



4N Donor Atoms Moiety of Transition Metal Complexes of a Schiff base Ligand: Synthesis, Characterization and Biological Activities Study

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Abstract

New Schiff base ligand [H₂L] with 4N donor atoms moiety was prepared by reacting amine derivative of o-phenylenediamine hydrazide moiety with benzaldehyde. Co(II), Ni(II), Cu(II) and Zn(II) of the new Schiff base were prepared by using a molar ratio of ligand: metal as (1:1). The structure of the Schiff base and the prepared complex was determined by ¹H NMR, UV-Vis, IR, Mass spectrometry and molar conductivity. The thermal stability of the complexes had been studied by TGA. The spectral statement displays that the ligand behaves as bidentate ligand. On the basis of the spectral studies, reveal that an octahedral geometry had been assigned for all complexes. The Anti-proliferative effect was screened against human hepatocellular liver carcinoma cell line (HepG2) and antimicrobial activity had been inspected. Result points that complexes demonstrate the increase cytotoxicity in proliferation to cell lines as compared to free ligand.

Keyword: complexes; spectral analyses; antimicrobial; anti-proliferative

1. Introduction

There is a considerable increase in the use of complexes for anti proliferative treatment after the accidental discovery of the biological activity of platinum complex, cisplatin, in 1965 by Rosenberg [1]. In recent years, many studies associated with metal-based drugs show promising biological activity and are of great interest in chemistry and biology [2]. Literature survey revealed that substituted heterocyclic upon reaction with transition metal salts form complexes that show enhanced physiochemical and pharmacological properties [3, 4]. Hetero aromatic moiety on combination with a positive charged metal centre leads to complexes that show well defined geometries, which can easily interact with biomolecules [5]. Schiff base metal complexes have acknowledged considerable interest because of their brilliant coordination potential and diverse pharmacological properties, notable for antibacterial, antifungal, antitumor activities [6 –8]. Metals like cobalt, nickel and copper have great affinity for coordination because of their smaller size, higher nuclear charge. To the best of our knowledge no work has been reported on the synthesis of complexes of new Schiff base derived from o- phenylenediamine hydrazide moiety and benzaldehyde. A new Schiff base ligand [H₂L] and its metal complexes were

prepared and characterized by ¹H NMR, mass, IR, spectrum and analysis data. The synthesized complexes were screened for their in vitro antiproliferative effect against HepG2 cell line and their antimicrobial activity has been deliberated.

2. 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 specified at the Analytical Unit of Cairo University, Egypt. A standard method [gravimetric] was used to determine metal (I)/(II)/(III) ions [9]. All complexes were dried under vacuum over P4O10. The IR spectra were measured as KBr and CeBr pellets using a Perkin-Elmer 683 spectrophotometer (4000-200 cm⁻¹). Electronic spectra were recorded on a Perkin-Elmer 550 spectrophotometer. The conductance of (10⁻³ M DMF) of the complexes were deliberated at 25°C with a Bibby conductimeter type MCl. ¹H-NMR spectrum of the ligand (1) was obtained with Perkin-Elmer R32-90-MHz spectrophotometer using TMS as internal standard. Mass spectra ligand (1) and Zn(II) (8) were recorded using JEULJMS-AX-500 mass spectrometer provided with data system. The thermal analyses (DTA and TGA) were carried out in air on a

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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 [10]. The magnetic moments were calculated from the equation: $\mu_{\text{eff}} = 2.828 \sqrt{n(n+2)}$. 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 the ligand and its complexes confirmed their purity.

Table 1. Analytical and physical data of the ligand [H₂L] and its metal complexes.

No.	Ligands/Complexes	Color	FW	M.P (°C)	Yield (%)	Anal./Found (Calc.) (%)					Molar conductance Λ_m ($\Omega^{-1}\text{cm}^2\text{mol}^{-1}$)
						C	H	N	M	Cl	
(1)	[H ₂ L] C ₂₂ H ₁₈ N ₄ O ₂	Brown	370.4	185	80	71.35 (71.34)	4.72 (4.90)	15.25 (15.13)	-	-	-
(2)	[(H ₂ L)Cu(OAc) ₂].2H ₂ O C ₂₆ H ₂₈ CuN ₄ O ₈	Dark green	588.07	>300	78	52.89 (53.10)	4.76 (4.80)	9.94 (9.53)	10.66 (10.81)	-	9
(3)	[(H ₂ L)Ni(OAc) ₂].3H ₂ O C ₂₆ H ₃₀ N ₄ NiO ₉	Dark green	601.23	>300	65	52.05 (51.94)	4.88 (5.03)	9.11 (9.32)	9.84 (9.76)	-	11
(4)	[(H ₂ L)Co(OAc) ₂].3H ₂ O C ₂₆ H ₃₀ CoN ₄ O ₉	Dark green	601.47	>300	72	51.65 (51.92)	4.85 (5.03)	9.25 (9.30)	9.66 (9.74)	-	12
(5)	[(H ₂ L)Mn(OAc) ₂].H ₂ O C ₂₆ H ₂₆ MnN ₄ O ₇	Pale brown	561.45	>300	71	55.15 (55.62)	4.60 (4.67)	9.54 (9.98)	9.56 (9.79)	-	15
(6)	[(L)Fe(Cl)(H ₂ O)].3H ₂ O C ₂₂ H ₂₄ ClFeN ₄ O ₆	Brown	531.75	>300	79	49.45 (49.69)	4.38 (4.55)	10.30 (10.54)	10.29 (10.50)	6.24 (6.67)	17
(7)	[(L)Cr(Cl)(H ₂ O)].2H ₂ O C ₂₂ H ₂₂ ClCrN ₄ O ₅	Dark green	509.88	>300	74	51.52 (51.82)	4.23 (4.35)	10.47 (10.99)	9.98 (10.20)	6.82 (6.95)	10
(8)	[(H ₂ L)Zn(OAc) ₂].2H ₂ O C ₂₆ H ₂₈ N ₄ O ₈ Zn	Pale brown	589.91	>300	65	52.57 (52.94)	4.58 (4.78)	9.63 (9.50)	11.21 (11.08)	-	8

