



Nano metal complexes in cancer therapy, preparation, spectroscopic, characterization and anti-breast cancer activity of new metal complexes of alanine Schiff-base.



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Abstract

There are many properties of metal ions that were useful for solving basic problems in medicine, metal complexes with particular properties can be covalently affected to biological macromolecules. Mono Co(II), Ni(II), Cu(II), Zn(II), Mg(II) and binuclear Zn(II)/Cu(II) and Ni(II)/Cu(II) complexes of new Schiff-base derived from alanine amino acid ester have been synthesized and characterized. They were studied using elemental and spectral analysis such as IR, UV-VIS, ¹H-NMR mass spectroscopy as well as conductivity, magnetism, thermal analysis (DTA and TGA), electron microscope and ESR measurements. Conductance measurements of metal complexes indicated non electrolytic in nature. Elemental and spectral analysis confirmed distorted octahedral structural for all complexes. ESR spectra of complexes showed anisotropic or isotropic spectra with covalent bond character. Electron microscope data showed that, complexes with high biological activity were found in Nano form. The ligand and some of its complexes were studied against breast cancer (in vitro) and exhibited moderate to high activity compared to standard drug (doxorubicin). The order of activity was (doxorubicin)= ligand (1) > Ni(II)/Cu(II) complex (19) > Zn(II)/Cu(II) complex (20) > Zn(II) complex (18).

Keywords:- Alanine, Schiff-bas, spectra, magnetism, Nano form.

1. Introduction

Amino acids are molecules that contain both a carboxyl and amino group with a side chain that varies between different amino acids. Although, many types of amino acids are known as α -amino acids, the monomers from which proteins are constructed [1]. Since amino acid contains these groups therefore, they contain potential donor sites such as (COOH) and (NH₂) which they could coordinate with metals ions [2-4]. The reaction of aldehyde and ketones with primary amines compounds of the type RNH₂ and ArNH₂ afforded an imine. N-Substituted imines are sometimes called Schiff's- bases, after Hugo Schiff who describes their formation in 1864. Schiff- base ligands have significant importance, especially in the development of Schiff -base complexes, because Schiff- base ligands are potentially capable of forming stable complexes with metal ions [5,6]. Also Schiff -bases have been studied extensively due to their applications in biological, clinical, analytical and pharmacological study [7-8]. Solvent free synthesis by microwave irradiation technique

has been done and this technique is rapid and efficient and very economical. Another wise the yield of products also high and purification is done by simple recrystallization [9]. Cisplatin is generally used in clinic for breast cancer treatment but with toxic side effects and develops resistance. Anti – tumor properties of copper and its coordination compounds have been explored intensively in recent years[10]. Metals are endowed with unique characteristic properties include redox activity , variable coordination mode and reactivity towards organic substances .Due to their reactivity , metals are tightly regulated under normal conditions and are associated with various pathological disorders ,including cancer. For these reasons, coordination complexes, either as drugs or prodrugs, become very attractive probes as potential anticancer agents[11] . The present study deals with the synthesis, characterization and anticancer activity of Schiff - bases derived from P-DL-alanine, and 2-amino-N-(2-aminophenyl) butanamide with its complexes.

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2. Experimental

Instrumentation and measurement:

The ligand and its metal complexes were analyzed for C, H, N and Cl at the Micro Analytical Center, Cairo University, Egypt. Standard analytical methods were used to determine the metal ion content. ¹H-NMR spectra were obtained on BRUKER 400 MHz spectrometer. Chemical shifts (ppm) are reported relative to TMS. IR spectra of the ligand and its metal complexes were measured using KBr discs by a Jasco FT/IR 300E Fourier transform infrared spectrophotometer covering the range 400-4000 cm⁻¹. Electronic spectra in the 200-900 nm regions were recorded on a Perkin-Elmer 550 spectrophotometer. The thermal analyses (DTA and TGA) were carried out on a Shimadzu DT-30 thermal analyzer from room temperature to 800 °C at a heating rate of 10 °C/min. Mass spectra of the ligand and some of its metal complexes were recorded using JEULJMS-AX500 mass spectrometer provided with data system. Magnetic susceptibilities were measured at 25°C by the Gouy method using mercuric tetrathiocyanatocobaltate(II) as the magnetic susceptibility standard. Diamagnetic corrections were estimated from Pascal's constant. The magnetic moments were calculated from the equation

$$\mu_{\text{eff.}} = 2.84 \sqrt{\chi_M^{\text{corr}} \cdot T}$$

The molar conductance of 10⁻³ M solution of the complexes in DMSO was measured at 25 °C with a Bibby conductometer type MCl. The resistance measured in ohms and the molar conductivities were calculated according to the equation:

$$\Lambda_M = \frac{V \times K \times g}{Mw \times \Omega}$$

Where: Λ_M = molar conductivity / $\Omega^{-1}\text{cm}^2 \text{mol}^{-1}$, V = volume of the complex solution/ mL, K = cell constant (0.92/ cm-1), Mw = molecular weight of the complex, g = weight of the complex/g, Ω = resistance/ Ω . ESR spectra were recorded using avarian E-109 spectrophotometer DPPH was used as a standard materials. T.L.C confirmed the purity of the prepared compounds.

Synthesis of the ligand(1), [H₃L]:

It was prepared as follow:- Alanine (20.0 g, 0.1mol) dissolved in 30 cm³ of ethanol in the presence of 5 drops of conc H₂SO₄ was refluxed with stirring for two hours and then left to cool at room temperature for an hour. O-phenylene diamine (29.0 g, 0.26 mol) dissolved in 30 cm³ of ethanol solution was added to the ester and the mixture was refluxed with stirring for another 2 hours. The mixture left to cool at room temperature,

filtered off the formed hydrazide. The ethanolic solution of hydrazide (24.0g, 0.08 mol) was added to 2-hydroxybenzaldehyde (22.9g, 0.17 mol) (1:2) molar ratio dissolved in 30 cm³ ethanol was refluxed and stirred for another three hours at 80 °C, then left to cool at room temperature. The solid product which formed was filtered off and then dried under vacuum over anhydrous CaCl₂ to give the ligand.. Analytical data of the ligand are given in **Table (1)**.

Scheme (1) show the method of preparation

Synthesis of metal complexes (2)-(20)

Complexes were prepared using (1L:1M) except (5), (8), (9), (13), (15), (17), (18) and (20) reacted as (1L:2M) molar ratio were used. They were prepared by refluxing with stirring a hot ethanolic 30cm³ solution of the ligand (1.0 g, 0.002 mole) with a hot ethanolic solution 30cm³ of the metal salts of (0.99 g, 0.002 mole) of MgSO₄.4H₂O, complex (2), (1.0 g, 0.002 mole) of Mg.Cl₂.5H₂O, complex (3), (0.08 g, 0.0002 mole) of Co(OAc)₂.4H₂O, complex (4), (0.16 g, 0.004 mol) of Co(OAc)₂.4H₂O, complex (5), (1.1 g, 0.002 mole) of CoSO₄.3H₂O, complex (6), (1.54 g, 0.002 mole) of CoCl₂.H₂O, complex (7), (0.64 g, 0.004 mol) of Ni(OAc)₂.4H₂O, complex (8), (1.01g, 0.004 mole) NiSO₄.4H₂O, complex (9), (0.89 g, 0.002 mole) of NiCl₂.6H₂O, complex (10), (1.25 g, 0.002 mole) of Cu(OAc)₂.H₂O, complex (11), (1.54 g, 0.002mol) of CuSO₄.5H₂O complex (12), (1.01g, 0.004 mole) of CuCl₂.2H₂O, complex (13), (0.8 g, 0.002 mole) of Zn(OAc)₂.4H₂O, complex (14), (0.16 g, 0.004 mole) of Zn(OAc)₂.4H₂O complex (15), (1.19 g, 0.002 mole) of ZnSO₄.5H₂O, complex (16), (2.4g, 0.004mole) of ZnSO₄.5H₂O, complex (17), (0.08 g, 0.0002 mole) of Zn(OAc)₂.4H₂O (0.08 g, 0.0002 mole) of Cu(OAc)₂.H₂O, complex (18), (0.08 g, 0.0002 mole) of Ni(OAc)₂.4H₂O (0.08 g, 0.0002 mole) of Cu(OAc)₂.H₂O, complex (19), and 0.08 g, 0.0002 mole) of ZnSO₄.H₂O (0.08 g, 0.0002 mole) of CuSO₄.5H₂O, complex (20). The reaction mixtures were refluxed with stirring for 1–3 hours range, depending on the nature of the metal ion and the anion. The precipitates so formed were filtrated off, washed with ethanol, and dried in desiccators over anhydrous CaCl₂. The analytical data are represented in table (1)

Transmission electron microscope characterization (TEM)

TEM samples for the colloidal suspensions of the ligand and the two complexes particles Ni(II)/Cu(II) and Zn(II)/Cu(II) in distilled water were prepared by dropping the colloids onto carbon-coated TEM grids (Carbon coated Cu grids, Ted

Pella, Redding, CA, USA) and allowing the liquid carrier to evaporate in air then assaying by a JEOL 1230 transmission electron microscope (120 kV).

