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Novel metal complexes of guanidine ligand; Synthesis, Spectroscopic Characterization and Biological Activity

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Abstract: Metal complexes of N- (amino [2- hydroxy] methylene) amino - methylene – carbono ctra of solid Cu(II) complexes show axial type symmetry with $g_{//} > g_{\perp} > 2.00$, indicating a $d_{(x2-y2)}$ ground state with significant covalent bond character, The spectrum of Cu(II) complex **(2)** $[(L)_2(Cu)_2(OAc)_2].3H_2O$ is a characteristic of a triplet state of a dimmer species and the distance found between the two Cu(II) centers is 4.2 A°. Complexes showed chemotherapeutic effects where they showed inhibitory effect on hepatocellular carcinoma (HepG- 2 cell line) in comparing with the standard drug.

Key words: Metal complexes, Guanidine ligand, Synthesis, Spectroscopic Characterization, Biological Activity.

Introduction

Growing interest in guanidinum Schiff base stems from their potential applications in the field of chelating chemistry. Guanidiniums are very weakly acidic molecules with the capacity to form intermolecular contacts mediated by H-bonding interactions[1]. The guanidinium moiety is common in natural products[2] and is often used in molecular recognition[3]. They also play important biological roles[4,7-11]. Various methods exist for the synthesis of guanidiniums from different starting materials and reagents [5]. One of the well-known methods is the conversion of thioureas into guanidiniums in the presence of a coupling reagent[6]. The conversion of thioureas into guanidiniums is usually accomplished with an electron withdrawing protecting group on the thiourea, that are not only capable of facile deprotection, but also activate the thiourea for the coupling reaction. Most thioureas that contain these activating groups can be only coupled with primary amines. Furthermore, the efficiency of guanylation depends on the group attached to the primary amine. Thioureas mostly react with primary amines attached to primary carbons due to the bulkiness of the protecting groups. Amines attached to electron withdrawing groups tend to give lower yields in guanylation. Recent advances have demonstrated the importance of the guanidinum group in receptors capable of binding molecular anions[7, 8]. A number of reviewed articles had been reported dealing with coordination chemistry of guanidinum derivatives, which has reflected great attention during the last years from avariety of reasons including as antitumer agent[9,10] green corrosion inhibitor for mild acidic solution[11], anti-glaucouma and cardiotonic derivatives, and for synthesis of polymer types[12,13]. Guanidinum groups serve as anion-building fragments in designed superamolecular receptors[7,8], used to improve insulin sensitivity [14] and to promote weight loss

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[G]corresponding author : asaeltabl@yahoo.com selectivity from a dipose tissue in animal models of non-insulin dependent diabetes mellitus[14]. Also, guanidinum derivatives affect on the mitochondrial function in the cell[15], in mineralization of guanidinum derivatives in soils[16]. The guanidinium ion also participates in numerous enzymatic transformations, as it is able to adopt a transition state assembly with the substrates to reduce the activation energy or to stabilize anionic intermediates, and is able to orient specific substrates based on their electronic properties[17].

Complexes of Schiff base (Figure 1) had been synthesized and characterized using different physical tools and the complexes have square planar or octahedral structure[18,19]. Boghaei[20] synthesized and investigated non-symmetrical tetradentate Schiff base complexes of nickel(II) and copper(II) ions. Some unsymmetrical diimino tetradentate Schiff bases derived from 3,4-diaminobenzophenone,(N-salicyliden-N'-5-OMe.salycyliden)-3,4-diamino-benzophenone (H_2sal-5-OMe.sal.dabp) (H_2L_1), (H_2sal-5-Br.sal.dabp) (H_2L_2), (H_2sal-5-Cl.sal.dabp)(H_2L_3) and (H_2sal-5-NO_2.sal.dabp) (H_2L_4) and their nickel(II) and copper(II) complexes were synthesized and characterized by elemental and spectral analyses[21]. Zinc(II), nickel(II) and copper(II) complexes of Schiff base, synthesized by condensation of o- vanilline with allyl thiourea have been prepared and spectroscopically characterized[22].

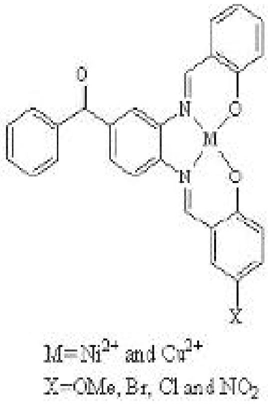


Figure (1)

Complexes with the general formula $MX_2(hppH)_2$, [hppH = 1,3,4,6,7,8- hexahydro- 2H- pyrimido]. Pyrimidine, have been synthesized and structurally characterized[23].

Due to guanidine ligands importance, we reported, synthesis, spectroscopic characterization and cytotoxic effect of new ligand N- (amino [2- hydroxy] methylene) amino - methylene – carbono hydrazonic diamide Ligand and its metal complexes.

Experimental

Materials

All the reagents were of the best grade available and used without further purification.

Physical measurements

C, H, N and Cl analyses were determined at the Analytical Unit of Cairo University, Egypt. A standard gravimetric method was used to determine metal ion [24]. All metal complexes were dried under vacuum over P_4O_{10}. The IR spectra were measured as KBr and CeBr pellets using a Perkin-Elmer 683 spectrophotometer (4000-200 cm^{-1}). Electronic spectra (qualitatively) were recorded on a Perkin-Elmer 550 spectrophotometer. The conductance of 10^{-3} M solutions of the complexes in DMF were measured at 25°C with a Bibby conductimeter type MCl. ^{1}H-NMR spectra (ligand and its Cd(II) complex) were obtained with Perkin-Elmer R32-90-MHz spectrophotometer using TMS as internal standard. Mass spectrum of the ligand was recorded using JEULJMS-AX-500 mass spectrometer provided with data system. The thermal analyses (DTA and TGA) were carried out in air on a Shimadzu DT-30 thermal analyzer from 27 to 800°C at a heating rate of 10°C per minute. Magnetic susceptibilities were measured at 25°C by the Gouy method using mercuric tetrathiocyanato cobalt(II) as the magnetic susceptibility standard. Diamagnetic corrections were estimated from Pascal's constant [25]. The magnetic moments were calculated from the equation: $\mu_{eff} = 2.84\sqrt{\chi_M^{corr}.T}$. The ESR spectra of solid complexes at room temperature were recorded using a varian E-109 spectrophotometer, DPPH was used as a standard material. The T.L.C of all compounds confirmed their purity.

Preparation of the ligand and its metal complexes

Preparation of the ligand, [HL], (1)

Ligand **(1)** was prepared by refluxing thiourea (20 gm, 0.3228 mol) and hydrazine hydrate (8 gm, 0.16 mol) in ethanol (100 cm^3) for 2 hours with stirring. Cool the product at room temperature and filter it to separate the hydrazide. Salicaldhyde (8.42 gm, 0.0689 mol) was added to the hydrazide crystals (8 gm, 0.0689 mol) and refluxed with stirring for 2 hours, the yellow precipitate was filtered off, washed by ethanol several times and dried in vaccum over P_4O_{10}. Analytical data are given in Table 1.

Synthesis of metal complexes (2) – (19)

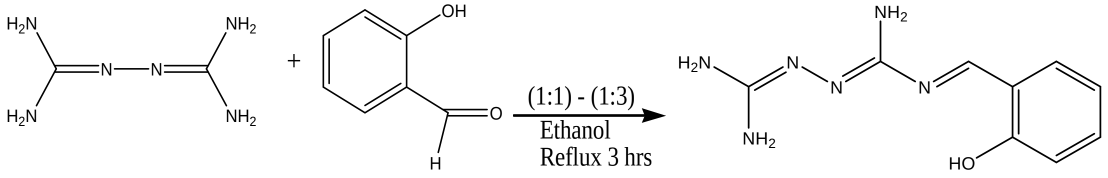
To the ligand **(1)** (5.0 gm, 0.0171 mol) in ethanol (50 cm^3) was added to (30 cm^3) ethanolic solution of (3.417 gm, 0.0171 mol) of $Cu(OAc)_2.H_2O$, (1L:1M), complex **(2),** (2.302 gm, 0.0171 mol) of $CuCl_2.2H_2O$, (1L:1M), complex **(3),** (2.73 gm, 0.0171 mol) of $CuSO_4.5H_2O$ (1L:1M), complex **(4),** (4.135 gm, 0.0171 mol) of $Cu(NO_3)_2.3H_2O$, (1L:1M), complex **(5)**, (4.26 gm, 0.0171 mol) of $Ni(OAc)_2.4H_2O$, (1L:1M), complex **(6),** (4.26 gm, 0.0171 mol) of $Co(OAc)_2.4H_2O$, (1L:1M), complex **(7),** (4.195 gm, 0.0171 mol) of $Mn(OAc)_2.4H_2O$, (1L:1M), complex **(8),** (3.755 gm, 0.0171 mol) of $Zn(OAc)_2.2H_2O$, (1L:1M), complex **(9),** (4.562 gm, 0.0171 mol) of $Cd(OAc)_2.2H_2O$, (1L:1M), complex **(10),** (7.259 gm, 0.0171 mol) of $UO_2(OAc)_2.2H_2O$, (1L:1M), complex **(11),** (5.454 gm, 0.0171 mol) of $Hg(OAc)_2$, (1L:1M), complex **(12),** (4.508 gm, 0.0171 mol) of Tl(OAc), (1L:1M), complex **(13),** (4.626 gm, 0.0171 mol) of $FeCl_3.6H_2O$, (1L:1M), complex **(14),** (4.561 gm, 0.0171 mol) of $CrCl_3.6H_2O$, (1L:1M), complex **(15),** (5.516 gm, 0.0171 mol) of $ZrOCl_2.8H_2O$, (1L:1M), complex **(16),** (2.516 gm, 0.0171 mol) of $CaCl_2.2H_2O$, (1L:1M), complex **(17),** (4.563 gm, 0.0171 mol) of $SrCl_2.8H_2O$, (1L:1M), complex **(18)** and (2.909 gm, 0.0171 mol) of $AgNO_3$, (1L:1M), complex **(19).** The mixture was refluxed with stirring for 2-4 hrs , depending on the nature of the metal ion and the anion. When the precipitate appeared, it was removed by filteration, washed with ethanol and dried in vacuo over P_4O_{10}. Analytical data are given in **Table 1.**

Biological activity

The Chemotherapeutic effect was measured invitro for the synthesized complexes using the Sulfo Rhodamine-B-stain (SRB) assay using the puplished methods[26]. Cells were plated in 96-multiwell plate (10^4 cells/well) for 24 hrs before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentrations of the compound in DMSO under test (0, 1.56, 3.125, 6.5, 12.5 and 25 µg/ml) were added to the cell monolayer triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 hrs at 37°C and in atmosphere of 5% CO_2. After 48 hrs, Cells were fixed, washed and stained with Sulfo-Rhodamine-B-stain. Excess stain was wash with acetic acid and attached stain was recovered with Tris EDTA buffer (10 mMTrisHCl, 1 mM disoduim EDTA, pH= 7.5- 8). Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration, is plotted to get the survival curve of each tumor cell line after the specified compound.