Preparation of metal complexes (2) - (8)

A filtered ethanolic (100 cm³) of Cu(OAc)₂.2H₂O (2.68 g, 0.025 mol) was added to an ethanolic (100 cm³) of the ligand, (1) (5.0 g, 0.025 mol) [1L:1M] complex (2), (3.36 g, 0.025 mol) of Ni(OAc)₂.4H₂O complex (3) [1L:1M], (3.34 g, 0.025 mol) of Co(OAc)₂.4H₂O complex (4) [1L:1M], (3.30 g, 0.025 mol) of Mn(OAc)₂.4H₂O complex (5) [1L:1M], (3.64 g, 0.025 mol) of FeCl₃.6H₂O complex (6) [1L:1M], (3.59 g, 0.025 mol) of CrCl₃.6H₂O complex (7) [1L:1M], (2.96 g, 0.025 mol) of Zn(OAc)₂.2H₂O complex (8) [1L:1M]. The mixture was refluxed with stirring for 3 hours, depending on the nature of metal ions; the coloured complex was filtered off, washed with ethanol and dried under vacuo over P4O10.

Anti proliferative activity

It is estimated that the anti-proliferative activity of this ligand and certain complexes has an effect on human liver cancer cell line (HEPG-2 cell line) in the concentration range 0.1–100 µg/l. The antitumor activity was measured in vitro for the prepared complexes according to Sulfo-Rhodamine-B-stain (SRB) assay using the published method [11]. Cells were plated in 96-multiwell plate (104

Preparation of the ligand and its metal complexes

Preparation of the ligand, [H₂L] (1)

Ligand (1) was prepared by refluxing with stirring (1: 2) molar ratio of o- phenylene diamine (10 g, 0.919 mol) with thio urea (13.98 g, 0.184 mol) in ethanol (100 cm³) for 2 hours. The product (8 g, 0.042 mol) obtained was added to bezaldehyde (8.74 g, 0.082 mol) by (1: 2) molar ratio then the brown product was filtered off, washed several times with ethanol and dried in vaccum over P4O10. Analytical data are given in Table (1).

cells/well) for 24 hours before treatment with the metal complexes to allow attachment of cell to the wall of the plate. Different concentrations of the metal complexes in DMSO (1.56, 3.125, 6.25, 12.5, 25 and 50 µg/ml) were added to the triplicate cell monolayer. Monolayer cells were incubated with the metal complexes for 48 hours at 37 °C using 5% CO₂. After 48 hours, cells were fixed, washed and stained with Sulfo-Rhodamine-B-stain. Excess stain was washed with acetic acid and the attached stain was recovered with Tris EDTA buffer (10 mM Tris HCl + 1 mM Disodium EDTA, PH 7.5-8). Color intensity was measured by ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve of each tumor cell line after addition of the specified metal complex. Irinotecan Hydrochloride and Sorafenib are used as standard drugs.

Antifungal activity

Fungicidal activity of tested complexes was assessed against *Aspergillus niger* by disc diffusion method.

Antibacterial activity

Antibacterial activity of the tested metal complexes was assessed against Gram Positive bacteria (*S.*

pneumonine and *B. subtilis*) and Gram Negative bacteria (*E. coli* and *P. aeruginosa*) by disc diffusion method. Linezolid was used as a positive control and solvent control (12 mm) was also used to know the activity of the solvent.

Testing method

Base layer was obtained by pouring about 10-15 ml of base layer medium into each sterilized petri dishes and were allowed to attain at room temperature. Overnight grown subcultures of fungi were mixed with layered media and immediately poured into petri dishes containing the base layer and then allowed to attain at room temperature. Antifungal discs having diameter of 6 mm, soaked in test solution, were dispensed on to the surface of inoculated agar plates. Each disc must be pressed down to ensure its complete contact with the agar surface. These plates were subsequently incubated at 37 °C for 36 hours. The zone of inhibition, if any, was measured in mm for the particular complex. Clotrinazole was used as positive control and solvent

control (12 mm) was also used to know the activity of the solvent.