Biological Activity

Cytotoxic activity:-

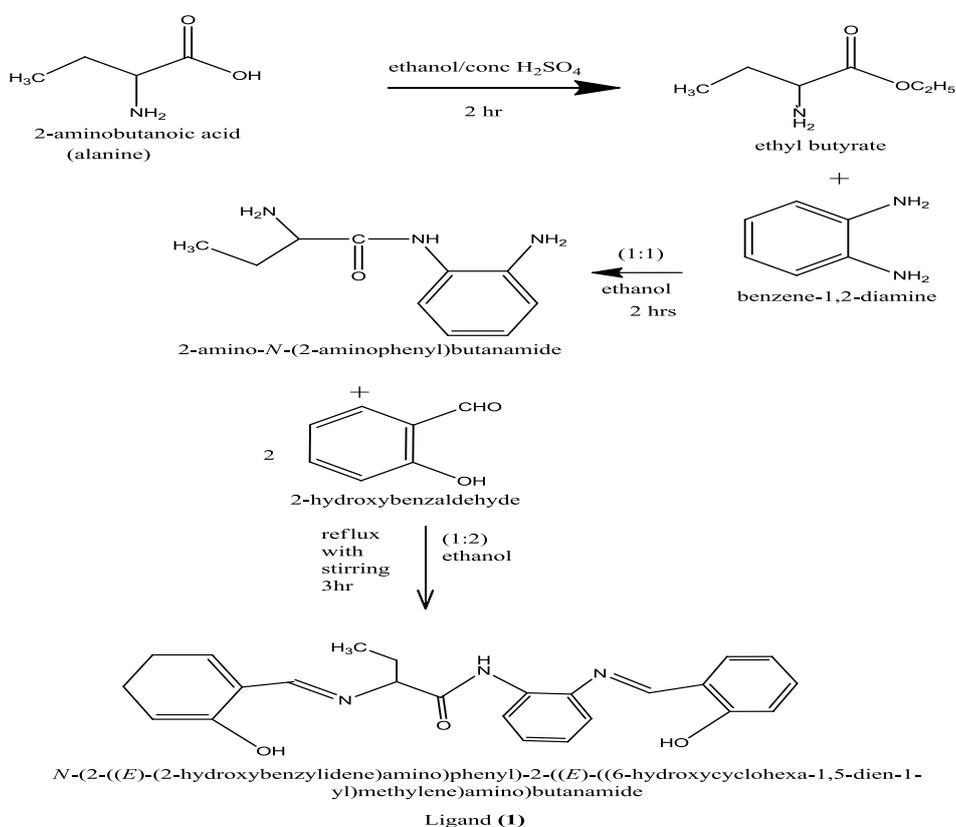
Evaluation of the cytotoxic activity of the ligand and some of its metal complexes was carried out in the Pathology Laboratory, Pathology Department, Faculty of Medicine, El- Menoufia University, Egypt. The process was carried out in-vitro using (Sulfo-Rhodamine-B-stain (SRB) assay published method [11, 15]. Cells were plated in 96-multiwellplate (10^4 cells/well) for 24 hrs. Before treatment with the complexes to allow attachment of cell to the wall of the plate. Different concentrations of the compounds under test in DMSO (1.8, 2.6, 3.9, 7.8, 15.6, 31.25, 62.5, 125 and 500 $\mu\text{g/ml}$) were added to the cell monolayer, triplicate wells being prepared for each individual dose. Monolayer cells were incubated with the complexes for 48 hours at 37°C using 5% CO_2 . After 48 hours cells were fixed, washed and stained with Sulfo-Rhodamine-B-stain (SRB. Excess stain was wash with acetic acid and attached stain was recovered with Tris EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and

drug concentration is plotted to get the survival curve for each tumor cell line after addition the specified compound.

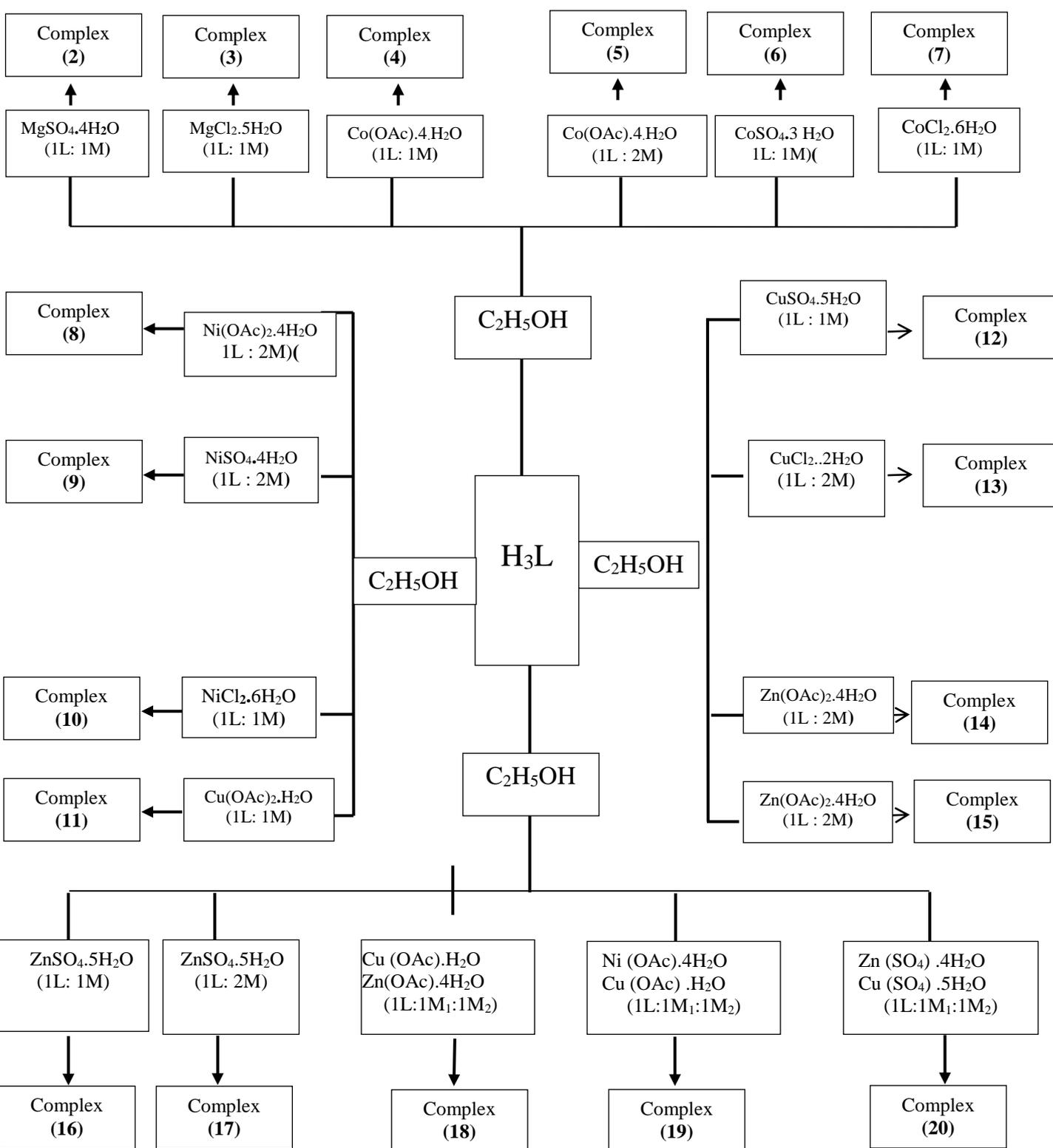
3. Results and discussion:-

All metal complexes are colored, crystalline solids, non-hygroscopic, and air stable solids at room temperature without decomposition for one year. The complexes are insoluble in water, ethanol, methanol, benzene, toluene, acetonitrile and chloroform, but appreciably soluble in both dimethylformamide (DMF) and dimethylsulfoxide (DMSO). The analytical and physical data (Table 1) and spectral data, (Tables 2-4) agree well with the proposed structures (Figure 1). The elemental analyses indicated that, all complexes were found to (1L:1M) and (1L: 2M) molar ratios. Scheme (2) represented the preparation of metal complexes.

Conductance measurements: The molar conductivities of the complexes were measured in DMSO solvent with 1.0×10^{-3} M. The low magnitudes of molar conductivities $< 1 \text{ cm}^2 \text{ mol}^{-1}$ (listed in Table 1) indicated that, all of the complexes possess non-electrolytic nature [27]. These values agree well with the analytical data and also confirmed the involvement of the anions groups in the metal coordination.



Scheme (1) Preparation of the ligand



Scheme(2) Preparation of metal complexes

Table 1:-Analytical and Physical Data of the Ligand [**H₃L**] (**1**) and its Metal complexes.