Result and discussion

The analytical and physical data (**Table 1), spectral data (Tables 2 and 3) reveal** that, the complexes are formed in (1:1) or (1: 2) (M: L) stiochiometric ratio. All the complexes are stable at room temperature, insoluble in common solvents, viz: MeOH, EtOH, $CHCl_3$, CCl_4 and $(CH_3)_2CO$ but soluble in DMSO[24, 25]. Ligand **(1),** was synthesized by condensation of tetraamine with salicaldhyde (1: 1) – (1: 3), molar ratios as shown in **Figure (2).**



(1)

Synthesis of the ligand

Figure (2)

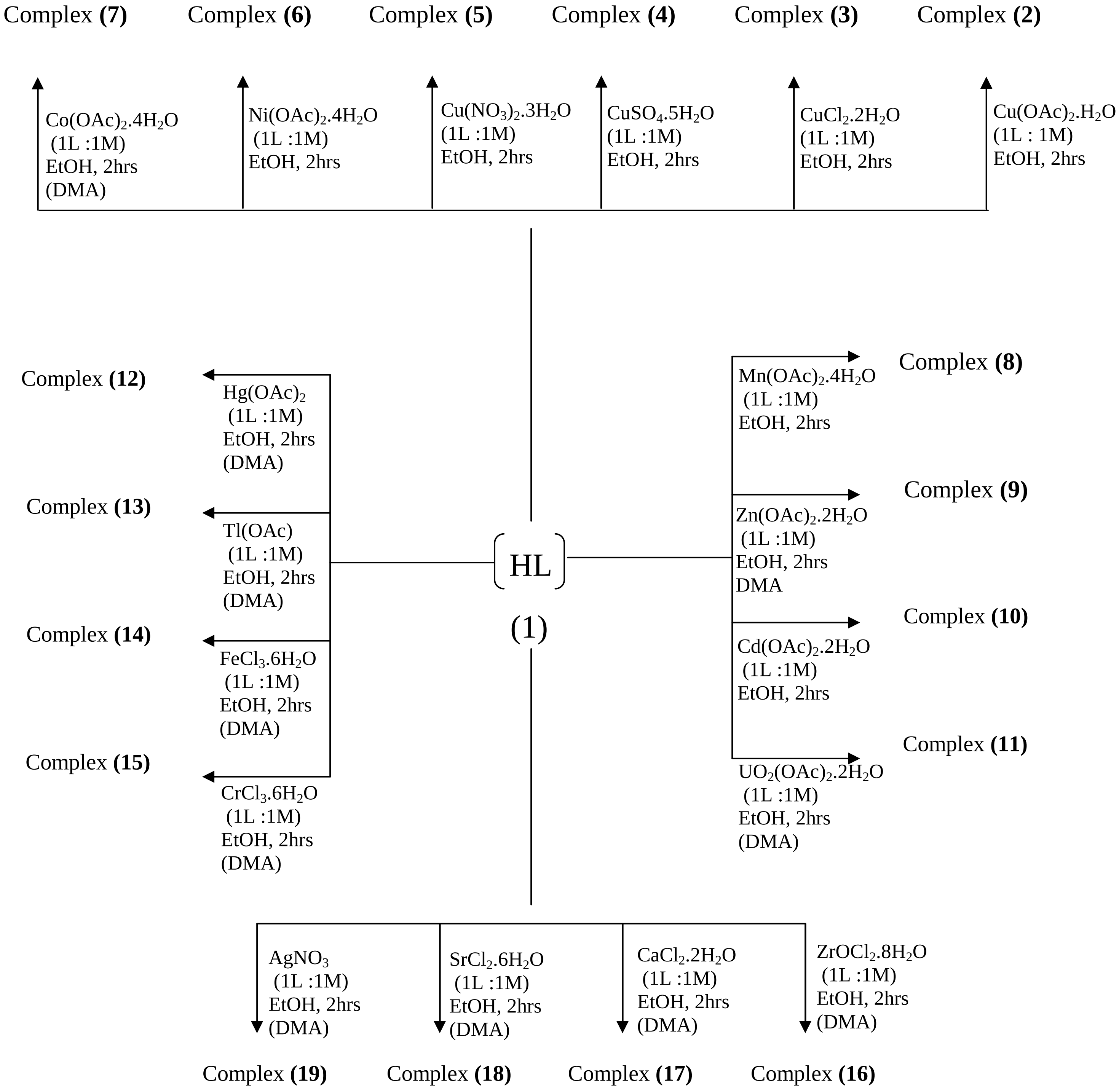
Table 1. Analytical and physical data of the ligand [HL] and its metal complexes.

No.	Ligands/Complexes	Color	FW	M.P (^{O}C)	Yield (%)	Anal./Found (Calc.) (%)					Molar conductance i m (t $^{-1}$cm^{2}mol^{-}
						C	H	N	M	Cl	
(1)	[HL]. $4H_2O$ $C_9H_{20}N_6O_5$	Yellow	292.29	185	74	37.14 (36.98)	6.56 (6.90)	28.55 (28.75)	-	-	-
(2)	$[(L)_2Cu_2(OAc)_2]$. $3H_2O$ $C_{22}H_{34}N_{12}O_9Cu_2$	Dark green	736.12	>300	82	36.4 (35.82)	4.4 (4.81)	22.12 (22.36)	16.75 (16.91)	-	12
(3)	$[(HL)_2Cu(Cl)_2]$. $2H_2O$ $C_{18}H_{26}N_{12}O_4CuCl_2$	Pale green	610.9	240	69	35.42 (35.4)	5.11 (4.62)	27.98 (27.51)	10.9 (10.4)	11.21 (11.61)	14
(4)	$[(HL)_2Cu(SO_4)(H_2O)]$ $C_{18}H_{26}N_{12}O_7Cus$	Dark green	618.09	230	71	34.51 (34.98)	4.54 (4.24)	27.78 (27.19)	11.52 (10.3)	-	13
(5)	$[(HL)_2Cu(NO_3)_2]$. $3H_2O$ $C_{18}H_{30}N_{14}O_{11}Cu$	Pale brown	682.06	>300	79	31.64 (31.7)	4.76 (4.43)	29.77 (28.75)	11.0 (9.32)	-	14
(6)	$[(HL)_2Ni(OAc)_2]$. $2H_2O$ $C_{22}H_{29}N_{12}O_6Ni$	Green	653.27	>300	80	40.55 (40.45)	5.4 (5.25)	25.32 (25.77)	8.8 (9.5)	-	15
(7)	$[(HL)Co(OAc)_2(H_2O)_2]$. $3H_2O$ $C_{13}H_{30}N_6O_{11}Co$	Brown	487.33	>300	76	31.2 (32.04)	5.73 (5.79)	16.22 (16.62)	11.21 (11.67)	-	16
(8)	$[(HL)_2Mn(OAc)_2]$. $2H_2O$ $C_{22}H_{33}N_{12}O_8Mn$	Dark green	649.52	>300	65	40.24 (40.68)	5.0 (5.28)	25.52 (25.92)	8.11 (8.47)	-	14
(9)	$[(HL)\ Zn(OAc)_2(H_2O)_2]$ $C_{13}H_{22}N_6O_7Zn$	Yellow	439.74	>300	68	35.06 (35.51)	4.92 (5.04)	18.78 (19.11)	14.52 (14.87)	-	12
(10)	$[(HL)_2\ Cd(OAc)_2]$. $2H_2O$ $C_{22}H_{34}N_{12}O_8Cd$	Orange	706.98	>300	65	37.1 (37.37)	4.52 (4.85)	23.45 (23.81)	15.32 (15.92)	-	13
(11)	$[(HL)\ (UO_2)(OAc)_2(H_2O)_2]$. 2H $C_{13}H_{26}N_6O_{11}U$	Orange	680.41	>300	73	22.19 (22.95)	3.59 (3.89)	12.0 (12.35)	34.1 (34.98)	-	18
(12)	$[(HL)\ Hg(OAc)_2]$ $C_{13}H_{18}N_6O_5Hg$	Dark green	538.96	>300	63	29.48 (28.97)	3.69 (3.37)	15.12 (15.59)	37.0 (37.22)	-	11
(13)	$[(HL)_2\ Tl(OAc)(H_2O)]$ $C_{22}H_{29}N_{12}O_5Tl$	Green	705.9	220	60	34.44 (39.09)	3.32 (4.10)	21.88 (23.79)	26.1 (28.31)	-	14
(14)	$[(L)_2\ Fe(Cl)(H_2O)].2H_2O$ $C_{18}H_{28}N_{12}O_5ClFe$	Dark brown	583.79	>300	61	36.72 (37.1)	4.52 (4.83)	28.32 (28.79)	9.1 (9.57)	5.98 (6.1)	19
(15)	$[(L)_2\ Cr(Cl)(H_2O)].2H_2O$ $C_{18}H_{28}N_{12}O_5ClCr$	Dark green	579.94	>300	64	36.92 (37.28)	4.71 (4.81)	28.5 (28.98)	8.5 (8.98)	5.75 (6.12)	20
(16)	$[(HL)\ ZrO(Cl)_2].3H_2O$ $C_9H_{18}N_6O_5Cl_2Zr$	Pale green	452.41	>300	61	23.22 (23.89)	3.8 (4.01)	18.12 (18.58)	19.2 (20.16)	15.23 (15.7)	22
(17)	$[(HL)\ Ca(Cl)_2(H_2O)_2]$. H_2O $C_9H_{18}N_6O_4Cl_2Ca$	Bright yellow	385.26	>300	67	27.62 (28.06)	4.5 (4.71)	21.33 (21.81)	10.0 (10.4)	18.0 (18.43)	21
(18)	$[(HL)\ Sr(Cl)_2(H_2O)_2]$. H_2O $C_9H_{18}N_6O_4Cl_2Sr$	Pale green	432.8	230	64	24.5 (24.98)	3.9 (4.2)	19.1 (19.42)	19.7 (20.2)	15.98 (16.4)	21
(19)	$[(HL)\ Ag(NO_3)]$ $C_9H_{12}N_7O_4Ag$	Dark green	407	>300	60	27.6 (29.5)	2.9 (4.21)	24.7 (24.08)	26.9 (26.49)	-	17

Table 2. IR frequencies of the bands (cm^{-1}) of ligand [HL] and its metal complexes and it`s assignments.