3. Results and Discussion

The complexes are stable at room temperature, non-hygroscopic, insoluble in water and partially soluble in mutual organic solvents such as CHCl_3 , but soluble in DMF and DMSO. The analytical and physical data of the ligand and its complexes are given in Table (1), spectral data Tables (2 - 6) are concordant with the proposed structures, Figure (1). The molar conductance's are in the (17 - 8) $\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$ range, Table (1), reference to non-electrolytic property [15]. The high value of some complexes indicates that they can be partially dismantled in DMF. Many attempts had been made to grow a single crystal but unfortunately, they were failed. Reaction of ligand (1) with metal salts using (1L:1M) molar ratio in ethanol gives complexes (2) - (8). The composition of the formative complexes depends on metal ions, the medium of the reaction and the molar ratio.

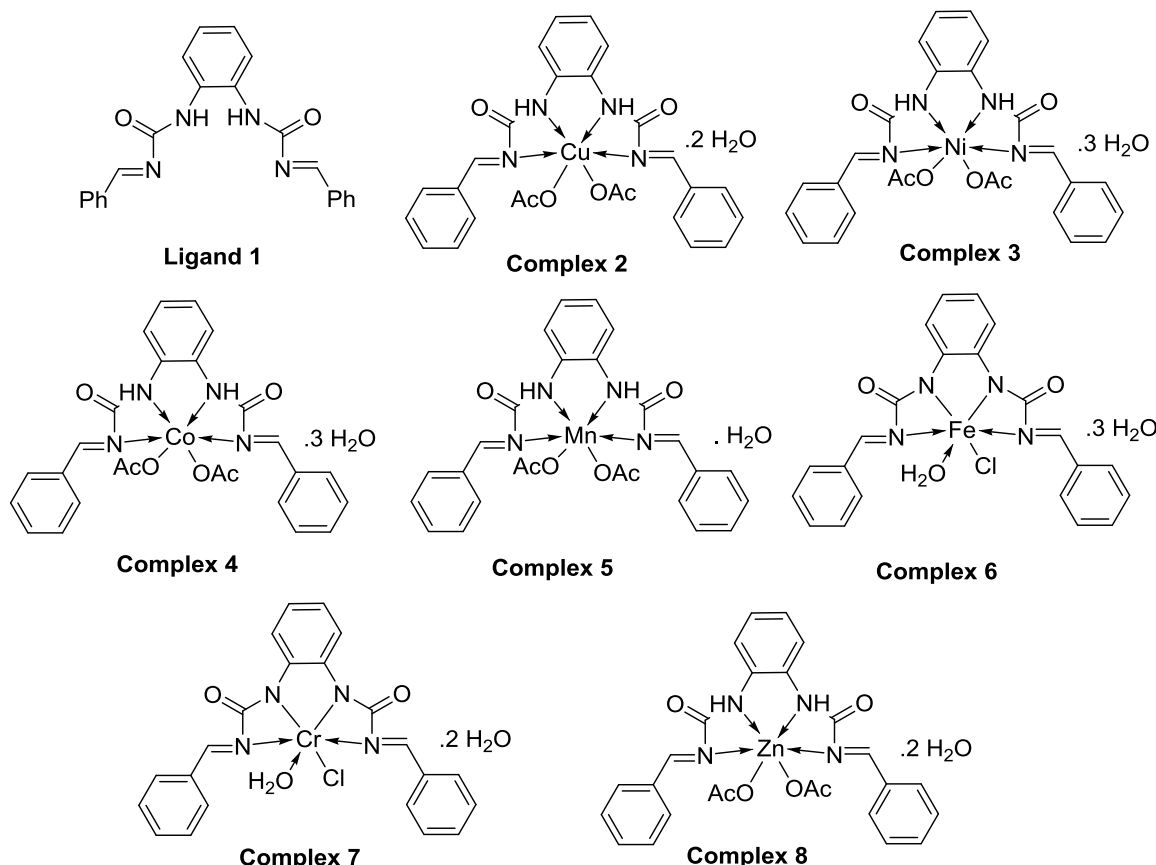


Figure (1):- suggested structures of ligand, (1) and its metal complexes

Metal complex	50 mg/ml	25 mg/ml	12.5 mg/ml	6.25 mg/ml	3.125 mg/ml	1.56 mg/ml
Ligand (1)	45.42	56.56	68.89	72.63	79.36	83.78
Complex (2)	8.42	17.18	20.72	30.25	67.84	74.44

Complex (3)	7.15	13.56	14.26	28.23	64.33	72.29
Complex (4)	12.25	19.04	23.50	33.09	71.38	76.35
Complex (5)	15.69	18.62	25.78	31.26	76.38	81.12
Complex (8)	36.42	56.58	72.19	75.34	100	100
Standard drug	26.21	18.89	21.19	31.18	73.12	88.5