No.	Ligand/Complexes	Color	FW	M.P(°C)	Yield(%)	Anal. /Found (Calc.) (%)					Molar conductance*
						C	H	N	M	Cl	
(1)	[H ₃ L] C ₂₃ H ₂₃ N ₃ O ₃	Reddish brown	389.45	>300	75	(70.12) (69.71)	(5.33) (5.11)	(10.22) (10.03)	-	-	
(2)	[(H ₃ L)Mg(SO ₄)(H ₂ O) ₂].2H ₂ O C ₂₃ H ₂₉ MgN ₃ O ₁₁ S	Pale brown	579.86	>300	60	(47.11) (46.92)	(4.82) (4.61)	(7.52) (7.23)	(4.1) (3.87)	-	4.52
(3)	[(H ₃ L)Mg(Cl) ₂ (H ₂ O) ₂]. 2H ₂ O C ₂₃ H ₂₇ Cl ₂ MgN ₃ O ₆	Gray	536.69	>300	65	(51.01) (50.78)	(4.91) (4.53)	(8.2) (7.91)	(4.25) (3.98)	(13.98) (13.67)	4.24
(4)	[(H ₃ L)Co(OAc) ₂ (H ₂ O)]. 2H ₂ O C ₂₇ H ₃₇ CoN ₃ O ₁₀	Yellowish brown	622.53	>300	70	(52.92) (52.53)	(5.78) (5.37)	(6.92) (6.34)	(9.89) (9.56)	-	5.09
(5)	[(H ₃ L)(Co) ₂ (OAc) ₄ (H ₂ O) ₂].2H ₂ O C ₃₁ H ₄₃ Co ₂ N ₃ O ₁₅	Dark brown	815.55	>300	73	(45.32) (45.00)	(5.0) (4.81)	(4.98) (4.68)	(14.12) (13.92)	-	3.64
(6)	[(H ₃ L) Co(SO ₄)(H ₂ O) ₂]. 2H ₂ O C ₂₃ H ₂₉ CoN ₃ O ₁₁ S	Brown	614.49	>300	80	(44.65) (44.11)	(4.23) (3.98)	(7.01) (6.92)	(9.87) (9.65)	-	4.77
(7)	[(H ₃ L) Co(Cl) ₂ (H ₂ O)]. H ₂ O C ₂₃ H ₂₅ Cl ₂ CoN ₃ O ₅	Rose	553.31	>300	70	(49.72) (49.35)	(4.33) (4.01)	(7.65) (7.34)	(10.78) (10.67)	(12.87) (12.81)	4.15
(8)	[(H ₃ L)(Ni) ₂ (OAc) ₄ (H ₂ O) ₂].3H ₂ O C ₃₁ H ₄₃ N ₃ Ni ₂ O ₁₆	Gray	833.09	>300	85	(44.33) (43.98)	(4.72) (4.23)	(5.01) (4.72)	(14.88) (14.65)	-	4.45
(9)	[(H ₃ L) (Ni) ₂ (SO ₄) ₂ (H ₂ O) ₄]. H ₂ O C ₂₃ H ₃₃ N ₃ Ni ₂ O ₁₆ S ₂	Greenish yellow	789.04	>300	69	(34.92) (34.57)	(3.95) (3.63)	(5.12) (4.87)	(14.92) (14.53)	-	4.97
(10)	[(H ₃ L) Ni(Cl) ₂ (H ₂ O)] H ₂ O. C ₂₃ H ₂₅ Cl ₂ Ni ₃ O ₁₅	Greenish brown	553.06	>300	68	(49.82) (49.68)	(4.41) (4.12)	(7.35) (7.11)	(10.37) (10.10)	(12.73) (12.43)	3.11
(11)	[(H ₃ L) Cu(OAc) ₂ (H ₂ O)]. C ₂₇ H ₃₄ CuN ₃ O ₈	Green	592.12	>300	75	(54.23) (53.89)	(5.35) (5.21)	(7.10) (6.87)	(10.25) (9.86)	-	4.49
(12)	[(H ₃ L)Cu(SO ₄)(H ₂ O) ₂]. 2H ₂ O C ₂₃ H ₂₉ CuN ₃ O ₁₁ S	Dark green	619.1	>300	69	(44.41) (44.11)	(4.22) (3.82)	(6.89) (6.55)	(10.37) (10.11)	-	3.87
(13)	[(H ₃ L) (Cu) ₂ (Cl) ₄ (H ₂ O) ₂] 2H ₂ O C ₂₃ H ₃₁ Cl ₄ Cu ₂ N ₃ O ₇	Pale brown	730.40	>300	75	(37.56) (37.13)	(3.63) (3.22)	(6.11) (5.89)	(17.89) (17.57)	(19.88) 19.67	5.49
(14)	[(H ₃ L)Zn(OAc) ₂ (H ₂ O)]. 2H ₂ O C ₂₇ H ₃₃ N ₃ O ₁₀ Zn	Pale Gray	624.96	>300	90	(51.21) (50.97)	(4.87) (4.33)	(6.87) (6.23)	(10.92) (10.72)	-	4.54
(15)	[(H ₃ L)(Zn) ₂ (OAc) ₄ (H ₂ O) ₂]. H ₂ O C ₃₁ H ₄₁ N ₃ O ₁₄ Zn ₂	Dark purple	810.45	>300	65	(45.67) (45.26)	(4.78) (4.57)	(5.01) (4.92)	(16.00) (15.87)	-	6.21
(16)	[(H ₃ L)(Zn)(SO ₄)(H ₂ O) ₂]. 2H ₂ O C ₂₃ H ₂₉ N ₃ O ₁₁ SZn	Brown	620.94	>300	68	(44.11) (43.87)	(4.31) (4.00)	(6.78) (6.45)	(10.89) (10.63)	-	3.94
(17)	[(H ₃ L)(Zn) ₂ (SO ₄) ₂ (H ₂ O) ₄].2H ₂ O C ₂₃ H ₃₅ N ₃ O ₁₇ S ₂ Zn ₃	Blue	885.83	>300	70	(30.98) (30.67)	(3.70) (3.32)	(5.10) (4.88)	(16.0) (15.79)	-	6.45
(18)	[(H ₃ L)(Zn)(Cu)(OAc) ₄ (H ₂ O) ₂].2H ₂ O C ₃₁ H ₄₃ CuN ₃ O ₁₅ Zn	Nepta	826.62	>300	82	(44.78) (44.34)	(4.41) (4.12)	(4.90) (4.72)	Zn (7.65)- (7.35) Cu(7.35)- (7.11)	-	4.48
(19)	[(H ₃ L) (Ni) (Cu) (OAc) ₄ (H ₂ O) ₂]. C ₃₁ H ₃₉ CuN ₃ NiO ₁₃	Dark red	783.89	>300	70	(47.1) (46.82)	(4.78) (4.57)	(4.40) (4.00)	Ni (6.98)- (6.63) Cu (7.65)- (7.17)	-	5.47
(20)	[(H ₃ L)(Zn)(Cu)(SO ₄) ₂ (H ₂ O) ₄].H ₂ O C ₂₃ H ₃₃ CuN ₃ O ₁₆ S ₂ Zn ₂	Gray	865.97	>300	79	(31.90) (31.33)	(3.99) (3.78)	(5.37) (5.15)	Zn (7.32)- (7.10) Cu(7.56)- (7.23)	-	5.37

*Λm(Ω⁻¹cm²mol⁻¹)

Mass spectra:

Mass spectrometry was used to confirm the molecular ion peaks of Schiff- base [H₃L](**1**) and also to investigate the fragment species. The recorded mass spectrum of ligand (**1**) revealed molecular ion peak at *m/z* 389, confirming its formula weight (F.W. 389) and the purity of the ligand prepared. The prominent mass fragmentation peaks observed at *m/z* = 65, 91, 103, 120, 152, 213, 241, 316, 370, and 389 amu was corresponding to C₅H₅, C₇H₇, C₈H₇, C₈H₈O, C₉H₁₄NO, C₁₄H₁₅NO, C₁₄H₁₅N₃O, C₂₀H₂₀N₃O, C₂₃H₂₀N₃O₂ and C₂₃H₂₃N₃O₃ moieties respectively supported the suggested structure of the ligand. The data shown in table (2, i).

The mass spectrum of the [(H₃L)Mg(SO₄)(H₂O)].2H₂O complex(**2**) showed the molecular ion peak at *m/z* 579 amu, confirming its formula weight (F.W. 579). The mass fragmentation patterns observed at *m/z* = 65, 77, 102, 120, 167, 196,

210, 269, 299, 316, 461 and 579 amu are due to C₅H₅, C₆H₅, C₈H₆, C₉H₁₂, C₁₃H₁₁, C₁₅H₁₆, C₁₅H₁₆N, C₁₆H₁₅NO₃, C₁₆H₁₅N₂O₄, C₁₆H₁₅N₂O₅, C₂₂H₂₇N₃O₈ and C₂₃H₂₉MgN₃O₁₁S moieties, respectively, strongly supported the suggested structure of the complex. The data is shown in table (2, ii)

However, the mass spectrum of the [(H₃L)Zn(SO₄)(H₂O)].2H₂O complex(**16**) showed the molecular ion peak at *m/z* 620 amu, confirming its formula weight (F.W. 620). The mass fragmentation patterns observed at *m/z* = 55, 77, 98, 119, 139, 167, 182, 210, 236, 489 and 620 amu correspond to C₄H₇, C₆H₅, C₈H₂, C₉H₁₁, C₉H₁₅O, C₁₁H₁₉O, C₁₁H₂₀NO, C₁₃H₂₄NO, C₁₄H₂₄N₂O, C₂₃H₂₇N₃O₉ and C₂₃H₂₉N₃O₁₁SZn moieties, respectively, supported the suggested structure of the complex. The data is shown in table (2, iii).

Table (2,i) Mass spectrum of the ligand [H₃L], (**1**)

<i>m/z</i>	Rel. Int.	Fragment
65	28	C ₅ H ₅
91	20	C ₇ H ₇
103	21	C ₈ H ₇
120	28	C ₈ H ₈ O
152	27	C ₉ H ₁₄ NO
213	28.00	C ₁₄ H ₁₅ NO
241	18.00	C ₁₄ H ₁₅ N ₃ O
316	55.0	C ₂₀ H ₂₀ N ₃ O
370	28.0	C ₂₃ H ₂₀ N ₃ O ₂
389	17.0	C ₂₃ H ₂₃ N ₃ O ₃

Table(2, ii) Mass spectrum of Mg (II) complex (**2**)

<i>m/z</i>	Rel. Int.	Fragment
65	28	C ₅ H ₅
77	43	C ₆ H ₅
102	100	C ₈ H ₆
120	22	C ₉ H ₁₂
167	45	C ₁₃ H ₁₁
196	61	C ₁₅ H ₁₆
210	58	C ₁₅ H ₁₆ N
269	32	C ₁₆ H ₁₅ NO ₃
299	45	C ₁₆ H ₁₅ N ₂ O ₄
316	70	C ₁₆ H ₁₅ N ₂ O ₅
461	55	C ₂₂ H ₂₇ N ₃ O ₈
579	29	C ₂₃ H ₂₉ MgN ₃ O ₁₁ S

Table (2, iii) Mass spectrum of Zn (II) complex (**16**)

<i>m/z</i>	Rel. Int.	Fragment
55	28.00	C ₄ H ₇
77	43.00	C ₆ H ₅
98	100	C ₈ H ₂
119	29.00	C ₉ H ₁₁
139	42.00	C ₉ H ₁₅ O

167	59.00	C ₁₁ H ₁₉ O
182	56.00	C ₁₁ H ₂₀ NO
210	29.00	C ₁₃ H ₂₄ NO
236	43.00	C ₁₄ H ₂₄ N ₂ O
489	69.00	C ₂₃ H ₂₇ N ₃ O ₉
620	52.00	C ₂₃ H ₂₉ N ₃ O ₁₁ SZn

¹H-NMR spectra of the ligand (1) and some of its metal complexes

The ¹H-NMR spectrum of the ligand was recorded in DMSO-d₆. The spectrum of the ligand showed two peaks at 8.5p.p.m [s, 2H] and 13.1p.p.m [s, 1H] assigned to the protons of (NH) and (OH) respectively [21]. Also, the peaks observed at 6.82-7.81 ppm range assigned to protons of aromatic rings, however, the peaks observed at 3.2 and 2.27 ppm corresponding to protons CH₃ and CH₂ group. The peaks of Mg(II) complex (3) and Zn(II) complex (17) observed at 8.4, 8.28, 13.0 and 12.82 ppm are due to NH and OH groups respectively. However, the aromatic proton peaks observed at 6.82 – 7.82 ppm range. The peaks of complexes observed as multiple ones at 2.7 – 3.4 ppm range may be assigned to protons CH₃ and CH₂ groups. These findings are going consistent with the proposed structure of the ligand and its metal complexes [22,23].