No.	ν(H_2O/OH)	ν(H-bond.)	N(NH_2)	ν(C=N)	ν(N-N)	ν(Ar)	ν(C-OH)/(C-O)	υ (OAc) /NO_3 /SO_4	υ(M-O)	υ(M-N)	υ(M-Cl)
(1)	3407 3500- 3220	3600- 3200 3180- 2950	3316, 3275	1617	1031	1546, 744	1266		-		-
(2)	3500- 3300	3580- 3190 3175- 2680	3300, 3270	1603	1022	1530, 754	1198	1570, 1420	503	462	-
(3)	3376 3540- 3220 3210- 3060	3580- 3190 3175- 2580	3255, 3235	1614	1025	1530, 752	1273	-	582	464	-
(4)	3378 3560- 3200	3560- 3100 3080- 2500	3346, 3235	1619	1028	1535, 749	1273	1120, 1028, 898, 685, 464	581	464	-
(5)	3410 3650- 3250 3180- 3040	3580- 3180 3170- 2980	3350, 3247	1621	1021	1569, 748	1273	1386, 1273, 827, 785	580	458	-
(6)	3416 3500- 3250	3525- 3150 3130- 2650	3265, 3230	1605	1026	1560, 756	1306	1545, 1440	509	454	-
(7)	3430 3600- 3250 3240- 3100	3560- 3180 3000- 2600	3335, 3270	1611	1026	1550, 754	1274	1537, 1382	583	487	-
(8)	3414 3550- 3200	3500- 3020 3000- 2800	3350, 3240	1609	1028	1580, 757	1274	1543, 1440	587	451	-
(9)	3422 3650- 3300	3560- 3300 3100- 2750	3355, 3260	1606	1015	1566, 760	1286	1540, 1380	503	461	-
(10)	3425 3600- 3200	3600- 3120 3100- 2850	3320, 3200	1621	1025	1567, 755	1281	1542, 1430	501	447	-
(11)	3429 3580- 3150 3100- 2650	3600- 3160 3150- 2500	3430, 3380	1602	1022	1569, 766	1281	1530, 1437	583	482	-
(12)	3410	3580- 3150 3130- 2650	3370, 3250	1619	1021	1567, 744	1299	1480, 1346	560	488	-
(13)	3420 3530- 3320	3550- 3200 3190- 2650	3416, 3370	1620	1030	1577, 750	1273	1530, 1380	558	464	-
(14)	3600- 3250 3235- 3100	3600- 3150 3100- 2800	3350, 3250	1601	1026	1576, 760	1199	-	580	463	410
(15)	3600- 3260 3250- 3120	3600- 2920 2800- 2600	3380, 3270	1617	1025	1563, 756	1201	-	537	464	412
(16)	3405 3580- 3230	3580- 3100 3080- 2900	3350, 3250	1611	1026	1570, 756	1270	-	540	434	430
(17)	3416 3250- 3120 3250- 3120	3600- 3170 3160- 2800	3400, 3380	1621	1025	1568, 748	1276	-	580	467	440
(18)	3428 3600- 3250	3600- 3190 3180- 2860	3150, 3090	1622	1026	1575, 750	1273	-	558	463	440
(19)	3427	3600- 3200 3190- 2750	3150, 3080	1619	1029	1576, 750	1273	1386, 1198, 840, 765	521	456	-

We notice that, (1:1) or (1:2) or (1:3) molar ratios of tetraamine with salicaldhyde give ligand **(1)**, may be due to the formation of strong hydrogen bondings or steric effect. The proposed structures of the complexes are shown in **Figure (3). Scheme (1)** illustrates that, the composition of the complexes formed depends on metal salts, the medium of the reaction and the molar ratios.



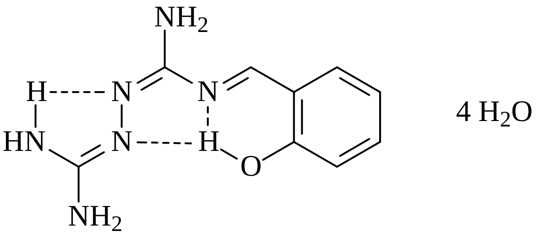
Scheme (1)

DMA = dimethyl amine

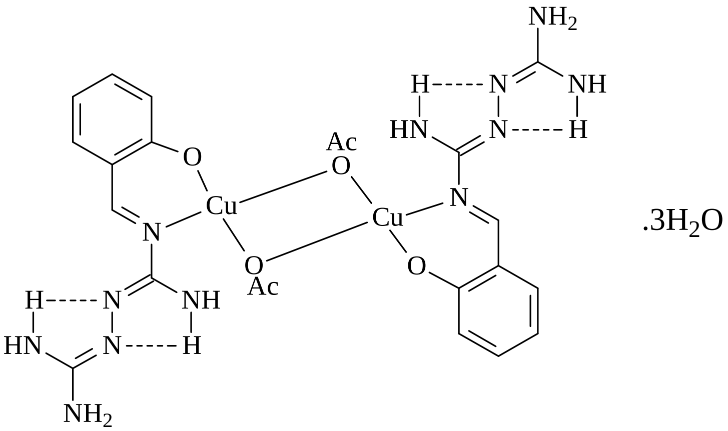
Table 3. The electronic absorption spectral bands (nm) and magnetic moment (B.M) for the ligand [HL] and its complexes.

No.	λ_{max}^{*} (ε)	«$_{eff}$ in BM
(1)	255 (ε= 6.15×10^{-3} mol^{-1} cm^{-1}), 319 (ε = 7.69×10^{-3} mol^{-1} cm^{-1}), 388 (ε = 9.36×10^{-3} mol^{-1} cm^{-1})	-
(2)	255, 321, 389, 490, 520, 581, 580	0.81
(3)	255, 318, 385, 519, 584, 647	1.76
(4)	255, 324, 390, 524, 582, 649	1.75
(5)	260, 319, 388, 505, 576, 640	1.68
(6)	260, 315, 380, 490, 625, 875	2.86
(7)	250, 321, 390, 550, 610	3.40
(8)	265, 315, 375, 465, 510, 605	4.90
(9)	270, 315, 380	Dia
(10)	265, 310, 385	Dia
(11)	265, 320, 380	Dia
(12)	260, 315, 385	Dia
(13)	265, 310, 350, 380	2.19
(14)	265, 315, 390, 450, 630	5.96
(15)	270, 320, 380, 440, 530, 630	3.94
(16)	260, 320, 375	Dia
(17)	265, 315, 390	Dia
(18)	270, 318, 385	Dia
(19)	255, 310, 380	Dia

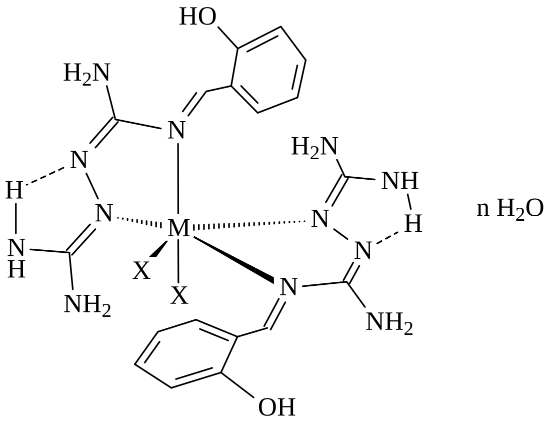
* in nm



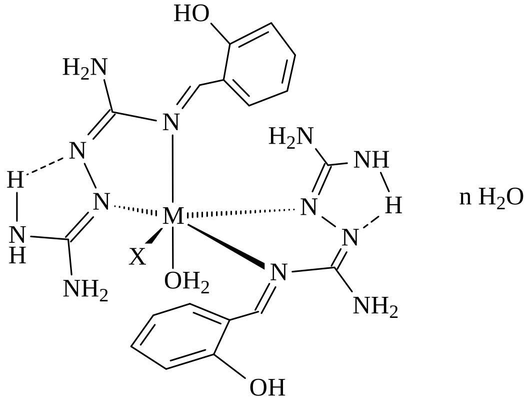
HL **(1)**



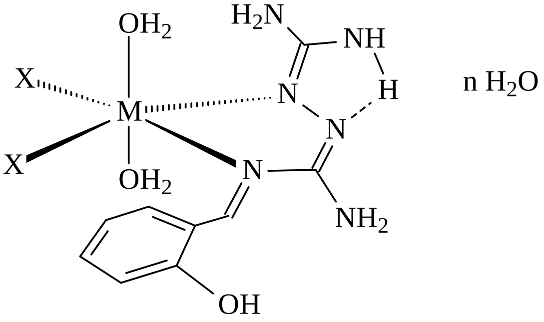
Complex **(2)**



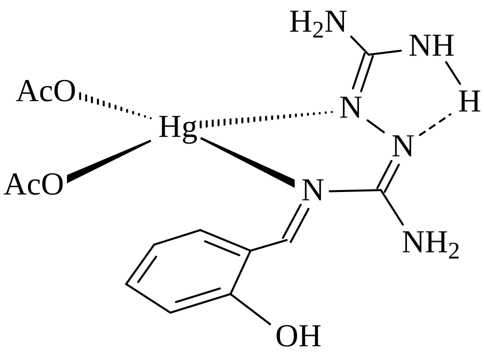
Complex **(3)** M = Cu(II), x = Cl, n=2
Complex **(5)** M = Cu(II), x = NO_3, n=3
Complex **(6)** M = Ni(II), x = OAc, n=2
Complex **(8)** M = Mn(II), x = OAc, n=2
Complex **(10)** M = Cd(II), x = OAc, n=2