¹H-NMR spectra

The ¹H-NMR spectra of the ligand (1) and its Zn(II) complex (8) in deuterated DMSO revealed signals consistent with the proposed structure as listed in Table (2). The ligand shows peaks at 4.52 and 3.81 ppm and is called the NH proton [16 -18]. The appeared peak at 2.18 ppm, is due to (CH) group [16, 18, 21]. Also, the spectrum showed a set of peaks as multiples in the 6.63 - 7.89 ppm range which are referred to the protons of aromatic rings [19, 20,

22]. On the other hand, in a various Zn(II) complex (8), the signal referred to the (NH) protons this lower value, may be due to hydrogen bonding involving the amino (NH) group or due to indicating its coordination the Zn(II) ion. A set of peaks appeared as multiples in the 6.24 - 7.78 ppm range corresponding to protons of aromatic rings [22]. The signals appeared at 2.08 ppm range were referred to (CH) group [22]. The appearance of new signal at 1.87 ppm is due to protons of methyl group of coordinated acetate groups [23, 24].

Table 2. Mass spectra of ligand(1) and its Zn(II), complex (8)

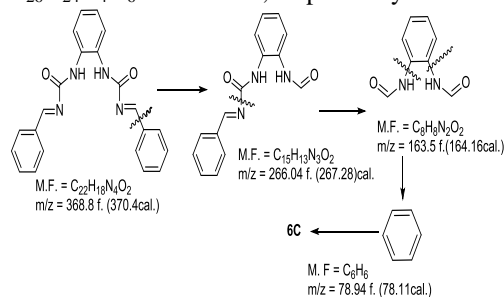
Compound No.	Fragment	m/z	Rel. Int.
(1)	C ₆ H ₅	77	25
	C ₈ H ₇ N ₂ O	147	30
	C ₉ H ₈ N ₃ O ₂	190	45
	C ₁₀ H ₉ N ₄ O ₂	217	20
	C ₁₆ H ₁₃ N ₄ O ₂	293	35
(8)	C ₂ H ₃ O ₂	59	18
	C ₆ H ₅	77	13
	C ₈ H ₈ N ₂ O	148	17
	C ₈ H ₈ N ₂ OZn	212	22
	C ₁₀ H ₁₀ N ₄ O ₂ Zn	282	26
	C ₁₄ H ₁₅ N ₄ O ₆ Zn	399	30
	C ₂₀ H ₁₉ N ₄ O ₆ Zn	475	28
	C ₂₆ H ₂₄ N ₄ O ₆ Zn	552	30

Table 3. IR frequencies of the bands (cm⁻¹) of ligand [H₂L] and its metal complexes and it's assignments.

No.	ν(H ₂ O)	ν(H-bond.)	N(NH)	ν(C=O)	ν(C=N)	ν(Ar)	ν (OAc)	ν(M-O)	ν(M-N)	ν(M-Cl)
(1)	-	3610- 3205 3190- 2850	3180, 3165	1735, 1720	1617, 1605	1575, 755 1546, 744	-	-	-	-
(2)	3540 -3120	3590 – 3175	3175, 3135	1730, 1710	1603, 1590	1560, 753 1555, 740	1475, 1320	543	435	-
(3)	3555 -3215	3610 – 3185 3170	3168, 3135	1715, 1705	1614, 1607	1580, 757 1565, 740	1460, 1315	572	444	-
(4)	3560-3180	3588 – 3150	3174, 3140	1719, 1705	1616, 1605	1584, 760 1564, 732	1458, 1330	566	465	-
(5)	3544 -3160	3592 –3175 3165 –2875	3145, 3125	1721, 1710	1614, 1609	1569, 748 1554, 735	1465, 1320	549	430	-
(6)	3630 -3214 3200 -3050	3585- 3170 3160- 2690	3175, 3130	1730, 1717	1615, 1605	1588, 756 1560, 736	-	565	455	410
(7)	3610- 3250 3235- 2980	3575 – 3164	3168, 3145	1725, 1716	1612, 1607	1580, 754 1540, 722	-	545	474	430
(8)	3525 – 3145	3590- 3120 3100- 2805	3157, 3145	1726, 1708	1613, 1609	1580, 757 1545, 720	1445, 1344	578	420	-

Mass spectra

The electron impact (EI) spectrum of the free ligand revealed a molecular ion peak at 370.4 amu, which is haphazard with the formula weight of the ligand and supports the identity of the Structure. Furthermore, the fragments observed at 77, 147, 190, 217 and 293 (m/z) correspond to C_6H_5 , $C_8H_7N_2O$, $C_9H_8N_3O_2$, $C_{10}H_9N_4O_2$ and $C_{16}H_{13}N_4O_2$ moieties, respectively. While, the Zn(II) The complex spectrum (8) shows a peak at 589.9 amu, which corresponds to the formula weight of the complex. Furthermore, the peaks observed at 59, 77, 148, 212, 282, 399, 475 and 552 are due to $C_2H_3O_2$, C_6H_5 , $C_8H_8N_2O$, $C_8H_8N_2OZn$, $C_{10}H_{10}N_4O_2Zn$, $C_{14}H_{15}N_4O_6Zn$, $C_{20}H_{19}N_4O_6Zn$ and $C_{26}H_{24}N_4O_6Zn$ moieties, respectively.