IR Spectra:

The mode of bonding between the ligand and the metal ion revealed by comparing the IR spectra of the ligand (1) and its metal complexes (2)-(20). The ligand showed bands in the 3660-3345, 3340-2680 cm⁻¹ ranges, commensurate the presence of two types of intra- and intermolecular hydrogen bonds of OH and NH groups with imine or amide group [24]. Strong band appeared at 1700 cm⁻¹ related to $\nu(\text{C}=\text{O})$. The medium band appeared at 3190 cm⁻¹ is assigned to $\nu(\text{NH})$ group [24, 25]. The $\nu(\text{NH})$ band in the complexes was shifted from the region of the free ligand indicating that, the NH group is involved in the coordination to the metal ion [26]. However, the characteristic bands of imine $\nu(\text{C}=\text{N})$ was observed at 1680 cm⁻¹. Strong band appeared at 1330 and 1240 cm⁻¹ is attributed to the $\nu(\text{C}-\text{OH})$ vibration. The bands appeared at 1580, 818 and 1469, 750 cm⁻¹, are assigned to $\nu(\text{Ar})$ vibration [26,27]. By comparing the IR spectra of the complexes (2)-(20) with that of the free ligand. It was found that, the IR spectra of the metal complexes (2)-(20) show bands in the 3650-3610, 3350-3230, 3320-3280 and 2875-2720 cm⁻¹ ranges, commensurate the presence of two types of intra- and intermolecular hydrogen bonds and also the presence hydrated or coordinated water molecules [27]. Also, the position of the $\nu(\text{C}=\text{N})$ band is shifted by 2-72 cm⁻¹ range towards lower wavenumber in the complexes indicating coordination through nitrogen of azomethine group

(CH=N) [26,27]. This is also confirmed by the appearance of new band in the 585-516 cm⁻¹ range, this has been assigned to the $\nu(\text{M}-\text{N})$ [27]. Complexes (2)-(20) show $\nu(\text{C}=\text{O})$ band at 1682-1651 range. Complexes (2)-(20) showed $\nu(\text{C}-\text{OH})$ in the 1320-1238 and 1230-1114 range, indicating coordination to the metal ion in protonated form and lowering the value of the group confirming coordinated to the metal ion [28]. The aromatic ring vibrations appeared in the 1568-1450 and 857-740 cm⁻¹ ranges [30]. In acetate complexes, the acetate ion may be coordinated to the metal ion in unidentate manner [29]. As in the case of acetate complexes (4), (5), (8), (11), (14), (15), (18) and (19) showed bands in the 1360-1330 and 1480-1430 cm⁻¹ ranges, assigned to the asymmetric and symmetric stretches of the COO⁻ group. The mode of coordination of acetate group has often been deduced from the magnitude of the observed separation between the $\nu_{\text{asym}}(\text{COO}^-)$ and $\nu_{\text{sym}}(\text{COO}^-)$. The separation value (Δ) between $\nu_{\text{asym}}(\text{COO}^-)$ and $\nu_{\text{sym}}(\text{COO}^-)$ in these complexes was in the 105-100 cm⁻¹ range suggesting the coordination of acetate group as a monodentate fashion [24,29]. The sulphato complexes (2), (6), (9), (12), (16), (17) and (20) showed bands at (1285-1240), (1180-1140), (1092-1010) and (750-730 cm⁻¹) range, which assigned to mono dentate sulphate group [30]. The chloro complexes (3), (7), (10) and (13) showed a new band at 468-440 cm⁻¹ range was assigned to (M-Cl). Complexes (2-20) showed band in the 585-516 cm⁻¹ is assigned to $\nu(\text{M}-\text{N})$ [29], and 660-612 cm⁻¹ range respectively corresponded to $\nu(\text{M}-\text{O})$ [29]. The IR data are shown in table (3).

Electronic spectra and magnetic moments.

The electronic absorption spectral data of the ligand and its metal complexes in DMF are listed in Table (4). The ligand showed two bands at 290 and 310 nm. The first band may be assigned to $\pi \rightarrow \pi^*$ transition which is nearly unchanged upon complexation, however, the second band corresponded to the $n \rightarrow \pi^*$ and charge transfer transitions of the azomethine and amide groups [30, 42]. These bands were shifted to lower energy upon complex formation, indicating participation of these groups in coordination with the metal ions. The electronic spectra of copper(II) complexes (11), (12), (13), (18), (19) and (20) were nearly identical and showing bands at (240-290), (300-380), (420-560) and (603-610) nm ranges. The first two bands are assigned to intraligand transitions.

Table 3:-IR Frequencies of the Bands (cm^{-1}) of the Ligand [H_3L], (**1**) and its Metal complexes:

No	$\nu(\text{H}_2\text{O})$	$\nu(\text{OH})$	$\nu(\text{H-bondings})$	$\nu(\text{C=N})$	$\nu(\text{C=O})$	$\nu(\text{NH})$	$\nu(\text{COH})$	$\nu(\text{Ar})$	$\nu(\text{OAc/S O}_4)$	$\nu(\text{M-O})$	$\nu(\text{M-N})$	$\nu(\text{M-Cl})$
(1)	-	3470,3374	3660-3345, 3340-2680	1680	1700	3190	1330,1240	1580,818 1469,750	-	-	-	-
(2)	3550-3340 3330-3160	3413,3366	3630-3288, 3210-2774	1678,	1680,	3180	1318,1114	1568,1530 727,750	1240,1140 1010,730	610	585	-
(3)	3550-3350 3330-3160	3423,3375	3640-3320, 3310-2773	1670	1683	3167	1320,1150	1530.1455 824,752	-	640	577	450
(4)	3530-3380 3300-3100	3453	3630-3330, 3280-2860	1660	1680	3174	1319,1190	1532,750 1575,827	1430,1330	637	583	-
(5)	3555-3320 3300-3150	3430,3379	3620-3230, 3210-2720	1665	1670	3160	1318,1194	1474,1532 858,826	1450,1345	650	582	-
(6)	3520-3375 3330,3130	3430,3380	3620-3280, 3260-2550	1673	1651	3175	1283,1189	1477,1535 830,740	1285,1180 1041,740	618	580	-
(7)	3550-3340 3330-3160	3410,3380	3630-3320, 3300-2679	1670	1660	3150	1280,1185	1450,870	-	612	582	468
(8)	3570-3365 3364,3325	3433,3370	3650-3260, 3250-2663	1660	1680	3160	1310,1190	1575,1533 857,830	1456,1340	615	586	-
(9)	3520-3375 3330,3130	3427,3370	3610-3290, 3280-2784	1664	1675	3155	1310,1191	1575,1533 857,820	1252,1167 1082,750	640	580	-
(10)	3330-3340 3340,3120	3432,3390	3650-3330, 3320-2867	1675	1655	3177	1315,1170	1570,1530 850,750	-	641	516	440
(11)	3620-3320 3300,3180	3432	3650-3330, 3320-2875	1665	1662	3150	1310,1220	1571,825 1538,760	1461,1340	640	520	-
(12)	3625-3340 3325,3120	3420,3390	3640-3350, 3320-2870	1660	1665	3160	1275,1180	1565,1528 850,770	1260,1170 1092,737	638	524	-
(13)	3635-3320 3325,3117	3425,3383	3620-3360, 3350-2750	1676	1660	3165	1270,1170	1560,1532 840,765	-	630	537	455
(14)	3520-3375 3330,3130	3430,3365	3620-3340 3330-2780	1660	1681	3170	1260,1175	1564,1530 860,750	1480,1360	635	538	-

30											
(1 5)	3330- 3340, 3340,31 20	3427,3370	3610- 3290, 3280-2784	1665	1676	3150	1310,11 90	1570,1544 857,830	1470,1345	643	584
(1 6)	3550- 3340 3330- 3160	3432,3390	3650- 3330, 3320-2867	1612,16 09	1655	3160	1315,11 77	1570,1530 850,750	1266,1174 1084,737	641	515
(1 7)	3550- 3350 3330- 3160	3432	3650- 3330, 3320-2875	1613,16 10	1672	3150	1320,12 20	1571,825 1538,750	1252,1167 1092,737	660	520
(1 8)	3530- 3380 3300- 3100	3420,3390	3640- 3350, 3320-2870	1610,16 07	1660	3170	1270,11 80	1560,1520 840,760	1455,1330	638	524
(1 9)	3555- 3320 3300- 3150	3425,3383	3620- 3360, 3350-2750	1610,16 08	1653	3165	1276,11 78	1570,1532 840,765	1460,1340	650	534
(2 0)	3520- 3375 3330,31 30	3430,3365	3620-3340 3330-2780	1614,16 05	1663	3178	1269,11 76	1574,1530 850,760	1240,1140 1110,740	635	538

however, the other bands are assigned to ${}^2B_{1g} \rightarrow {}^2A_{1g}v_1(dx^2-y^2 \rightarrow dz^2)$, ${}^2B \rightarrow {}^2B_{2g}$, $v_2(dx^2-y^2 \rightarrow dxy)$, and ${}^2B_{1g} \rightarrow {}^2E_g$, $v_3(dx^2-y^2 \rightarrow dxy, dyz)$ transitions, respectively. These transitions indicated that, the copper(II) ion has a tetragonally distorted octahedral geometry. This could be due to the Jahn-Teller effect that operates on the d^9 , electronic ground state of six coordinate system, elongating one trans pair of coordinate bonds and shortening the remaining four ones [43]. The magnetic moments for copper(II) complexes at room temperature were in the 1.69-1.71 range B.M., supporting that, the complexes have octahedral geometry [44]. Nickel(II) complexes (8), (9), (10) and (19) displayed bands ,285,298,350,450,585,680,740nm,267,295,321,448,580,608,735nm,270,290,380,450,545,670,750 nm and 270,295,321,445,555,603,745 nm, respectively. The first bands are corresponding to intraligand transition, however, the other bands are due to ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(v_1)$, ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(v_2)$, and ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(v_3)$ transitions, indicating octahedral nickel(II) complexes, the $v_2/v_1 = 1.08-1.23$ range indicating distorted octahedral structures [26, 45]. The values of magnetic moments for nickel(II) complexes (8), (9), (10) and (19) were in the 2.68 -3.11 B.M. range, which are consistent with two unpaired electrons state, confirming octahedral geometry around nickel(II) ion [45]. The spectra of cobalt(II) complexes (4)-(7), showed bands at 263,295,320,450,573,610 nm, 265,293,321,462,580, 608 nm,267, 290,320,440,565,655, 750 nm and 265,293,320,455,568,607 nm assignable to ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (v_1), ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (v_2) and ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$ (v_3) transitions respectively,

suggesting octahedral cobalt(II) geometries. The lower ratio of v_2/v_1 than that reported for octahedral cobalt(II) complexes (1.5-1.7), may be due to distortion of the octahedral structure [32]. The magnetic moment values of cobalt complex were in the 4.01- 4.23 B.M range which are close to a high spin cobalt(II), [d^7]. The observed bands for zinc (II) complexes (14)-(17), and Mg(II) complexes (2) and (3) (Table 4) are due to intraligand transitions within the ligand and showed diamagnetic property [37-43].