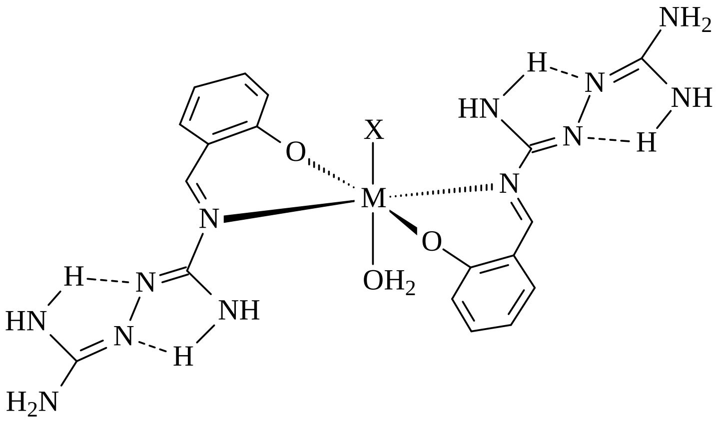
Complex **(4)** M = Cu(II), x = SO_4, n = 0
Complex **(13)** M = Tl(I), x = OAc, n = 0



Complex **(7)** M = Co(II), x = OAc, n = 3
Complex **(9)** M = Zn(II), x = OAc, n = 0
Complex **(11)** M = UO_2(II), x = OAc, n = 2
Complex **(17)** M = Ca(II), x = Cl, n = 1
Complex **(18)** M = Sr(II), x = Cl, n = 1

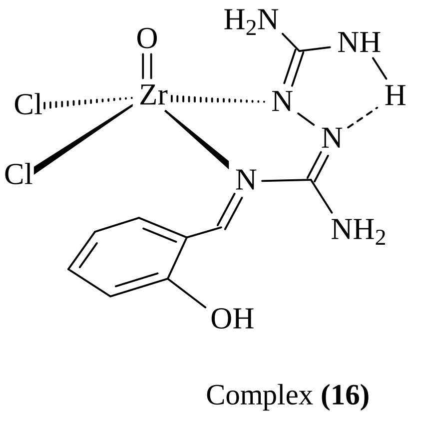


Complex **(12)**



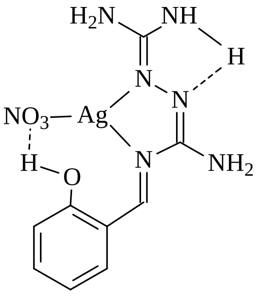
n H_2O

Complex **(14)** M = Fe(III), x = Cl, n = 2
Complex **(15)** M = Cr(III), x = Cl, n = 2



3 H_2O

Complex **(16)**



Complex **(19)**

Figure (3)

Mass spectrum of the ligand, (1)

The mass spectrum of the ligand supported, the suggested structure, Figure (2) revealing a molecular ion peak (m/z) at 294.1, coincident with the molecular weight of the ligand. Morever, the fragmentation pattern splits a parent ion peak at (m/z) = 67 a.m.u. corresponding to C_2HN_3 while the fragments at (m/z) = 121, 135, 207 and 222 a.m.u. 84, 93 correspond to $C_2H_4N_4$, C_6H_5O, $C_7H_7N_2O$, $C_8H_{11}N_6O$ and $C_9H_{12}N_6O$, respectively (**Table 1).**

^{1}H – NMR spectra

The ^{1}H – NMR spectra of ligand and its cadmium(II) complex **(10)** in deuterated DMSO show signals consistent with the proposed structure. The peak at 11.3 p.p.m is due to proton of OH group[28, 29]. The signals observed at 3.42 and 2.5 p.p.m, are due to the protons of NH_2 group[30]. The azomethine proton of CH =N group appears at 9.1 p.p.m[28,31]. The peaks observed as multiple ones at 6.0 – 7.7 p.p.m may be assigned to aromatic protons[28]. The spectrum of cadmium(II) complex **(10)** shows, the protons of NH_2 group at 3.32 and 2.49 p.p.m and the signal characteristic to the phenolic hydroxyl group (OH) appeared in the same position of the ligand, indicating that, the hydroxyl group did not participate in the coordination[28]. Complexation leads to a significant downfield shift of the azomethine proton (8.9 p.p.m) relative to the free ligand confirms that, the azomethine nitrogen atom coordinates to the metal (N - Cd)[28]. The aromatic protons appear in the 6.1- 8.0 p.p.m range [31]. A new signal was observed at 1.84 p.p.m which may be assigned to the protons of the coordinated acetate group[31, 32].

Conductivity

The molar conductance values of the complexes in DMF (10^{-3} M) lie in the 22 – 11 Ω mol^{-1}cm^2 range (Table 1), indicating that, all the complexes are not electrolytes [27, 33]. This confirms that, the anion is coordinated to the metal ion.

IR spectra

The modes of bonding between the ligand and the metal ion can be revealed by comparing the IR spectra of the solid complexes with that of the ligand. The IR spectral data of the ligand and its metal complexes are presented in Table 2. The IR spectrum of the ligand shows broad medium bands in the 3600- 3200 and 3180- 2950 cm^{-1} ranges, attributed to intra- and intermolecular hydrogen bonds between aromatic OH or –NH_2 with C=N groups[34,35]. Thus, the higher frequency band is associated with a weaker hydrogen bond and the lower frequency band with a stronger hydrogen bond. The spectrum also shows bands at 3407 and 3316 and 3275 cm^{-1}, assigned to the stretching vibrations of the phenolic hydroxyl ν(OH) and amino ν(NH_2) associated through intermolecular and intramolecular hydrogen bondings[28,36, 37]. The relatively strong bands located at 1617, 1266, 1031 and 1546 cm^{-1} are assigned to the ν(C=N)imine, ν(OH), ν(N-N), ν$(C=C)_{Ar}$ respectively[28]. A broad band appears in the 3500- 3220 cm^{-1} range corresponds to the hydrated water molecules [38]. In all complexes, the band due to azomethine ν$(C=N)_{imine}$ was shifted with decreasing its intensity indicating its coordination to the central metal ion[28,39]. The ν(NH_2) and ν(OH) groups appear in the 3430 – 3230 and 3430 - 3376 cm^{-1} ranges[40,41] and ν(N-N) group observed in the 1028- 1015 cm^{-1} range which are shifted to lower frequency compared to the ligand. The ν$(C=C)_{Ar}$ appears in the 1580- 1530 and 766- 744 cm^{-1} ranges[40,41]. The complexes show broad bands in the 3650 – 2900 and 3270 – 2650 cm^{-1} ranges except complexes **(12)** and **(13)**, assigned to the presence of hydrated or coordinated water molecules[40]. However, the bands appear in the 3600 – 2920 and 3190 – 2500 cm^{-1} ranges, are due to intra- and intermolecular hydrogen bondings[28, 36, 37]. New bands in the 616 – 501 and 488 – 434 cm^{-1} ranges were taken as indication of coordination between the metal ions with oxygen and nitrogen atoms [39, 40]. Complexes **(3) – (13), (16) – (19)** show bands in the 3430 – 3376 cm^{-1} ranges are due to ν(OH) group [44]. Complex **(4)** shows bands at 1120, 1028, 898, 685 and 464 cm^{-1} due to the coordinated monodentate sulphate group[45]. Extensive IR spectral studies reported on metal acetate complexes[42] indicate that, the acetate ligand coordinates [39] in either a monodentate, bidentate or bridging manner, the ν_a (CO_2) and ν_s(CO_2) of the free acetate are at 1560 and 1416 cm^{-1} respectively. In monodentate, coordination ν(C=O) is at higher energy than ν_a (CO_2) and ν(C-O) is lower than ν_s(CO_2). As a result, the separation between ν(CO) bands is much larger in monodentate complexes. In complexes **(6) – (13),** the bands is due to ν_a(CO_2) appeared in the 1545 – 1480 cm^{-1} and the ν_s(CO_2) observed in the 1440 – 1346 cm^{-1} ranges. The difference between these two bands is in the 160 – 103 cm^{-1} range, suggesting that, the acetate group coordinates in unidentate manner with the metal ions [28]. However, bridging acetate group with both oxygen atoms coordinated (as in copper(II) acetate) have ν(CO) bands close to the free ion values [28, 46] as found for complex **(2)**, ν_a(CO_2) = 1570 and ν_s(CO_2) = 1420 cm^{-1} . A new band observed in the 440 – 410 cm^{-1}, may be assigned to ν(M-Cl) in the chloro complexes **(14) – (18)**[47]. Complexes **(5)** and **(19)** show bands at 1386, 1273, 827 and 785 and 1386, 1198, 840 and 765 cm^{-1} respectively, assigned to coordinated nitrate group[34, 38]. The complex **(19)** has a monomeric trigonal planar in which the guanidine coordinates as a pseudo- bidentate ligand interacting with silver ion and nitrate group via N_{imine} and NH moieties[23]. The complexes show ν(OH) band in the 1306 – 1270 cm^{-1}, except complexes **(2)**, **(14)** and **(15)** show ν(CO) band at 1198, 1199 and 1201 cm^{-1} respectively[38, 48]. The appearance of ν(OH) group at higher wave number comparing to the ligand (1266 cm^{-1}), indicating non- coordinated of this group to the metal ion. However, complexes **(2)**, **(14)** and **(15)** show bands at lower wave number (Table 2) indicating deprotonated of the OH group due to coordination to the metal ion. Complex **(11)** shows band at 885 cm^{-1} due to O=U=O[49], however, complex **(16)** shows a band at 848 cm^{-1}, assigned to ν(ZrO) vibration[50].

Magnetic moments

The room temperature magnetic moments of the complexes **(2) – (19)** are shown in Table (3). Copper(II) complexes **(3)**, **(4)** and **(5)** show values 1.76, 1.75 and 1.68 B.M., corresponding to one unpaired electron in an octahedral structure[34,51], however, complex **(2)** shows a value 0.81 B.M. which is well below the spin only value (1.73 B.M.), indicating that, spin – exchange interactions take place between the copper(II) ions through acetate group in an square planar geometry[34,51]. Nickel(II) complex **(6)** gives 2.86 B.M., confirmed t_2g^6 eg^2 electronic configuration with two unpaired electrons in an octahedral Ni(II) complex[34,52]. Cobalt(II) complex **(7)** and manganese(II) complex **(8)** show values 3.4 and 4.9 B.M., indicating high spin octahedral structure [34, 50]. Thalium(I) complex **(13)** gives 2.19 B.M., indicating an octahedral structure. Iron(III) complex **(14)** and chromium(III) complex **(15)** show values 5.96 and 3.94 B.M., indicating high spin octahedral structure[34,53]. Zinc(II) complex **(9),** cadmium(II) complex **(10)**, uranyl complex **(11)**, zirconyl(II) complex **(16)**, calcium(II) complex **(17)**, strontium(II) complex **(18)** and silver(I) complex **(19)** show diamagnetic values.