Scheme 1:- Proposed mass fragmentation of ligand (1).

IR spectra

The IR spectra of the ligand [H2L], (1) and its complexes (2) - (8) are given in Table (3). The spectrum data of the ligand [H2L] (1) pointed one band at 3180, 3165 cm^{-1} band which may be referred to $\nu(NH)$ amino group, the appearance of two broad bands in the 3610- 3205 cm^{-1} and 3190 – 2850 cm^{-1} ranges, commensurate the presence of two types of intra-and intermolecular hydrogen bonding [25]. Also, the spectrum showed bands at (3180, 3165), (1735, 1720) and (1617, 1605) cm^{-1} , which were referred to $\nu(NH)$, $\nu(C=O)$ and $\nu(C=N)$ imine, respectively [20, 26, 27]. The bands appeared at 1530 and 640 cm^{-1} were referred to the o-substituted aromatic ring [29]. The IR spectra of the metal complexes displayed that, the $\nu(C=N)$ imine stretching frequency undergone a shift to lower frequency by (2 - 27) cm^{-1} . This shift indicates to coordination of the azomethine nitrogen to the metal ion [30, 31]. The $\nu(C=O)$ of the carbonyl group appeared in the 1735 - 1705 cm^{-1} range. The $\nu(NH)$ band appeared in the 3180 - 3125 cm^{-1} range [16, 33], whereas the bands observed in the 1617 - 1590 cm^{-1} and 1588 - 1540 and 757 - 720 cm^{-1} ranges are due to $\nu(C=N)$ imine and aromatic groups vibrations, respectively [29, 30]. Also, complexes displayed broad bands in the 3610 - 3100 and 3205 - 2657 cm^{-1} , ranges, corresponding to intra-and intermolecular hydrogen bondings [25]. The bands referred to

hydrated and coordinated water molecules appeared in the 3630 - 3145 and 3235 - 2980 cm^{-1} ranges [15, 31 - 36]. The appearance of two characteristic bands in the range 1475 - 1445 and 1344 - 1320 cm^{-1} in spectra of complexes (2), (3), (4), (5) and (8), are attributed to $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$, respectively, indicating the participation of the acetate oxygen in the complex formation [29, 37]. The mode of coordination of acetate group has often been deduced from the magnitude of the observed separation between the $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$. The separation value (Δ) between $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ for complexes (2), (3), (4), (5) and (8) were in the (30 - 24) cm^{-1} range suggesting the coordination of acetate group in a monodentate fashion [29, 37, 38]. Metal complexes (6), (7) showed bands in the 410, 430 cm^{-1} range, assigned to $\nu(M-Cl)$ [40]. The bonding of the metal ions to the ligand through the oxygen and nitrogen atoms is further supported by the presence of new bands in the 572 - 543 and 474 - 420 cm^{-1} ranges, respectively [30, 40, 41 - 44].

Magnetic moments

The magnetic moments for the complexes (2) - (8) were listed in Table (4). Cu(II) complex (2) recorded value 1.72 B.M., corresponding to one unpaired electron in an octahedral structure [37, 40]. Ni(II) complex (3) showed value of 2.76 B.M., indicating an octahedral geometry around the Ni(II) ion [46]. Co(II) complex (4) recorded 3.35 B.M., indicating high spin octahedral Co(II) complexes [16, 47]. Mn(II) complex (5) recorded 4.85 B.M., suggesting high spin octahedral geometry around the Mn(II) ion [16, 47]. complex Fe(III) complex (6) and Cr(III) complex (7) showed values 5.08 and 3.74 B.M., indicating high spin octahedral structure [47]. The lower values of magnetic moments are due to spin-exchange interactions between metal ions. Zn(II) complex (8) showed diamagnetic property.

Electronic spectra

The electronic spectral data for the ligand and its metal complexes in DMF were summarized in Table (4). Ligand in DMF solution showed two bands at 265 ($\epsilon = 6.15 \times 10^{-3} \text{ mol}^{-1} \text{ cm}^{-1}$), 315 ($\epsilon = 7.69 \times 10^{-3} \text{ mol}^{-1} \text{ cm}^{-1}$) and 375 ($\epsilon = 9.36 \times 10^{-3} \text{ mol}^{-1} \text{ cm}^{-1}$) which may be assigned to the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions, respectively [48]. Cu(II) complex (2) showed bands in 255, 323, 389 nm range, these bands are due to intraligand transitions, while, the bands observed in the 420, 581, 660 nm range are assigned to $O \rightarrow Cu$ charge transfer, $2B_1 \rightarrow 2E$ and $2B_1 \rightarrow 2B_2$ transitions, indicating a distorted octahedral structure around the Cu(II) ion [49-51]. Ni(II) complex (3) showed bands at 260, 315, 385, 498, 625, 755 nm, respectively, the first three bands are within the