Electron spin resonance (ESR)

To obtain further information about the stereochemistry and the nature the metal ligand bonding, ESR spectra of solid copper(II) complexes (11), (12), (13) and (18) (Table 5) have been carried out. [54]. The complexes exhibited anisotropic signals with g values $g_{||} = 2.24, 2.20, 2.26$ and 2.26 and $g_{\perp} = 2.09, 2.05, 2.09,$ and 2.07 respectively. These values are characteristic for a species d^9 , configuration with an axial symmetry type of a $d(x^2-y^2)$ ground state [55]. The values of $g_{||}$ and g_{\perp} are closer to 2.00 and showed $g_{||} > g_{\perp} > g_e$ (2.0023) indicating that, the complexes possessed a distorted octahedral copper(II) geometry corresponding to an elongation along the four fold symmetry z-axis [56]. Also, the value of $g_{||}/A_{||}$ may be considered as a diagnostic of the stereochemistry. It has been suggested that, this quotient may be used as an empirical index of geometry [57]. The range reported for square-planar complexes are 105-135 cm^{-1} and for tetrahedral distorted complexes 150-250 cm^{-1} . The $g_{||}/A_{||}$ values for the complexes under consideration lie just in the range which expected for distorted octahedral copper(II) complexes. In addition, the exchange

coupling interaction between copper(II) ions is explained by Hathaway expression which stated that $G = (g_{||} - 2) / (g_{\perp} - 2)$. If the value of G is greater than four, the exchange interaction is negligible whereas when the value of G is less than four a considerable interaction is present in solid complexes. The G values of the copper(II) complexes are 2.-3.7 range [Table 5], since the interaction between copper(II) ions are present. Kivelson and Neiman noted that, for an ionic environment, $g_{||}$ is normally 2.3 or larger but for covalent environment $g_{||}$ is less than 2.3. The values of the present complexes are less than 2.3, so there a significant degree of covalence in the metal-ligand bonding [58].

The σ - parameter (α^2) was calculated from the following equations

$$\alpha^2 = (g_{||} - 2.0023) + 3/7 (g_{\perp} - 2.0023) - (P) + 0.04 \dots \dots \dots (1)$$

Where P is the free ion dipolar term which is equal 0.036, $A_{||}$ is the parallel coupling constant expressed in cm^{-1} . The α^2 values of the copper complexes [Table 5], these values indicate to the presence of a significant in-plane σ covalent character [59].

$$K_{||}^2 = (g_{||} - 2.0023) \Delta E_{xz} / 8\lambda_o \dots \dots \dots (2)$$

$$K_{\perp}^2 = (g_{\perp} - 2.0023) \Delta E_{xy} / 2\lambda_o \dots \dots \dots (3)$$

$$K^2 = (k_{||}^2 + 2k_{\perp}^2) / 3 \dots \dots \dots (4)$$

Where λ_o is the spine orbit coupling of free copper ion (-828 cm^{-1}) and ΔE_{xy} and ΔE_{xz} are the electronic transition energies of $2B_1 \rightarrow 2B_2$ and $2B_1 \rightarrow 2E$ respectively. For the purpose of calculation, it was assumed that, the maximum in the band corresponds to ΔE_{xy} and ΔE_{xz} can be taken from the wavelength of these bands. From the above relations, the orbital reduction factors ($K_{||}$, K_{\perp} and K) which are a measure of covalency can be calculated. For an ionic environment, $K=1$ and for a covalent environment $K < 1$; the lower the value of K , the greater is the covalent character. The values of K for copper (II) complexes were less than one which inductive to considerable covalent bond character. The plane and out-of-plane π -bonding coefficients (β^2_1 and β^2_2) respectively are dependent upon to values of ΔE_{xy} and ΔE_{xz} in the following β^2 equations:-

$$\alpha^2 \beta^2 = (g_{\perp} - 2.002) \Delta E_{xy} / 2\lambda_o \dots \dots \dots (5)$$

$$\alpha^2 \beta^2_1 = (g_{||} - 2.002) \Delta E_{xz} / 8\lambda_o \dots \dots \dots (6)$$

The copper complexes (11), (12), (13) and (18) showed β^2_1 values 1.12, .92, 2.02 and .98 respectively indicating a moderate degree of covalent character in the in-plane π -bonding, while β^2 are 1.63, 1.56, 3.3 and 1.33 respectively indicating covalent character in the out - of-plane π -bonding.

$$A_{||} = A_{\text{iso}} - 2B [1 \pm (7/4) \Delta g_{||}] \dots \dots \dots (7)$$

$$a^2 d = 2B / 2B^o \dots \dots \dots (8)$$

Where $2B^o$ is the calculated dipolar coupling for unit occupancy of d orbital. When the data are analyzed using the Cu^{63} hyperfine coupling and considered all the sign combinations. The orbital populations for complexes (11), (12), (13) and (18) are 62.3%, 53.2%, 91.6% and 85.1% respectively, indicating a $d(x^2-y^2)$ ground state. Cobalt(II) complexes (5), and (7) showed isotropic type with $g_{\text{iso}} = 2.07$ and 2.09 represented indicating distorted octahedral structural [69].

Thermal analyses (DTA and TGA):

The thermal data of the complexes are given in Table (6). Such data corroborate the stoichiometric formula, number of water molecules, and end products [63-66]. Thermogravimetric curves of complexes (2), (4), (5), (9), (16) and (17) were introduced as representative examples. Thermogram of complex (2) $[(\text{H}_3\text{L})(\text{Mg})(\text{SO}_4)(\text{H}_2\text{O})(\text{H}_2\text{O})_2] \cdot 2\text{H}_2\text{O}$ exhibited five-steps decomposition, the first step involving breaking of H-bondings accompanied with endothermic peak at 45°C . In the second step, two hydrated water molecules were lost endothermically with appearance of a peak at 75°C accompanied by 3.54% (Calc. 3.3%) weight loss. Such a low temperature endothermic dehydrations indicated that, the water molecules which were coordinated to the metal by two molecules lost at 130°C that by weight loss of 6.2 (Calc. 6.8%). The weight loss 9.2 (Calc. 9.7%) accompanied by an endothermic peak at 270°C was assigned to loss of one sulphate group (SO_4). The endothermic peak observed at 360°C refers to the melting point of the complex. The final step was observed as exothermic peaks which observed in the $400\text{-}660^\circ\text{C}$ range with 16.2% weight loss (Calc. 16.6%), refers to complete oxidative decomposition of the complex which ended up with the formation of MgO . Complex (4) $[(\text{H}_3\text{L})\text{Co}(\text{OAc})_2(\text{H}_2\text{O})] \cdot 2\text{H}_2\text{O}$ exhibited multiple decomposition steps, the first step involving breaking of H-bondings accompanied with endothermic peak at 50°C . In the second step, two molecules of hydrated water molecules were lost endothermically with a peak at 90°C accompanied by 6.35% (Calc. 6.1%) weight loss, then two molecules of coordinated water molecules were lost endothermically with a peak at 120°C accompanied by 3.1% (Calc. 3.2%) weight loss. 21.8% (Calc. 22.1%) weight loss accompanied by an endothermic peak at 320°C was assigned to loss of coordinated two acetate group $2(\text{OAc})$. The endothermic peak appeared at 370°C referred to the melting point of the complex. The final step was observed as exothermic peaks at $440\text{-}630^\circ\text{C}$ range with 18.1% weight loss (Calc. 18.7%), refers to complete oxidative decomposition of the complex which ended up with the formation of CoO . Complex

(5) $[(H_3L)(Co)_2(OAc)_4(H_2O)_2].2H_2O$ exhibited multiple decomposition steps, the first step involving breaking of H-bonding accompanied with endothermic peak at 40°C. In the second step, two molecules of hydrated water molecules were lost endothermically with a peak at 90°C accompanied by 4.32% (Calc-4.6%) weight loss. 2.3% (Calc-1.8%) weight loss accompanied by an endothermic peak at 160°C was assigned to loss of two coordinated water molecules. 33.2% (Calc-33.1%) weight loss accompanied by an endothermic peak at 310°C was assigned to loss of coordinated four acetate group 4(OAc). The endothermic peak observed at 350°C refers to the melting point of the complex. The final step observed as exothermic peaks at 440-600 °C range with 15.7% weight loss (Calc 15.3%), referred to complete oxidative decomposition of the complex which ended up with the formation of 2 (CoO). Complex (9) $[(H_3L)(Ni)_2(SO_4)_2(H_2O)_4].H_2O$ exhibited multiple decomposition steps, the first step involving breaking of H-bonding accompanied with endothermic peak at 45°C. In the second step, one molecule of hydrated water was lost endothermically with a peak at 75°C accompanied by 2.5% (Calc-2.3%) weight loss then four molecules of coordinated water were lost endothermically with a peak at 130°C accompanied by 9.1% (Calc-9.5%) weight loss. 28.2 (Calc-28.1%) weight loss accompanied by an endothermic peak observed at 260 °C was assigned to loss of two coordinated sulphate group (SO₄) [65]. The endothermic peak observed at 360 °C referred to the melting point of the complex. The final step observed as exothermic peaks at 450-600 °C range with 15.1% weight loss (Calc-15.5%), referred to complete oxidative decomposition of the complex which ended up with the formation of 2(NiO). Complex (16) $[(H_3L)(Zn)(SO_4)(H_2O)_2].2H_2O$ exhibited multiple decomposition steps, the first step involving breaking of H-bonding accompanied with endothermic peak at 50°C. In the second step, two molecules of hydrated water were lost endothermically with a peak at 80°C accompanied by 6.35% (Calc-6.1%) weight loss, then two molecules of coordinated water were lost endothermically with a peak at 140°C accompanied by 6.1% (Calc-6.5%) weight loss. 17.8% (Calc-18%) weight loss accompanied by endothermic peaks appeared at 320°C were assigned to loss of one coordinated sulphate group (SO₄). The endothermic peak observed at 370°C referred to the melting point of the complex. The final step observed as exothermic peaks at 470-620 °C range with 19.3 weight loss (Calc-19.5%), referred to complete oxidative decomposition of the complex which ended up with the formation of ZnO Complex (17) $[(H_3L)(Zn)(SO_4)(H_2O)_2].2H_2O$ exhibited multiple decomposition steps, the first step involving breaking of H-bonding accompanied with endothermic peak at

45 °C. In the second step, two molecules of hydrated water were lost endothermically with a peak at 90 °C accompanied by 4.12% (Calc-4.5%) weight loss, then four molecules of coordinated water were lost endothermically with a peak at 150 °C accompanied by 4.2% (Calc-4.5%) weight loss. 25.98% (Calc-26.11%) weight loss accompanied by endothermic peaks appeared at 300 °C were assigned to loss of two coordinated sulphate group 2(SO₄). The endothermic peak observed at 370°C refers to the melting point of the complex. The final step observed as exothermic peaks at 430-650 °C range with 31.4 weight loss (Calc-31.1%), referred to complete oxidative decomposition of the complex which ended up with the formation of 2 (ZnO).