Electronic spectra

The electronic spectral data for the ligand and its metal complexes in DMF solution are summarized in Table (3). The ligand in DMF solution shows three bands at 388 nm ($\varepsilon = 9.36\times10^{-3}$ mol^{-1}cm^{-1}), 319 nm ($\varepsilon = 7.69\times10^{-3}$ mol^{-1}cm^{-1}) and 255 nm ($\varepsilon = 6.15\times10^{-3}$ mol^{-1}cm^{-1}), which may be assigned to the $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transitions respectively [54]. Copper(II) complexes **(3), (4)** and **(5)** show bands in the 265 – 255, 324 – 318 and 390 – 385 nm ranges, these bands are due to intraligand transitions, however, the bands appear in the 524 – 505, 584 – 576 and 649 – 640 nm ranges are assigned to O→Cu charge transfer, $^2B_1\rightarrow{}^2E$ and $^2B_1\rightarrow{}^2B_2$ transitions, indicating a distorted tetragonal octahedral structure [27, 55, 56]. However, cu(II) complex **(2)** shows bands at 255, 321 and 389 nm, these bands are within the ligand and bands at 490, 520 and 580 nm are corresponding to $^2B_{1g}\rightarrow{}^2B_{2g}$, $^2B_{1g}\rightarrow{}^2E_g$ and $^2B_{1g}\rightarrow{}^2A_{1g}$ respectively, suggesting a square planar geometry [57, 58]. Nickel(II) complex **(6)** shows bands at 260, 315,380,490,625 and 875 nm respectively, the first three bands are within the ligand and the other three bands are attributable to $^3A_{2g}(F)\rightarrow{}^3T_{1g}(P)(\nu_3)$, $^3A_{2g}(F)\rightarrow{}^3T_{1g}(F)(\nu_2)$ and $^3A_{2g}(F)\rightarrow{}^3T_{2g}(F)(\nu_1)$ transitions respectively, indicating an octahedral Ni(II) complex[27,59]. The ν_2/ν_1 ratio for the complex is 1.4, which is less than the usual range of 1.5 – 1.75, indicating a distorted octahedral Ni(II) complex[27,60]. Cobalt(II) complex **(7)** shows bands at 250, 321, 390, 550 and 650 nm, the first three bands are within the ligand and the other bands are assigned to $^4T_{1g}(F)\rightarrow{}^4A_{2g}$ and $^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$ transitions respectively, corresponding to high spin Co(II) octahedral complexes[61]. Manganese(II) complex **(8)** shows bands at 265, 315, 375, 465, 510 and 605 nm, respectively, the first three bands are within the ligand, however, the other bands are corresponding to $^6A_{1g}\rightarrow{}^4E_g$, $^6A_{1g}\rightarrow{}^4T_{2g}$ and $^6A_{1g}\rightarrow{}^4T_{1g}$ transitions which are compatible to an octahedral geometry around the Mn(II) ion[62]. Tl(I) complex **(13)** gave bands at 265, 310 and 350 nm, respectively. These bands are due to intraligand transitions since these bands appear almost in the spectrum of the ligand, additional weak band appears at 380 nm, which may be assigned to the $^1S_0\rightarrow{}^3P_1$ transition of Tl(I) complex[63]. Iron(III) complex **(14)** shows bands at 265, 315, 390,450 and 650 nm respectively, the first three bands are within the ligand while the other bands are due to charge transfer and $^6A_1\rightarrow{}^4T_1$ transitions, suggesting distorted octahedral geometry around the iron(III) ion [44, 64]. While chromium(III) complex **(15)** shows bands at 270, 320, 380, 440, 530 and 630 nm respectively. The first three bands are assigned to $^4A_{2g}\rightarrow{}^4T_{1g}(F)$, $^4A_{2g}\rightarrow{}^4T_{2g}$ and $^4A_{2g}\rightarrow{}^2T_{2g}$ transitions respectively, indicating octahedral structure around the Cr(III) ion [65, 66]. Zinc(II) complex **(9)**, cadmium(II) complex **(10)**, uranyl(II) complex **(11)**, mercury(II) complex **(12)**, zirconyl(II) complex **(16)**, calcium(II) complex **(17)**, strontium(II) complex **(18)** and silver(I) complex **(19)** show three bands in the 270 – 255, 320 – 310 and 390 – 375 nm ranges, which are assigned to intraligand transitions.

Electron Spin Resonance (ESR)

The ESR spectral data for complexes **(2)**, **(3)**, **(5)**, **(7)**, **(8)** and **(14)** are presented in Table 4.The spectra of copper(II) complexes **(2)**, **(3)** and **(5)** are characteristic of species, d^9 configuration and having axial type of a $d_{(x2-y2)}$ ground state which is the most common for copper(II) complexes[67, 68]. The complexes show $g_{\parallel} > g_{\perp} > 2.0023$, indicating square planar or octahedral geometry around copper(II) ion[69, 70]. The g- values are related by the expression[69, 71], $G=(g_{\parallel}-2)/(g_{\perp}-2)$, if $G > 4.0$, then, local tetragonal axes are aligned parallel or only slightly misaligned, if $G < 4.0$, the significant exchange coupling is present. Complexes **(2)** and **(5)** show values 3.71 and 3.86 indicating spin – exchange interactions take place between copper(II) ions through acetate group **(2)** or hydrogen bondings **(5)**. This phenomenon is further confirmed by magnetic moments (0.81 and 1.68 B.M. respectively). However, complex **(3)** shows 4.0 indicating tetragonal axes are present in this complex. Also, the $g_{\parallel}/A_{\parallel}$ values considered as diagnostic of stereochemistry[72],in the range reported for square planar complexes are 105 to 135 cm^{-1} and for tetragonal distorted octahedral complexes 150 to 250 cm^{-1}. The $g_{\parallel}/A_{\parallel}$ values lie just within the range expected for the complexes **(Table 4).** The g- value of the copper(II) complexes with a $^2B_{1g}$ ground state ($g_{\parallel}>g_{\perp}$) may be expressed [73] by

$$g_{\parallel} = 2.002 - (8k^2_{\parallel}\lambda_o/\Delta E_{xy}) \;\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ (1)$$

$$g_{\perp} = 2.002 - (2k^2_{\perp}\ \lambda_o/\Delta E_{xz}) \;\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(2)$$

where $k_{\parallel}$ and $k_{\perp}$ are the parallel and perpendicular components respectively of the orbital reduction factor (K), λ ° is the spin – orbit coupling constant for the free copper, ΔE_{xy} and ΔE_{xz} are the electron transition energies of $^2B_{1g}\rightarrow{}^2B_{2g}$ and $^2B_{1g}\rightarrow{}^2E_g$. From the above relations, the orbital reduction factors ($K_{\parallel}$, $K_{\perp}$,K), which are a measure of covalency [73] 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 covalency

$$K^2_{\perp} = (g_{\perp} - 2.002)\ \Delta E_{xz}/2\lambda_o \;\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(3)$$

$$K^2_{\parallel} = (g_{\parallel} - 2.002)\ \Delta E_{xy}/8\lambda_o \;\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(4)$$

$$K^2 = (K^2_{\parallel} + 2K^2_{\perp})/3 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(5)$$

K (Table 4), for the copper(II) complexes **(2), (3)** and **(5),** indicating covalent bond character [48, 74]. Kivelson and Neiman[75] noted that, for ionic environment $g_{\parallel} \geq 2.3$ and for a covalent environment $g_{\parallel} < 2.3$. Theoretical work by Smith [76] seems to confirm this view. The g- values reported here (Table 4) show considerable covalent bond character [48]. Also, the in-plane δ- covalency parameter, α^2(Cu) was calculated by

$$\alpha^2(Cu)=(A_{\parallel}/0.036)+(g_{\parallel}-2.002)+3/7(g_{\perp}-2.002)+0.04.\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots(6)$$

The calculated **values (Table 4)** suggest a covalent bonding [45, 48, 74]. The in-plane and out of- plane π- bonding coefficients B_1^2 and B^2 respectively, are dependent upon the values of ΔE_{xy} and ΔE_{xz} in the following equations [69].

$$\alpha^2\beta^2 = (g_{\perp} - 2.002)\ \Delta E_{xy}/2\lambda_o \;\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(7)$$

$\alpha^2 ß_1^2 = (g_{\|} - 2.002)\ \Delta E_{xz}/8\lambda_o$ ……………………………………….…. ….(8)

in this work, the complexes show $ß_1^2$ values 0.78 and 0.72 **(2)** and **(3)**, indicating a moderate degree of covalency in the in-plane π- bonding, however, complex **(5)** shows 1.02 indicating ionic character [74, 77]. While $ß^2$ for complexes **(3)** and **(5)** are 0.87 and 0.82 respectively, indicating covalent bonding character out of- plane π- bonding, however, complex **(2)** shows 1.1, indicating ionic character of the out of- plane [74, 77]. It is possible to calculate approximate orbital populations for s, p or d orbitals [78] by

$A_{\|} = A_{iso} - 2B\ [1 \pm (7/4)\ \Delta g_{\|}]$……..………………………………………..…..(9)

$A_{\perp} = A_{iso} + B\ [1 \pm (7/2)\ \Delta g_{\perp}]$………………………………………………..(10)

$a^2_s = A_{iso} / A°$, $a^2_{p,d} = 2B / 2B°$ …………………………………........…(11)

where A° and 2B° are the calculated dipolar coupling for unit occupancy of s and d orbitals respectively. The calculated orbital publications for the copper(II) complexes **(2), (3)** and **(5),** (Table 4), indicate a $d_{(x2-y2)}$ ground state [42]. The ESR spectrum for complex **(2)** shows seven lines in the low and high field regions with some lines in the centre field region were also observed. This is a characteristic of the triplet state for a dimmer species. The zero field splitting parameter (D) for the parallel components of the dimmer complex **(2)** was estimated from the spectrum and is equal to 500 G. The distance between the two copper centers was calculated using the following equation [48, 79]

$D = {}^{3\mu}B/2R^3\ (3\cos^2\theta - 1)$…….. ……………………………………………(12)

Where ${}^{3\mu}B$ is the magnetic moment of the electron and R, is the distance (A°) between the electrons. For parallel component (D), θ = 0, by substitute in equation (12), D is equal to ${}^{3\mu}B/R^3$ for a bi-radical system in the triplet state, it is found that, D for the parallel components is equal to 402 G and the distance between the two radicals is equal to 5.2 A°. From these data, the distance between the two copper(II) centers was calculated and is equal to 4.2 A°. This value is close to that for a dimeric copper(II) compound in the triplet –state [48, 80]. Cobalt(II) complex **(7),** manganese(II) complex **(8)** and iron(III) complex **(14)** show isotropic spectra with values 2.1, 2.008 and 2.09, respectively confirmed octahedral structure [48, 68].