ligand and the other three bands are attributable to $3A_2g(F) \rightarrow 3T_1g(P)(\square_3)$, $3A_2g(F) \rightarrow 3T_1g(F)(\square_2)$ and $3A_2g(F) \rightarrow 3T_2g(F)(\square_1)$ transitions, respectively, indicating an octahedral Ni(II) complex [49, 52]. The \square_2/\square_1 ratio for the complex is 1.15, which is less than the usual range of 1.5–1.75, indicating a distorted octahedral Ni(II) complex [49, 53]. Co(II) complex (4) showed bands at 250, 325, 390, 550, 617, 730 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 [54]. Mn(II) complex (5) showed bands at 265, 315, 370, 455, 515, 615 nm, respectively, the first three bands are in 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 [55]. Fe(III) complex (6) showed bands at 270, 325, 383, 448, 535, 635 nm, respectively, The first three bands are located in the ligand, while the other three bands are caused by charge transfer and the $6A_1 \rightarrow 4T_1$ transition, which indicates that the octahedral geometry around the Fe(III) ion is distorted [56 - 58]. Cr(III) complex (7) showed bands at 270, 318, 385, 455, 540, 620 nm, respectively. The first three bands are within the ligand and the other 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 [59, 60]. Zn(II) complex (8) shows three bands at 260, 320, 370 nm, which are assigned to intraligand transitions.

Table 4. The electronic absorption spectral bands (nm) and magnetic moment (B.M) for the ligand [H₂L] and its complexes.

No.	λ_{max}^* (□)	μ_{eff} in BM
(1)	265 ($\epsilon = 6.15 \times 10^{-3} \text{ mol}^{-1} \text{ cm}^{-1}$), 315 ($\epsilon = 7.69 \times 10^{-3} \text{ mol}^{-1} \text{ cm}^{-1}$), 375 ($\epsilon = 9.36 \times 10^{-3} \text{ mol}^{-1} \text{ cm}^{-1}$)	-
(2)	255, 323, 389, 420, 581, 660	1.72
(3)	260, 315, 385, 498, 625, 755	2.76
(4)	250, 325, 390, 550, 617, 730	3.35
(5)	265, 315, 370, 455, 515, 615	4.85
(6)	270, 325, 383, 448, 535, 635	5.08
(7)	270, 318, 385, 455, 540, 620	3.74
(8)	260, 320, 370	Dia

* in nm

Table 5. Thermal data for some of metal complexes

Compound	Temp. (°C)	DTA (peak)		TGA(wt.loss)		Assignments
		Endo	Exo	Calc.	Found	
Complex (2)	45	endo	-	-	-	Broken of H-bondings
	90	endo	-	6.13	6.26	Loss of (2H ₂ O) hydrated water molecules
	185	endo	-	21.41	20.69	Loss of coordinated two (OAc) groups
	315	-	Exo	-	-	Melting point
	430 - 660	-	Exo	18.35	17.98	Decomposition process with formation of CuO
Complex (4)	43	endo	-	-	-	Broken of H-bondings
	85	endo	-	8.98	8.53	Loss of (3H ₂ O) hydrated water molecules

Electron spin resonance (ESR)

The ESR spectral data for metal complexes (2-7) are presented in Table (5). Complex (2) showed broad signal in the low and high field regions indicating spin-exchange interactions taking place between Cu(II) ions which is confirmed by the magnetic moment value. The spectra of Cu(II) metal complex are characteristic of species, d⁹ configuration and having axial type of a d(x²-y²) ground state which is the most common for Cu(II) complexes [61, 62]. The metal complexes showed $g_{\parallel} > 2.0023$, indicating octahedral geometry around the Cu(II) ion [63, 64]. The g-values are related by the expression [63, 65], $G = (g_{\parallel} - 2) / (g_{\perp} - 2)$, 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. In addition, the value of $g_{\parallel} / A_{\parallel}$ is considered to be a diagnosis of stereochemistry [66]. The $g_{\parallel} / A_{\parallel}$ values lie just within the range expected for the metal complexes. The orbital reduction factors (K_{\parallel} , K_{\perp} , K), which are a measure of covalency can be calculated [67]. K values Table (5), for the Cu(II) complex (2), indicating covalent bond character [47, 68]. The g-values show considerable covalent bond character [47, 69, 70]. Also, the in-plane σ -covalency parameter, $\alpha_2(\text{Cu})$ suggests a covalent bonding [39, 47, 68]. The metal complexes showed β_{12} values 0.62 indicating covalent bonding character out-of-plane π -bonding [68, 71]. Other metal complexes (3 - 7) show isotropic spectra with $g_{iso} = 2.10, 2.14, 2.15, 2.08$ and 2.007 values, respectively.[43, 62].