Table (4): The electronic spectra (nm) and magnetic moments (B.M.) for the ligand (1), and its complexes

No.	λ_{max} (nm)	μ_B in B.M.	v/v
(1)	290 nm (log ϵ =3.98), 310 nm (log ϵ =4.25)	-	
(2)	265,293,325	Diamg	
(3)	265,290,322	Diamg	
(4)	263,295,320,450,573,610	4.23	1.06
(5)	265,293,321,462,580,608	4.11	1.04
(6)	267,290,320,440,565,615,655	4.01	1.14
(7)	265,293,320,455,568,607	4.12	1.06
(8)	285,298,350,450,585,680,740	3.09	1.08
(9)	267,295,321,448,580,608,735	2.7	1.2
(10)	270,290,380,450,545,605,750	3.11	1.11
(11)	240,265,300,420,540,610	1.70	1.16
(12)	255,295,310,430,560,610	1.71	1.24
(13)	268,295,321,435,571,603	1.69	-
(14)	265,298,325	Diamg	-
(15)	266,298,325	Diamg	-
(16)	265,298,323	Diamg	-
(17)	265,297,325	Diamg	-
(18)	270,295,325,440,570,610	1.71	-
(19)	270,295,321,445,555,603	2.68	1.23
(20)	270,295,320,435,562,605	1.72	-

Table 5.ESR data for some Cu(II) complexes:-

No.	g_{\parallel}	g_{\perp}	g_{iso}^a	A_{\parallel} (G)	A_{\perp} (G)	A_{iso}^b (G)	G^c	ΔE_{xy}	ΔE_{xz}	K_{\perp}^2	K_{\parallel}^2	K	K^2	$g_{\parallel}/A_{\parallel}$	α^2	β^2	β_1^2	2β	$a_d^2(\%)$
(5)	-	-	2.07	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(7)	-	-	2.09	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(11)	2.24	2.09	2.11	100	10	40	2.0	18619	21809	.97	.66	-	.87	224	.59	1.63	1.12	146.3	62.3%
(12)	2.20	2.05	2.7	120	15	50	3.0	17857	22608	.95	.56	-	.15	184.2	.61	1.56	.92	125	53.2%
(13)	2.26	2.09	2.15	100	10	40	3.2	17513	22988	1.2	.73	.98	1.05	226	.61	3.3	2.02	215.3	91.6%
(18)	2.26	2.07	2.19	110	15	30	3.7	17346	22707	.93	.65	-	.84	173.8	.69	1.33	.98	200	85.1%

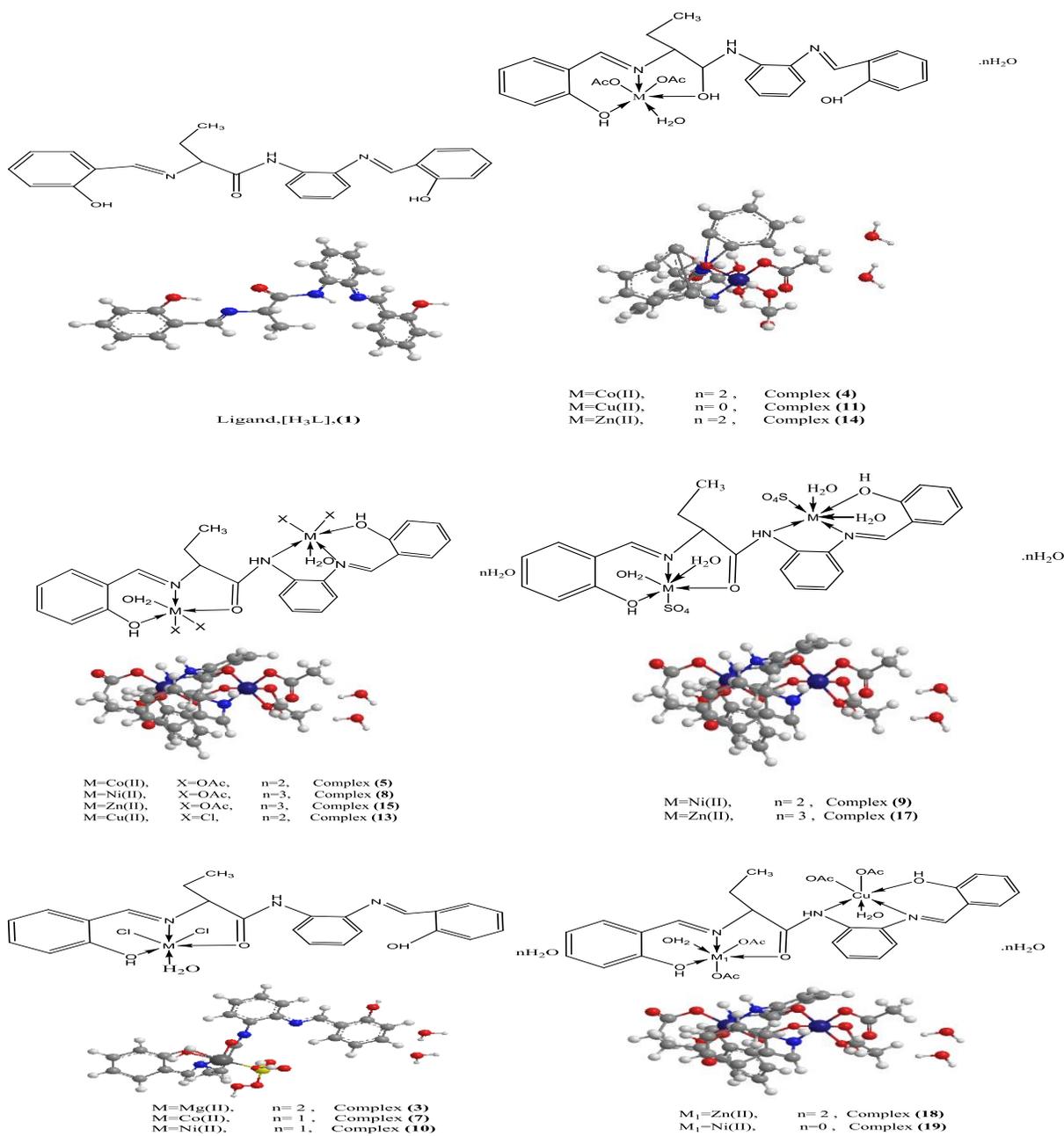
$$a) g_{iso} = (2g_{\perp} + g_{\parallel})/3, b) A_{iso} = (2A_{\perp} + A_{\parallel})/3, c) G = (g_{\parallel} - 2) / (g_{\perp} - 2)$$

Table (6): Thermal analyses for some metal (II) complexes:

Compound No. Molecular formula	Temp. (C°)	DTA (peak)		TGA (Wt.loss %)		Assignments
		Endo	Exo	Calc.	Found	
Complex (2) [(H ₃ L)Mg(SO ₄)(H ₂ O) ₂].2H ₂ O C ₂₃ H ₂₇ MgN ₃ O ₉ S	45	endo	-	-	-	Broken of H-bondings
	75	endo	-	3.3	3.53	Loss of (H ₂ O) hydrated water molecule
	130	endo	-	6.8	6.2	Loss of 2(H ₂ O) coordinated water molecules
	270	endo	-	9.7	9.2	Loss of coordinated (SO ₄) group
	360	endo	-	-	-	Melting point
	400,530,620,620,660	-	Exo	16.6	16.2	Decomposition process with the formation of (MgO)
Complex (4) [(H ₃ L)Co(OAc) ₂ (H ₂ O)].2H ₂ O C ₂₇ H ₃₄ CoN ₃ O ₈	50	endo	-	-	-	Broken of H-bondings
	90	endo	-	6.1	6.35	Loss of (H ₂ O) hydrated water molecule
	120	endo	-	3.2	3.1	Loss of 2(H ₂ O) coordinated water molecules
	320	endo	-	22.1	21.8	Loss of coordinated 2(OAc) group
	370	endo	-	-	-	Melting point
	440,570,610,600,630	-	Exo	18.7	18.1	Decomposition process with the formation of CoO
Complex (5) [(H ₃ L)(Co) ₂ (OAc) ₄ (H ₂ O) ₂].2H ₂ O C ₃₁ H ₃₉ Co ₂ N ₃ O ₁₃	40	endo	-	-	-	Broken of H-bondings
	90	endo	-	4.6	4.32	Loss of (2H ₂ O) hydrated water molecules
	160	endo	-	1.8	2.3	Loss of 2(H ₂ O) coordinated water molecules
	310	endo	-	33.11	33.21	Loss of coordinated 4 (OAc) group
	350	endo	-	-	-	Melting point
	440,480,500,520,600	-	Exo	15.3	15.7	Decomposition process with the formation of 2 (CoO)

Complex (9) [(H ₃ L)(Ni) ₂ (SO ₄) ₂ (H ₂ O) ₄].H ₂ O C ₂₃ H ₃₁ N ₃ Ni ₂ O ₁₅ S ₂	45	endo	-	-	-	Broken of H-bondings
	75	endo	-	2.3	2.53	Loss of (H ₂ O) hydrated water molecules
	130	endo	-	9.5	9.1	Loss of 4(H ₂ O) coordinated water molecule
	260	endo	-	28.1	28.20	Loss of coordinated 2 (SO ₄) group
	360	endo	-	-	-	Melting point
	450,530,610,610,600	-	Exo	15.5	15.1	Decomposition process with the formation of 2(NiO)
Complex (16) [(H ₃ L)(Zn)(SO ₄) ₂ (H ₂ O)].2H ₂ O C ₂₃ H ₂₇ N ₃ O ₉ SZn	50	endo	-	-	-	Broken of H-bondings
	80	endo	-	6.1	6.35	Loss of 2(H ₂ O) hydrated water molecule
	140	endo	-	6.5	6.1	Loss of 2(H ₂ O) coordinated water molecule
	320	endo	-	18	17.83	Loss of coordinated (SO ₄) group
	370	endo	-	-	-	Melting point
	470,560,640,620,620	-	Exo	19.5	19.3	Decomposition process with the formation of ZnO
Complex (17) [(H ₃ L)(Zn) ₂ (SO ₄) ₂ (H ₂ O) ₄].2H ₂ O C ₂₃ H ₃₁ N ₃ O ₁₅ S ₂ Zn ₂	45	endo	-	-	-	Broken of H-bondings
	90	endo	-	4.5	4.12	Loss of (2H ₂ O) hydrated water molecules
	150	endo	-	4.8	4.2	Loss of 4(H ₂ O) coordinated water molecule
	300	endo	-	26.11	25.98	Loss of coordinated 2 (SO ₄) group
	370	endo	-	-	-	Melting point
	430,480,500,510,650	-	Exo	31.1	31.42	Decomposition process with the formation of 2 (ZnO)