Table 4. ESR data for the metal (II/ III) complexes

No.	g_{∞}	$g_{\{}$	$g_{iso}{}^a$	A_{∞} (G)	$A_{\{}$ (G)	$A_{iso}{}^b$ (G)	G^c	ΔE_{xy}	ΔE_{xz}	$K_{\{}^2$	K_{∞}^2	K	g_{∞}/A_{∞}	α^2	$ß^2$	$ß_1^2$	-2 ß	a_d^2 (%)
(2)	2.26	2.07	2.13	220	50	106.7	3.71	19230	25641	1.05	0.75	0.97	113	0.96	1.0	0.78	205	87
(3)	2.20	2.05	2.10	140	20	60	4.0	15456	19268	0.56	0.46	0.73	157.1	0.64	0.87	0.72	303	90
(5)	2.27	2.07	2.14	150	15	65	3.86	15625	19802	0.64	0.8	0.83	142.7	0.78	0.82	1.02	244.3	72.8
(7)	-	-	2.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(8)	-	-	2.007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(14)	-	-	2.09	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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

Thermal Analyses [DTA and TGA]

Since the IR spectra indicate the presence of water molecules, thermal analyses (DTA and TGA) were carried out to a certain their nature. The thermal curves in the temperature 27 - 800°C range for complexes **(2), (5), (7)** and **(9)** are thermally stable up to 35°C. Dehydration is characterized by endothermic peaks within the temperature 70 - 90°C range, corresponding to the loss of hydrated water molecules[81, 82]. The decomposition step for complex **(2)** occurred at 90°C with 7.33% weight loss (Calc. 6.92%), which could be due to the elimination of $3H_2O$. Another thermal decomposition at 175 and 257°C with 29.32% weight loss (Calc. 30.6%), which could be due to the loss of $C_4H_{12}N_{10}$ moiety. Also, the complex shows two endothermic peaks at 263 and 321°C with 24.2% weight loss (Calc. 24.48%), corresponding to the loss of two acetate groups. Endothermic peak observed at 335°C gwith no weight loss may be due to melting point. Finally, the complex shows exothermic peaks in the 400 - 600°C range, corresponding to oxidative thermal decomposition which proceeds slowly with final residue at 660°C, assigned to CuO[81]. Complex **(5)** shows endothermic peak at 70°C, with 3.3% weight loss (Calc. 3.2%), due to one hydrated water, however, the peak observed at 140°C with 7.2% weight loss (Calc. 6.69%), assigned to two coordinated water molecules, $C_4H_{12}N_{10}$ moiety decomposed at 180 and 215°C with 40.67% weight loss (Calc. 39.84%). The endothermic peak observed at 315°C may be assigned to the melting point. Oxidative thermal decomposition occurs in the 350 - 650°C range with exothermic peaks, leaving CuO 26.27% weight loss (Calc. 26.32%)[83]. Complex **(7)** shows endothermic peak at 70°C with 11.0% weight loss (Calc. 11.1%) due to three hydrated water molecules, however, endothermic peak observed at 135°C with 7.8% weight loss (Calc. 8.3%), due to the loss of two coordinated water. However, the endothermic peak appears at 170°C with 22.8% weight loss (Calc. 23.1%) is assigned to $C_2H_6N_5$ moiety. The endothermic peak observed at 237°C with 35.1% weight loss (Calc. 35.43%) is due to the loss of two coordinated groups. The endothermic peak observed at 370°C may be assigned to the melting point. Oxidative thermal decomposition occurs in the 400 - 650°C range with exothermic peaks, leaving CoO with 34.2% weight loss (Calc. 34.88%)[83]. Finally, complex **(9)** shows endothermic peak at 150°C with 8.4% weight loss (Calc. 8.2%) due to the loss of two coordinated water molecules, another endothermic peak is appeared at 213°C with 24.37% weight loss (Calc. 24.74%) is assigned to the loss of $C_2H_6O_5$ moiety, however, the acetate group lost as endothermic peak at 363°C with 39.49% weight loss (Calc. 38.81%). The endothermic peak appears at 413°C may be assigned to the melting point, oxidative thermal decomposition occurs in the 430 - 590°C range with exothermic peaks, leaving ZnO at 590°C with 43.6% weight loss (Calc. 43.55%) [83].

Table 5. Thermal data for the metal complexes

No.	Temp. (^oC)	DTA (Peak)	TGA (wt. loss %)		Assignments
			Calc.	Found	
(2)	90	Endo	6.92	7.33	Loss of three molecules of hydrated water
	175, 257	Endo	30.6	29.32	Loss of $C_4H_{12}N_{10}$ moiety
	263, 321	Endo	24.48	24.2	Loss of two acetate groups
	335	Endo	-	-	Melting point
	400- 600	Exo	-	-	Decomposition and formation of 2CuO
(5)	70	Endo	3.2	3.3	Loss of one molecule of hydrated water
	140	Endo	6.69	7.2	Loss of two coordinated water molecules
	180, 215	Endo	39.84	40.67	Loss of $C_4H_{12}N_{10}$ moiety
	315	Endo	-	-	Melting point
	350- 650	Exo	26.32	26.27	Decomposition and formation of CuO
(7)	70	Endo	11.1	11.0	Loss of three molecules of hydrated water
	135	Endo	8.3	7.8	Loss of two coordinated water molecules
	170	Endo	23.1	22.8	Loss of $C_2H_6N_5$ moiety
	237	Endo	35.43	35.1	Loss of two acetate groups
	370	Endo	-	-	Melting point
	400- 650	Exo	34.88	34.2	Decomposition and formation of CoO
(9)	150	Endo	8.2	8.4	Loss of two coordinated water molecules
	213	Endo	24.74	24.37	Loss of $C_2H_6N_5$ moiety
	363	Endo	38.1	39.49	Loss of two acetate groups
	413	Endo	-	-	Melting point
	430- 590	Exo	43.55	43.6	Decomposition and formation of ZnO

Table 6. Mass spectrum of (1)

m/z	Rel. Int.	Fragment
H_6N_3	48	150
C_2N_2	52	100
C_2HN_3	67	100
CH_4N_3	74	90
C_7H_6O	84	40
$C_7H_7N_2O$	135	50
$C_8H_{11}N_6O$	207	85
$C_9H_{12}N_6O$	222	8

Biological activity

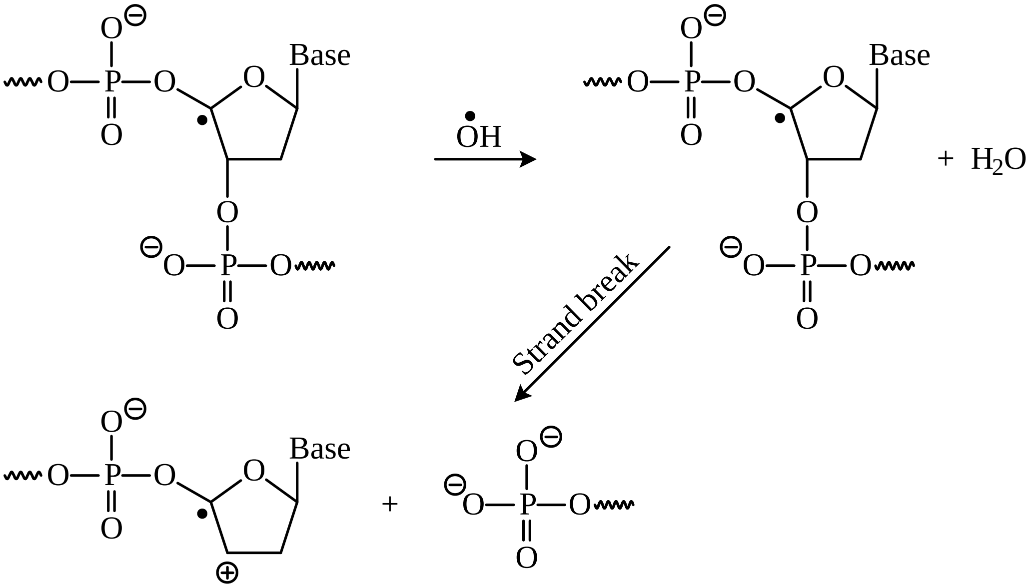
The biological activity of the ligand, (**1**) and its metal complexes **(2), (4), (9),(10)** and **(13)** were evaluated against HEPG- 2 cell line. In this study, we try to know the chemotherapeutic activity of the tested complexes by comparing them with the standard drug (IMURAN® **(**azathioprine**)**). The treatment of the different complexes in DMSO showed similar effects in the tumoral cell line used as it was previously reported[84]. The solvent (dimethyl sulphoxide, DMSO) shows no effect in cell growth. The ligand **(1)**, shows a weak inhibition effect at ranges of concentration used, however, the complexes showed moderate effect against HEPG- 2. The obtained data indicate, the surviving fraction ratio against HEPG- 2 tumor cell line increasing with the increase of the concentration in the range of the tested concentration. Also, the Cd(II) complex **(10)** shows a high potency of around 65% inhibition at 25Mg/mℓ against HEPG- 2, compared with a standard drug[83]. This can be explained because cadmium(II) binds to DNA. It seems that, change the anion and the nature of the metal ion has effect on the biological behavior, due to alter binding ability of the DNA binding, so testing of different complexes is very interesting from this point of view. Chemotheraputic activity of the complexes may be attributed to the central metal atom which was explained by Tweedy's chelation theory [84, 85]. Also, the positive charge of the metal increases the acidity of coordinated ligand that bears protons, leading to stronger hydrogen bonds which enhance the biological activity [86 - 88]. Moreover, Gaetke and Chow had reported that, metal has been suggested to facilitate oxidated tissue injury through a free-radical mediated pathway analogous to the Fenton reaction[89]. By applying the ESR-trapping technique, evidence for metal - mediated hydroxyl radical formation in vivo has been obtained [72]. ROS are produced through a Fenton-type reaction as follows:

$$LM(II) + H_2O_2 \rightarrow LM(I) + {}^{\cdot}OOH + H^+$$
$$LM(I) + H_2O_2 \rightarrow LM(II) + {}^{\cdot}OH + OH^-$$