	176	endo	-	28.58	28.48	Loss of coordinated two (OAc) groups
	330	exo	-	-	-	Melting point
	430 - 610	-	Exo	17.48	17.82	Decomposition process with the formation of CoO
Complex (6)	50	endo	-	-	-	Broken of H-bondings
	85	endo	-	10.17	10.67	Loss of (3H ₂ O) hydrated water molecules
	135	endo	-	15.73	15.62	Loss of (H ₂ O) coordinated water molecule
	175	endo	-	7.44	7.23	Loss of coordinated one (Cl) group
	340	endo	-	-	-	Melting point
	450 - 660	-	Exo	36.01	35.79	Decomposition process with the formation of Fe ₂ O ₃
Complex (8)	44	endo	-	-	-	Broken of H-bondings
	90	endo	-	6.11	6.03	Loss of (2H ₂ O) hydrated water molecules
	180	endo	-	21.34	21.13	Loss of two (OAc) groups
	320	exo	-	-	-	Melting Point
	455 - 670	-	Exo	18.36	18.22	Decomposition process with the formation of ZnO

Table 6. 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	β ²	β ₁ ²	-2 β	a _d ² (%)
(2)	2.14	2.06	2.08	160	10	16	2.17	19606	23809	0.83	0.38	0.68	0.82	134	0.62	1.32	180	75
(3)	-	-	2.10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(4)	-	-	2.14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(5)	-	-	2.15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(6)	-	-	2.08	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(7)	-	-	2.007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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

Thermal analyses (DTA and TGA)

The thermal curves in the temperature 27-800 °C range for metal complexes (2), (4), (6) and (8) show that the metal complexes are thermally stable up to 50 °C. The weight loss recorded in the 55 - 80 °C range is due to the elimination of hydrated water [74, 75]. Complex (2) showed an endothermic peak at 45 °C, without weight loss corresponding to a loss of hydrogen bonding. Another endothermic peak was observed at 90 °C; with 6.13 % weight loss (Calc. 6.26%) corresponds to the loss of two hydrated water molecules. Another endothermic peak was observed at 185 °C; with 21.41 % weight loss (Calc. 20.69%) corresponds to the loss of two acetate groups. The endothermic peak observed at 315oC is designated as its melting point. Finally, the compound has an exothermic peak at (430-660) °C, with weight loss 18.35% (Calc. 17.98%), corresponding to thermal decomposition with the formation of two CuO molecules. Complex (4) showed an endothermic peak at 43 °C, without weight loss corresponding to the loss of hydrogen bonding. Another endothermic peak was observed at 85 °C, with 8.98 % weight loss (Calc. 8.53%) corresponding to the loss of three hydrated water molecules. Another endothermic peak was observed at 176 °C, with 28.58 % weight loss (Calc. 28.48%) corresponding to the loss of two coordinated acetate groups. The endothermic peak observed at 330 oC is assigned to its melting point. Finally, the compound has an exothermic peak at (430-610) °C, with weight loss 17.48% (Calc. 17.82%), corresponding to thermal decomposition

with the formation of two COO molecules. Complex (6) showed an endothermic peak at 50 °C, without weight loss corresponding to the loss of hydrogen bonding. Another endothermic peak was observed at 85 °C, with 10.17 % weight loss (Calc. 10.67%) corresponding to the loss of three hydrated water molecules. Another endothermic peak was observed at 135°C; with 15.73% weight loss (Calc. 15.62%) corresponds to the loss of a coordinated water molecule. Also, endothermic peak was observed at 175°C, with 7.44% weight loss (Calc. 7.23%) corresponding to the loss of one coordinated chloride molecule. The endothermic peak observed at 340 oC is assigned to its melting point. Finally, the compound has an exothermic peak at (450-660)°C, weight loss 36.01% (calculated 35.79%), which corresponds to thermal decomposition and formation of two Fe2O3 molecules. Complex (8) showed an endothermic peak at 44 °C, without weight loss corresponding to the loss of hydrogen bonding. Another endothermic peak was observed at 90 °C, with 6.11 % weight loss (Calc. 6.03%) corresponds to the loss of two hydrated water molecules. Another endothermic peak was observed at 180 °C, with 21.34 % weight loss (Calc. 21.13%) corresponds to the loss of two coordinated acetate groups. The endothermic peak observed at 320 oC is assigned to its melting point. Finally, the compound showed an exothermic peak at (455 - 670) °C, and the weight was reduced by 18.36% (Calc. 18.22%), corresponding to thermal decomposition with the formation of two ZnO molecules.

4. Antiproliferative activities

The antitumor effect of the ligand (1) and its metal complexes in DMSO were evaluated against human liver cancer cell line (HEPG-2) using Sorafenib as standard drugs, respectively.