The structures of the ligand and its metal complexes



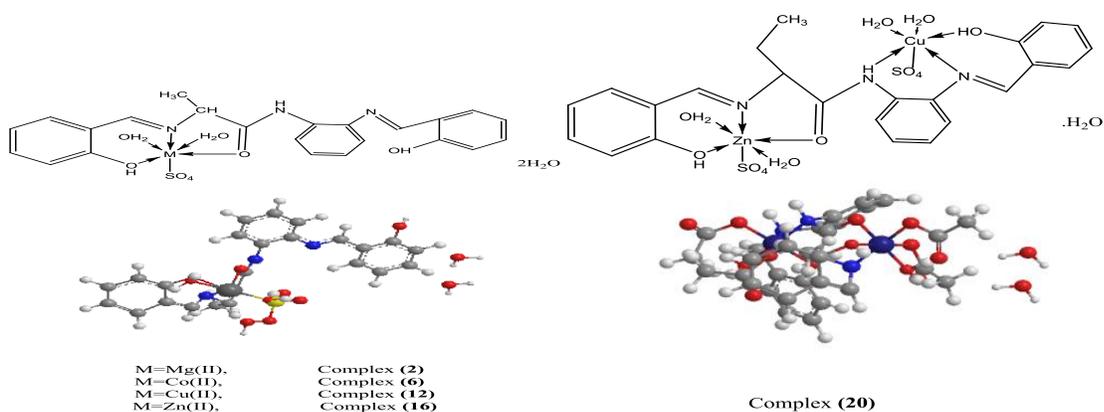


Figure (3): Proposed structures for the ligand (1) and its metal complexes

Transmission electron microscope characterization (TEM): The average diameter of the ligand and the two complexes particles Ni(II)/ Cu(II) and Zn(II)/Cu(II) was determined to be 40.5 ± 16.0 nm, 38.8 ± 10.2 nm, and 31.5 ± 10.2 nm, respectively. All complexes are present in nano size particles i.e., their particles present in a diameter between 1 and 100 nm in size. The complexes (18), (19) and the ligand show sign with ratio that exhibit new or enhanced size-dependent properties compared with larger particles of the same material with many advantages such as:

Increased bioavailability, dose proportionality, decreased toxicity, smaller dosage form (i.e., smaller tablet), stable dosage forms of drugs which are either unstable or have unacceptably low bioavailability in non-nanoparticulate dosage forms, increased active agent surface area results in a faster dissolution of the active agent in an aqueous environment, such as the human body, faster dissolution generally equates with greater bioavailability, smaller drug doses, less toxicity and reduction in fed/fasted variability.

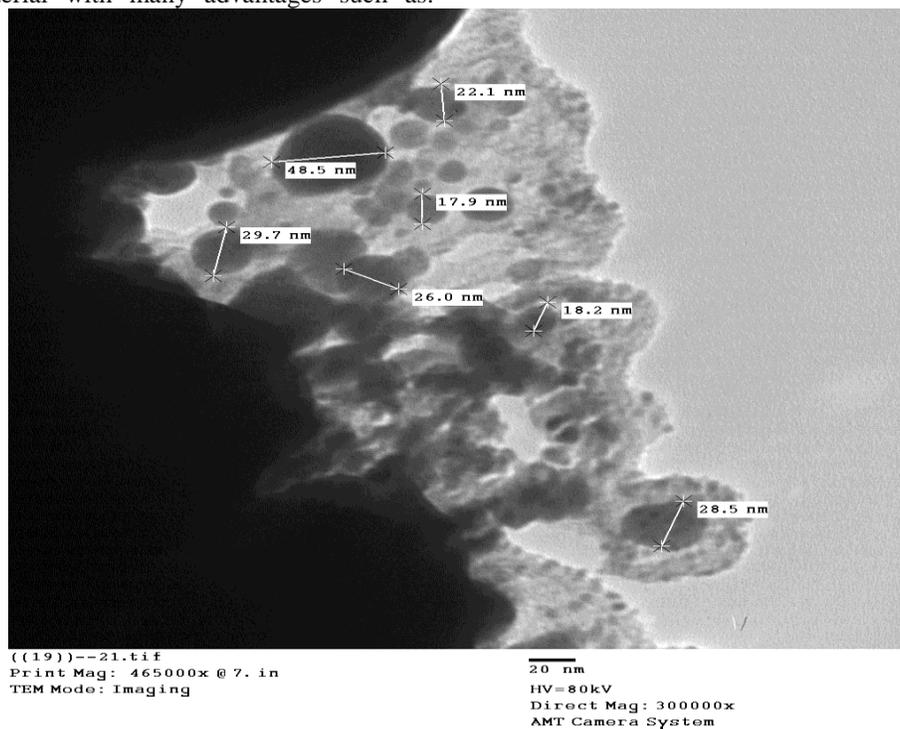


Figure (4): TEM images for ligand nanoparticles

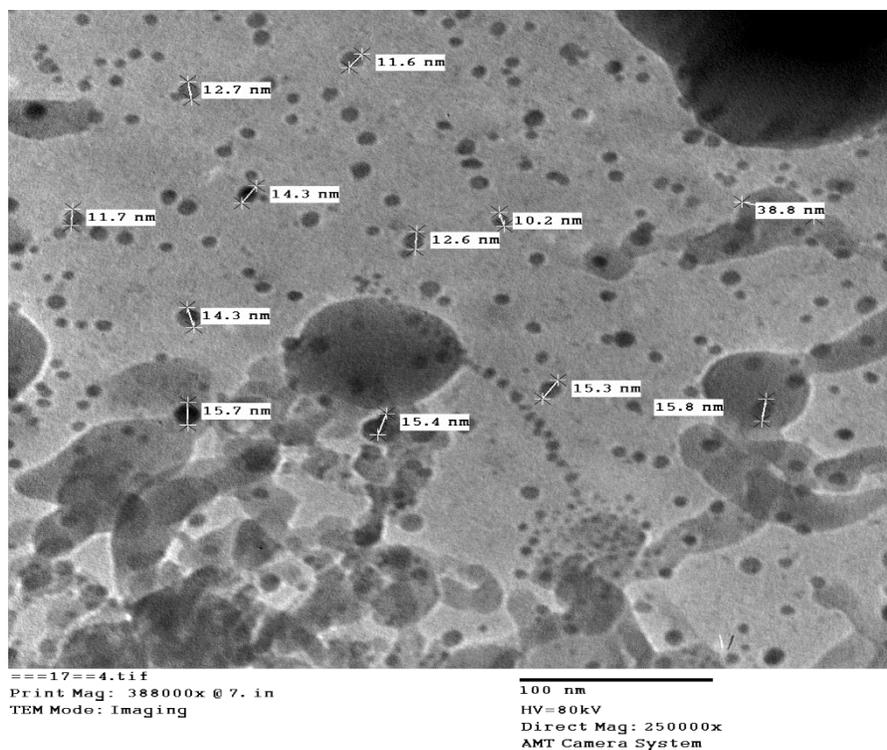


Figure (5):TEM images fo Ni(II)/Cu(II) complex (19) nanoparticles

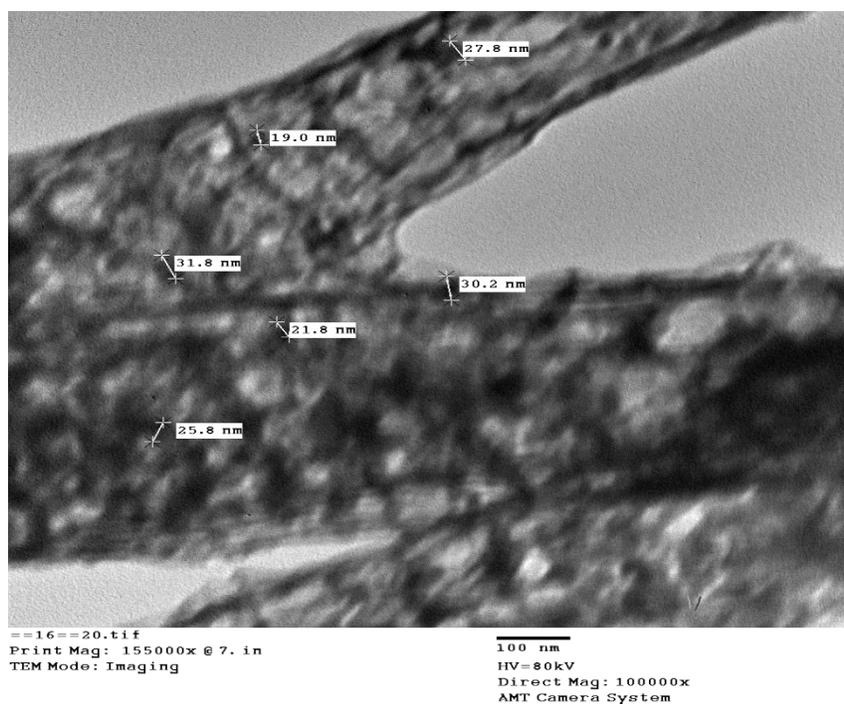


Figure (6):TEM images fo Zn(II)/Cu(II) complex (18) nanoparticles

Cytotoxic Activity:

The cytotoxic activity of the ligand H₃L (**1**) and some of its metal complexes (**15**), (**18**) and (**19**) was evaluated against human breast cancer (MCF-7) cell within 0.1–500 µg/L concentration range as shown in figure (2). The IC₅₀ values were calculated for each compound and the results are presented in Figure (3) and Table (7). As shown, most complexes displayed significantly cytotoxic activities compared to standard drug (Doxorubicin). Cytotoxicity activity of the complexes may be attributed to the central metal atom which was explained by Tweedy's chelation theory [60,61]. Cytotoxicity results indicated that, all tested complexes (IC₅₀ = 12.6–25.9 µM) demonstrated potent cytotoxicity against breast cancer cells. Zn(II)/Cu(II) complex (**18**) showed the highest cytotoxicity effect with IC₅₀ value of 12.6 µM, followed by Ni (II)/Cu(II) complex (**19**) with IC₅₀ value 14.4 µM and then Zn(II) complex (**15**) with IC₅₀ value 25.9 µM. It was observed that, all complexes are less active than the free ligand. The enhancement ligand (**1**) with IC₅₀ value 6.09 µM This indicated enhancing of the antitumor activity upon of cytotoxic activity may be assigned to that the positive charge of the metal increased the acidity of coordinated ligand that bears protons, leading to stronger hydrogen bonds which enhanced the biological activity [62,63]. It seems that, changing the anion, coordination sites, and the nature of the metal ion has a pronounced effect on the biological behavior by altering the binding ability of DNA [64,