Where L, organic ligand

Also, metal could act as a double-edged, sword by inducing DNA damage and also by inhibiting their repair[90]. The OH radicals react with DNA sugars and bases and the most significant and well-characterized of the OH reactions is hydrogen atom abstraction from the C_4 on the deoxyribo usenit to yield sugar radicals with subsequent β-elimination,

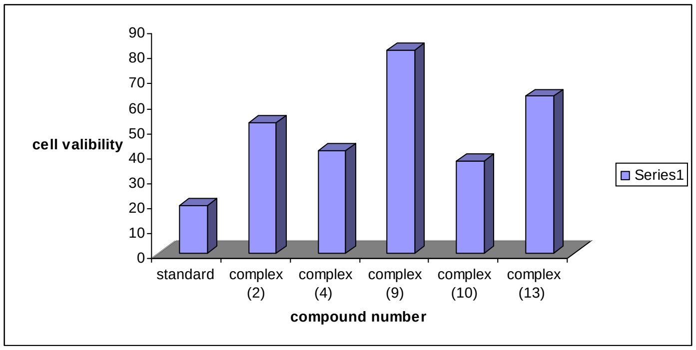
Scheme 2. By this mechanism strand breakage occurs as well as the release of the free bases. Another form of attack on the DNA bases is by solvated electrons, probably via a similar reaction to those discussed below for the direct effects of radiation on DNA [90] **Figure 3.**



Scheme (2)

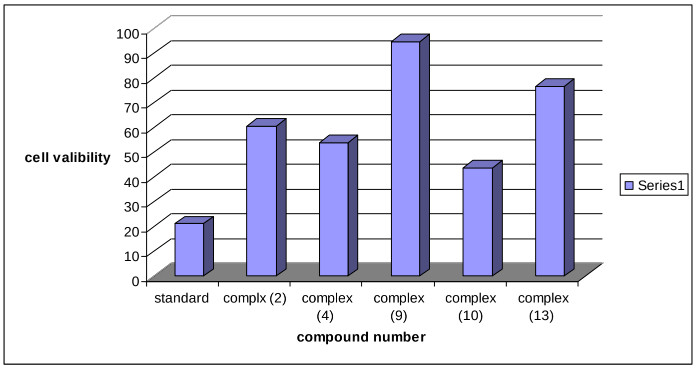
In the ranges of concentrations used, the obtained data indicate that, the order of chemotherapeutic effect. At concentrations 25, 12.5 and 6.5 µg is standard > Cd(II) complex **(10)** > Cu(II) complex **(4)** > Cu(II) complex **(2)** > Tl(I) complex **(13)** > Zn(II) complex **(9)**, however, at concentration 3.125 µg is Cd(II) complex **(10)** > Cu(II) complex **(4)** > standard > Cu(II) complex **(2)** > Tl(I) complex **(13)** > Zn(II) complex **(9)** and at 1.56 µg is Tl(I) complex **(13)** > Cd(II) complex **(10)** >Zn(II) complex **(9)** > standard > Cu(II) complex **(2)** = Cu(II) complex **(4)** Although, the complexes are octahedral structures and have the same anions, the variable activity of the complexes may be used to oxidation – reduction potentials. The chemotherapeutic effect of a standard drug and metal complexes in the ranges of concentrations used against human HEPG- 2 cancer cell line are shown in **Figure 4.**

standard	Complex **(2)**	Complex **(4)**	Complex **(9)**	Complex **(10)**	Complex **(13)**
18.89	52.33	41.17	81.46	37	62.86



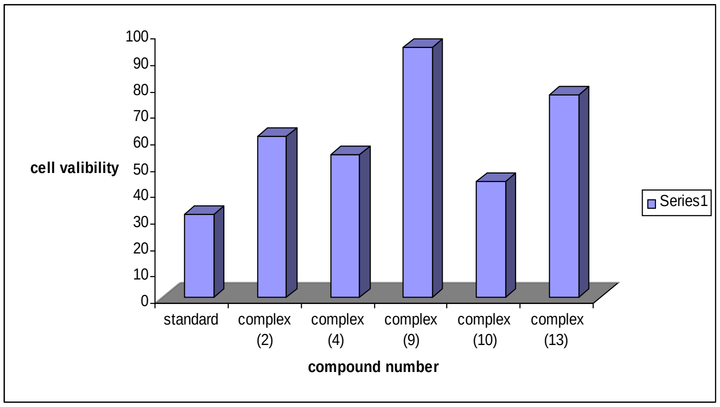
Chemotherapeutic effect of complexes **(2), (4), (9), (10)** and **(13)** against HEPG - 2 liver cell line at 25 µg

standard	Complex **(2)**	Complex **(4)**	Complex **(9)**	Complex **(10)**	Complex **(13)**
21.19	60.67	53.83	94.72	43.67	76.72



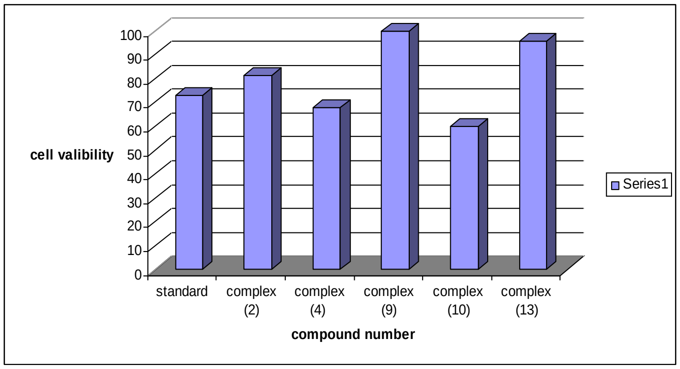
Chemotherapeutic effect of complexes **(2), (4), (9), (10)** and **(13)** against HEPG - 2 liver cell line at 12.5 µg

standard	Complex **(2)**	Complex **(4)**	Complex **(9)**	Complex **(10)**	Complex **(13)**
31.18	60.67	53.83	94.72	43.67	76.73



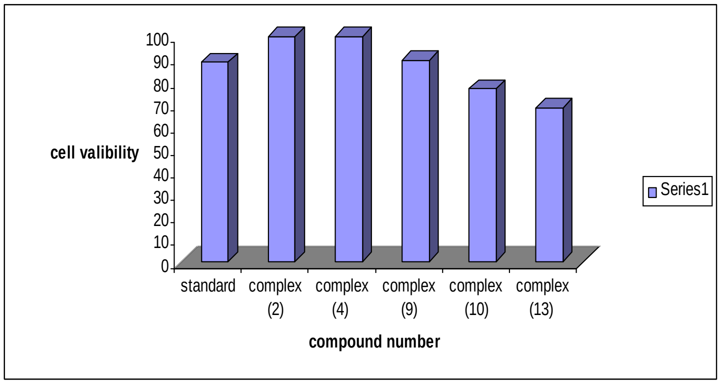
Chemotherapeutic effect of complexes **(2), (4), (9), (10)** and **(13)** against HEPG - 2 liver cell line at 6.5 µg

standard	Complex **(2)**	Complex **(4)**	Complex **(9)**	Complex **(10)**	Complex **(13)**
73.12	81.17	68	100	60.17	95.57



Chemotherapeutic effect of complexes **(2), (4), (9), (10)** and **(13)** against HEPG - 2 liver cell line at 3.125 µg

standard	Complex **(2)**	Complex **(4)**	Complex **(9)**	Complex **(10)**	Complex **(13)**
88.5	100	100	89.33	76.67	68.33



Chemotherapeutic effect of complexes **(2), (4), (9), (10)** and **(13)** against HEPG - 2 liver cell line at 1.56 µg

Figure 4

References

[1] Burgess K.; Chen J, In Solid-Phase Organic Synthesis; Ed. John Wiley & Sons: New York, 2000;Chapter 1.

[2] Greenhill J.V.; Lue L, In Progress in Medicinal Chemistry; Ellis GP; Luscombe DK, Eds.; Elsevier Science: New York, 1993; 30, Chapter 5.

[3] Schneider S.E.; O'Neil S.; Anslyn E.V., J. Am. Chem.Soc. 2000, 122, 542.

[4] Hannon C.L.; Anslyn E.V., Bioorganic Chemistry Frontiers; Springer: Berlin, 1993, 3, 193 .

[5] Dodd D.S.; Kozikowski AP, Tetrahedron Lett., 1994, 977, 35 .

[6] (a) Poss M.A., Iwanowicz E., Reid J.A., Lin J., Tetrahedron Lett., 1992, 33, 5933; (b) Schneider S.E., Bishop P.A., Salazar M.A., Bishop O.A., Anslyn E.V., Tetrahedron, 1998, 54, 15063 .

[7] Schug K.A., Linder W., Chem.Rev., 2005, 105, 67 .

[8] Best M.D., Tobey S.L. and Anshyn E.V., Coord.Chem., Rev., 2003, 240, 3.

[9] Meurling L., Marquez M., Nilson S. and Holmberg A.R., Int. J. of Oncol., 2009, 35, 281 .

[10] Brozozowski Z., Saczewski F. and Slawinski J, Eur. J. of Med. Chem., 2007, 42, 1218 .

[11] Khaled K.F., Int. J. Electrochem., Sci., 2008, 3, 462 .

[12] Benemann O., Haase R., Jesser A., Beschitt T., Doring A., Kuckling D., Vieira I., Florke U. and Herres-Pawlis S., Eur. J. Inorg. Chem., 2011, 2367 .

