxygen-flask combustion or wet combustion". *Microchemical Journal*, 14 (2): 199-206.
52. Prakash A, Singh BK, Bhojak N, Adhikari D (2010) "Synthesis and characterization of bioactive zinc(II) and cadmium(II) complexes with new Schiff bases derived from 4-nitrobenzaldehyde and acetophenone with ethylenediamine".

- Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 76 (3): 356-362.
53. Geary WJ (1971) "The use of conductivity measurements in organic solvents for the characterisation of coordination compounds". *Coordination Chemistry Reviews*, 7 (1): 81-122.
  54. Ibrahim OB, Mohamed MA, Refat MS (2014) "Nano sized schiff base complexes with Mn (II), Co (II), Cu (II), Ni (II) and Zn (II) metals: synthesis, spectroscopic and medicinal studies". *Can. Chem. Trans.*, 2 (2): 108-121.
  55. Al-Amoudi M, Salman M, Megahed A, Refat M (2012) "Synthesis and characterization of nano composites having a catalytic activities using microwave techniques". *European Chemical Bulletin*, 1 (8): 293-304.
  56. Chen D, Peng F, Cui QC, Daniel KG, Orlu S, Liu J, Dou QP (2005) "Inhibition of prostate cancer cellular proteasome activity by a pyrrolidine dithiocarbamate-copper complex is associated with suppression of proliferation and induction of apoptosis". *Front Biosci.*, 10 (2): 2932-2939.
  57. De Vizcaya-Ruiz A, Rivero-Muller A, Ruiz-Ramirez L, Kass G, Kelland L, Orr R, Dobrota M (2000) "Induction of apoptosis by a novel copper-based anticancer compound, casiopeina II, in L1210 murine leukaemia and CH1 human ovarian carcinoma cells". *Toxicology in Vitro*, 14 (1): 1-5.
  58. Sun RW-Y, Ma D-L, Wong EL-M, Che C-M (2007) "Some uses of transition metal complexes as anti-cancer and anti-HIV agents". *Dalton Transactions*, (43): 4884-4892.
  59. Holla BS, Veerendra B, Shivananda M, Poojary B (2003) "Synthesis characterization and anticancer activity studies on some Mannich bases derived from 1, 2, 4-triazoles". *European Journal of Medicinal Chemistry*, 38 (7-8): 759-767.
  60. Creaven BS, Duff B, Egan DA, Kavanagh K, Rosair G, Thangella VR, Walsh M (2010) "Anticancer and antifungal activity of copper (II) complexes of quinolin-2 (1H)-one-derived Schiff bases". *Inorganica Chimica Acta.*, 363 (14): 4048-4058.