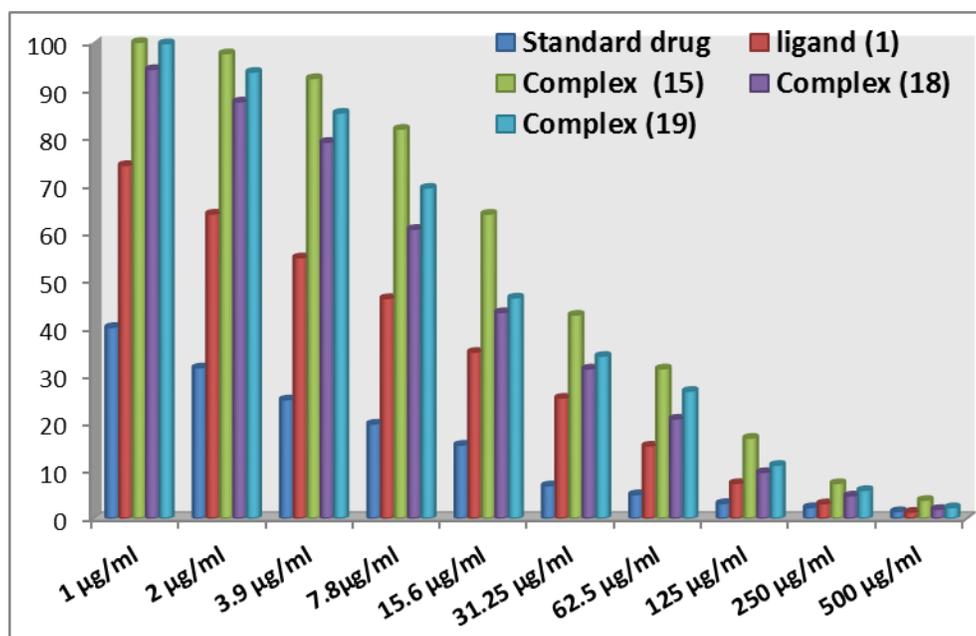
65]. Gaetke and Chow had reported that, metal has been suggested to facilitate oxidative tissue injury through a free radical mediated pathway analogous to the Fenton reaction [66].

By applying the ESR-trapping technique, evidence for metal - mediated hydroxyl radical formation in-vivo has been obtained [67]. Reactive oxygen species are produced through a Fenton-type reaction as follows:



Where L, organic ligand

Furthermore, metal could act as a double-edged sword by inducing DNA damage and also by inhibiting their repair [68]. The OH radicals react with DNA sugars and radicals react with DNA sugars and bases, resulting in the release of free bases and strand break occurs. Bases and the most significant and well characterized of the OH reactions is hydrogen atom abstraction from the C4 on the deoxyribose unit to yield sugar radicals with subsequent β-elimination. By this mechanism strand break occurs as well as the release of the free bases. Another form of attack on the DNA bases is by solvated electrons, probably via a similar reaction to those discussed below for the direct effects of radiation on DNA [66-75]



Figure(7); Mean inhibition zone of the ligand and some of its metal complexes(15), (18), and (19) against *breast carcinoma MCF-7*.

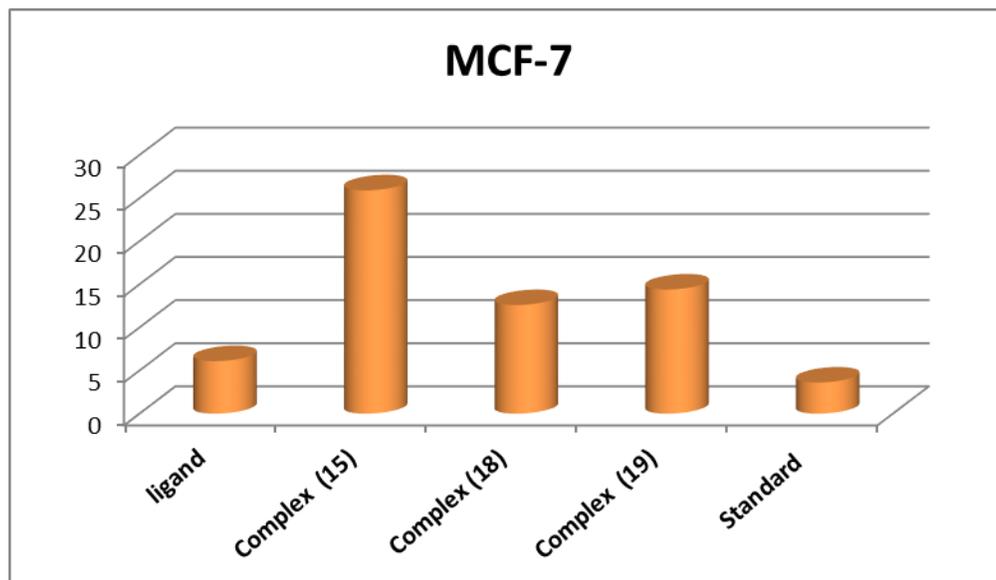
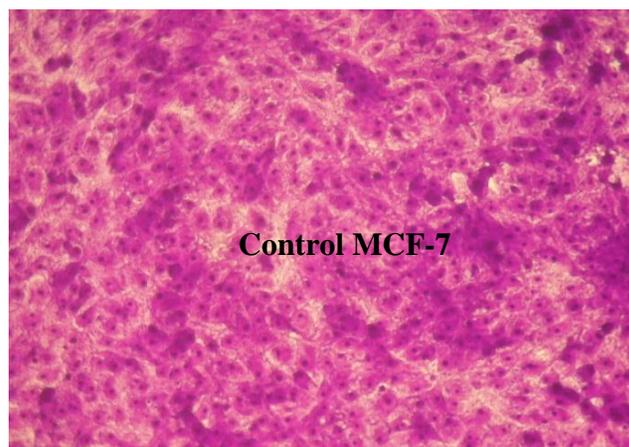


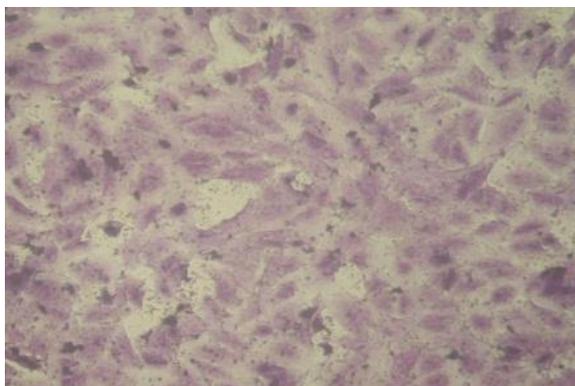
Figure (8): IC₅₀ for the ligand and some of its metal complexes

Table 7: Cytotoxic activity (IC₅₀) of the ligand and some metal complexes against human breast MCF-7

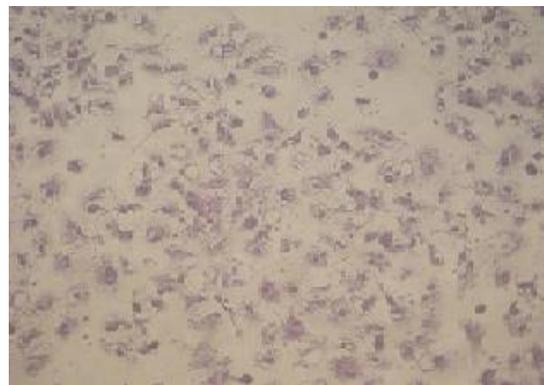
Compound No.	Compound	(IC ₅₀) MCF-7 (µg/ml)
Ligand (1)	[H ₄ L]	6.09
(15)	[(H ₄ L)(Zn) ₂ (OAc) ₄ (H ₂ O) ₂].H ₂ O	25.9
(18)	[(H ₄ L(Zn)(Cu)(OAc) ₄ (H ₂ O) ₂].2H ₂ O	14.4
(19)	[(H ₄ L) (Ni) (Cu) (OAc) ₄ (H ₂ O) ₂].	12.6



[A]

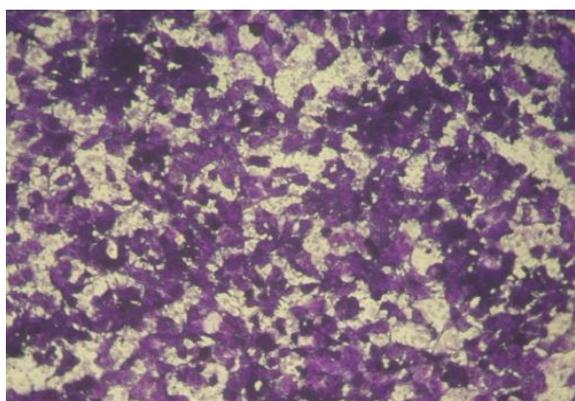


[A]

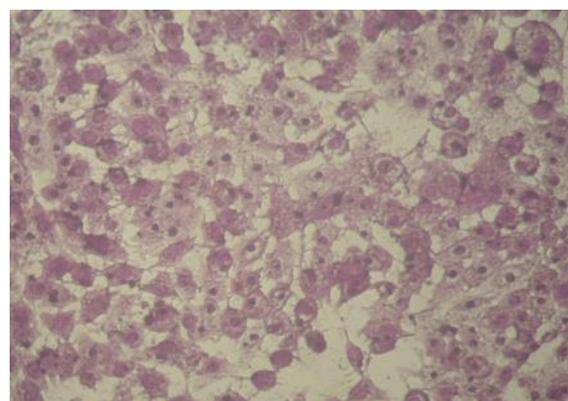


[B]

[A] Histogram of complex(12)_ at concentration 500 µg/ml
 [B] Histogram of complex(12)_ at concentration 31.25 µg/ml



[C]



[D]

[C] Histogram of complex(15)_ at concentration 62.5 µg/ml
 [D] Histogram of complex(15)_ at concentration 250 µg/ml

Figure (9): Histograms of cytotoxicity of control MCF-7 and some tested complexes

From histogram (figure 4), we found that:-

- (1) Decrease in the number of available cells.
- (2) Most of the remaining observed degeneration changes in the form of the irregular cell membrane opaque and not well formed chromatin regulated of swelling cytoplasm, other showed optatic change in the formed of chrunked cells and increase esinophilia cells, and picknitoic nucleus.

CONCLUSIONS

In the present study, new metal(II) complexes of N-(2-((E) (2hydroxybenzylidene)amino) phenyl)-2-((E)-((6-hydroxycyclohexa-1,5-dien-1-yl)methylene) amino) butanamide were prepared.

Structural and spectroscopic properties revealed that, the ligand adopted a tridentate or hexadentate ligand fashion; on the other hand, the metal complexes adopted a tetragonal distorted octahedral geometry around metal ions. All the complexes are non-electrolytic in nature as suggested by molar conductance measurements. The ligand coordinated to the central metal ion forming five or six membered rings including the metal ions. The antitumor activities of the ligand as well as some of its metal complexes were assessed that, the toxicity of both ligand and metal complexes was found to be concentration dependent, the cell viability decreased with increasing the concentration of complexes.

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