[13] Zhakouskaya A, Gorls H, Vaughan G and Plass W, Inorg. Chem. Comm., 2005, 8, 1145

[14] Wilson M.D., Yau J.M., Robinson J.H., Wyse D.D. and Desouza B.M., J. Phar.Macol. Exp. Ther., 1933, 266, 1454 .

[15] Davidoff F, J. Biolog. Chem., 1971, 246, 4017.

[16] Kumar P and Brumme R, Nut. Cyc. in Agroco., 1999, 53, 133.

[17] Ube H., Uraguchi D. and Terada M., J. Organomet. Chem., 2007, 692, 545 .

[18] El-Tajoury A.N., El-ajaily M.M., Maihub A.A., S.F. Ben Geweirif, Pure & app. J., 2006, 5, 108 .

[19] Maihub A.A., El-ajaily M.M., Filog S.M., Al-Abhath Al-Yarmouk J., 2005,14, 119. El-ajaily M.M. et al., Int.J. PharmTech Res., 2009, 4, 1103 .

[20] Boghaei D.M., Lashanizadegan D.M., Syn. React. Inorg. Met. Org. Chem., 2000, 30, 1393 .

[21] Asadia, M. and Setoodeh Khaha M., J. Iran. Chem. Soc., 2010,7, 875 .

[22] Rizwana B. and Santha S.L., Inter. J. Chem. Tech. Res., 2012, 4, 464.

[23] Oakley S.H., Soria D.B., Coles M.P. and Hitchcock P.B., polyhedron, 2006, 25, 1247 .

[24] A.I. Vogel," A text Book of Quantitative Inorganic Analysis" (Longman Suffolk, 1961).

[25] J. Lewis and R.G. Wilkins, "Modern Coordination Chemistry, Interscience, New York, 1960, P. 403.

[26] Skehan, P., Storeng, R.,et al, J. Natl. Cancer Inst., 1990, 82, 1107 .

[27] El-Tabl, A.S. and El-Enein, S.A., J. Coord. Chem., 2004, 57, 281 .

[28] Fouda, M. F. R., ABD- El- Zaher, M. M., Shakdofa, M. M., El- Sayed, F. A., Ayad, M. I. and El- Tabl, A. S., J. Coord. Chem., 2008, 61, 1983 .

[29] El- Mariah, F., J. Chem. Resa., 2009, 588 .

[30] Mayadevi, S., Prasad, P. G. and Yusuff, K. K. M., Synth. and Rea Inorg. and Met. Org. Chem., 2003, 33, 481 .

[31] El-Tabl, A. S., El-Bahnasawy, R. M., Shakdofa, M. M. E. and Abdalah, A. El-Deen, J. Chem., Reas., 2010, 88 .

[32] Baligar, R. S. and Revankar, V. K., J. Serb. Chem. Soc., 2006, 71, 1301 .

[33] Geary, W. J., Coord. Chem. Rev., 1971, 7, 81.

[34] El- Tabl, A. S., Issa, R. M. and Morsi, M. A., Trans. Met. Chem., 2004, 57, 265 .

[35] El-Tabl, A. S., Trans. Met. Chem., 1997, 22, 400.

[36] Tas, E., Aslanoglu, M., Kilic, A. and Tara, Z., Trans. Met. Chem., 2005, 30, 758 .

[37] Chandra, S. and Kumar, U., Spectrochim. Acta part, 2005, 61, 219 .

[38] Nakamoto, S. K., Infrared and Raman spectra of Inorganic and Coordination Compounds, 3 rded, John Wiley & Sons, New York, 1977, pp. 244- 247.

[39] Youssef, N. S., El-Zahery, E. and El-Seidy, A. M. A., phosphorous, sulfur and silicon, 2010, 185, 785 .

[40] El-Tabl, A. S., El-Saied, F. A., Al-Hakimi, A. N., and plass, W., Spectro Chemica Acta, 2008, 67, 265.

[41] El-Tabl, A. S., El-Baradie, K. and Issa, R. M., J. Coord. Chem., 2003, 56, 1113.

[42] El-Tabl A. S., J. Res., 2002, 529 .

[43] El-Tabl, A. S. and Issa, R. M., J. Coord. Chem., 2004, 57, 509.
[44] El-Tabl, A. S., El-Saied, F. A. and Al-Hakimi, A. N., J. Coord. Chem., 2008, 61, 2380.
[45] Kuska, H. A. and Rogers, M. T. “ Coordination chemistry” A. E. Martell, Ed: Van Nostrad Reihold Co: New York, 1971.
[46] Roenson, S. D. and Uttly, M. F., J. Chem. Soc. Dalton Trans., 1973, 1912.
[47] El-Bahnasawy, R. M., El-Tabl, A. S., El-shereafy, E., Kashar, T. I. and Issa, Y. M., polish J. Chem., 1999, 73,1925 .
[48] Al-Hakimi, A. N., Shakdofa, M. M. E., El- Seidy, A. M. A. and El-Tabl, A. S., J. Korean Chem. Soc., 2011, 55, 418 .
[49] Lai, R. A. and Kumar, A., Ind. J. Chem., 1999, 38A, 839 .
[50] Raman, N., Pitchaikani, Y. and Kulandaisamy, A., Proc. Indian Acta. Sci (Chem. Sci), 2001,133, 183
[51] Gudasi, K. B., Patel, S. A., Vadvavi, R. S., Shenoy, R. V. and Nethaji, M., Transition Met. Chem., 2006, 31, 586.
[52] Nag, J. K., Pal, S. and Sinha, C., Transition Met. Chem., 2005, 30, 523 .
[53] Murukan, B. and Mohanan, K., Transition Met. Chem., 2006, 31, 441 .
[54] Gudasi, K. B., Patil, S. A., Rashmi, R. S., Shenoy, V. and Nethaji, M., Trans. Met. Chem., 2006, 31, 580
[55] Ainscough, E. W., Brodie, A. M., Dobbs, A. J., Ranford, J. D. and Waters, J. M., Inorg. Chem. Acta, 1998, 267, 27 .
[56] Sallam, S. A., Orabi, A. S., El-Shetary, B. A. and Lentz, A., Trans. Met. Chem., 2002, 27, 447 .
[57] Ravinder, V., Swamy, S. J., Srihari, S. S. and Longaiah, P., Polyhedron, 1985, 4, 1511 .
[58] Atkin, R., Brewer, G., Kokot, E., Mochier, G. M. and Sinn, E., Inorg. Chem., 1985, 24, 127 .
[59] Takkar, N. V. and Bootwala, S. Z., Indian J. Chem., 1995, 34A, 370 .
[60] Chinvmia, G. C., Phillips, D. J. and Rae, A. D., Inorg. Chim. Acta, 1995, 238, 197.
[61] Krishna, C. H., Mahapatra, C. M. and Dush, K. C., J. Inorg. Nucl. Chem., 1997, 39, 1253 .
[62] Parihari, R. K., Patel, R. K. and Patel, R. N., J. Ind. Chem. Soc., 2000, 77, 339 .
[63] Sabin, F. and Vogler, A., Monta. Chem., 1992, 123, 705 .
[64] Singh, N. K. and Singh, S. B., Transition Met. Chem., 2001, 26, 487 .
[65] Abu El-Reash, G. M., Ibrahim, K. M. and Bekheit, M. M., Trans. Met. Chem., 1990,15, 148.
[66] Lever, A. B. P., Inorganic Electronic Spectroscopy, Elsevier pub. Company, New York, 1968, p. 275.
[67] El-Tabl, A. S., Bull. Korean Chem. Soc., 2004, 25, 1.
[68] El-Tabl, A. S., Shakdofa, M. M. E. and El-Seidy, A. M. A., J. Korean Chem. Soc., 2011, 55, 603.
[69] El-Boraey, H. A. and El-Tabl, A. S., polish J. Chem., 2003, 77, 1759.
[70] El-Tabl, A. S., Trans. Met. Chem., 1998, 23, 63 ..
[71] Procter, I. M., Hathaway, B. J. and Nicholls, P. N., J. Chem. Soc. (A), 1969,1678 .
[72] Nickless, D. E., Power, M. J. and Urbach, F. L., Inorganic Chem., 1983, 22, 3210 .
[73] Ray, R. K., Inorg. Chim, Acta, 1990,174, 257 .
[74] El-Tabl, A. S., J. Chem. Reas., 2004, 19 .
[75] Kivelson, D. and Neiman, R., J. Chem. Phys., 1961, 35, 149 .
[76] Smith, D. W., J. Chem. Soc. A, 1970, 3108 .
[77] Bhadbhade, M. M. and Srinivas, D., Inorg. Chem., 1993, 32, 2458 .
[78] Symons, M. C. R. “ Chemical and Biological Aspects of Electron Spin Resonance, Van Nostrand Reinhold, Wokingham 1979.
[79] Natarajian, C., Shanthi, P., Athappan, P., Murugesan, R., Trans. Met. Chem., 1992, 17, 39 .
[80] Bertrand, J. A., Black, T. D., Eller, P. G., Helm, F. T. and Mahmood, R., Inorg. Chem., 1976, 15, 2965.
[81] El-Tabl, A. S. and Imam, S. M., Trans. Met. Chem., 1997, 22, 259.
[82] Gaber, M. and Ayad, M. M., Thermochim. Acta, 1991,176, 21.
[83] El-Tabl, A. S. and Abou-Sekkina, M. M., polish J. Chem., 1999, 73, 1937 .
[84] Illan – Cabeza, N. A., Garcia – Garcia, A. R., Moreno – carretero, M. N., Martinez – Martos, J. M. and Ramirez – exposito, M. J., J. Inorg. Biochem., 2005, 99, 1637 .
[85] Hall, I. H., Lee, C. C., Ibrahim, G., Khan, M. A. and Bouet, G. M., Appl. Organomet. Chem., 1997, 11, 565.

[86] Feng, G., Mareque-Rivas, J.C., Rosales, R.T. and Williams, N.H., J. Am. Chem. Soc., 2005,127, 13470 .
[87] Mareque, J. C., Prabaharan, R. and Parsons, S., Dalton Trans., 2004, 1648.
[88] Bauer-Siebenlist, B., Meyer, F., Farkas, E., Vidovic, D. and Dechert. S.,J. Chem. Eur., 2005,11, 4349 .
[89] Gaetke, L. M. and Chow, C. K., Toxicology, 2003,189, 147 .
[90] Rouzer, C. A., Chemical Research in Toxicology, 2010, 23, 1517.

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