The solvent DMSO showed no effect on cell growth [77]. Both the ligand [H2L] (1), and the tested metal complexes showed a strong inhibition effect at ranges of the concentrations used against (HEPG-2) cell line. The order of activity of the metal complexes follows the sequence:-

oNi(II) complex (3) > Zn(II) complex (8) > Cu(II) complex (2) > Mn(II) complex (5) > standard > Co(II) complex (4) [for (HEPG-2) cell line].

• Ni(II) complex (3) demonstrated the highest potency inhibition activity among all tested compounds against and (HepG-2) cell line. Effect of varying concentrations of the metal complexes on their antiproliferative activity was also studied as shown in Figures (2). It is shown that, there is a positive correlation between the surviving fraction ratio of tumor cell lines and the metal complexes concentrations. 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 [77-81]. 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 [82].

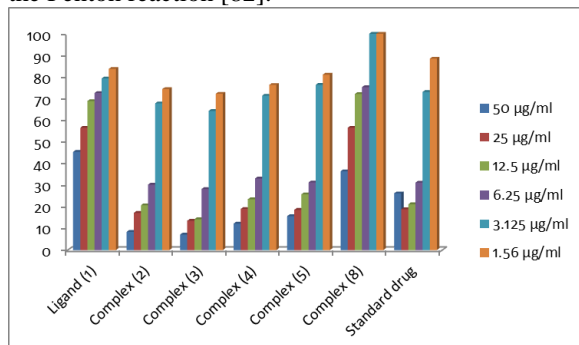
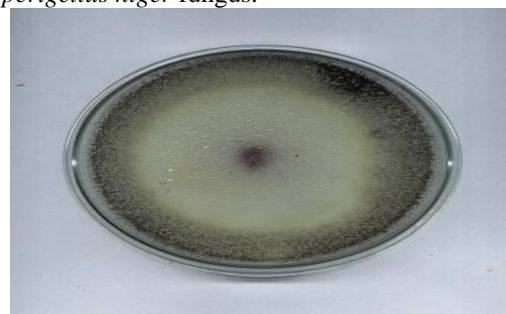


Figure (2): Antiproliferative activity hepatocellular carcinoma (HEPG-2) cell line at different concentrations of ligand (1) and its complexes (2 - 5) and (8)

Antifungal screening

The results of antifungal activity of the ligand and its metal complexes obtained are presented in Figure (3). The ligand is biologically inactive against the fungus, *Asperigellus niger*. On the other hand, complexes (3), (6) and (8) showed more potent fungicidity than the ligand and the standard antifungal drug (Amphotricene B). Hence, they may serve as vehicles for activation of the ligand

as principle cytotoxic species. This enhancement in the activity can be explained on the basis of chelation theory. The variation in activity against microorganisms depends either on the impermeability of the cells of the microbes or differences in ribosome's microbial cells. This antifungal activity of the complexes may be due to the fact that the positive charge of the metal is partially shared with the donor atoms present in the ligands and there is π -electron delocalization over the whole chelated ring. This, in turn, increases the lipophilic character of the metal complex and favors its permeation through the lipid layers of the microorganism membranes. On the other hand, inhibition of microorganisms growth may be due to the inhibition of the glucose uptake, RNA and protein synthesis. This result revealed that the metal complexes induced microbial cell death. The other tested metal complexes (2 - 8) showed no effect on *Asperigellus niger* fungus.



Ni(II) - Complex (3) Inhibition Zone (5.2 Cm)



Cu(II) - Complex (2) Inhibition of Sporylation (4.3 Cm)



Ligand (1) (Negative)

Figure (3): Antifungal activity of compounds (1), (2) and (3) against *Asperigellus niger*.

Complex	<i>S. pneumoniae</i>	<i>B. subtilis</i>	<i>E.coli</i>	<i>P.aeruginosa</i>
Standard	23.8	32.4	19.9	17.3
Ligand (1)	20.6	30.3	18.3	15.77

Complex (2)	19.5	19.8	16.8	14.98
Complex (3)	15.2	14.9	10.23	10.5
Complex (5)	16.3	17.6	11.23	11.78
Complex (6)	16.9	18.2	13.12	13.65
Complex (8)	12.3	12.7	9.33	8.99
DMSO	0	0	0	0

5. Antibacterial screening

The antibacterial activity of the ligand (1) and its metal complexes was studied against two bacterial strains: Gram Positive bacteria (*S.pneumoniae* and *B.subtilis*) and Gram Negative bacteria (*E.coli* and *P.aeruginosa*) strains. The results were compared with the standard drug Tetracycline. The data indicated that, the complexes displayed good activity as antibacterial agents. Cu(II) complex (2), Mn(II) complex (5), Zn(II) complex (8), recorded antibacterial activities against both Gram Positive (*S.pneumoniae* and *B.subtilis*) and Gram Negative (*E.coli* and *P.aeruginosa*) bacteria. It was found that the metal complexes displayed a greater activity than the ligand [83]. The tested Cu(II) complex showed a wide range of bactericidal activities against Gram Negative bacteria. Cu(II) and Mn(II) complexes showed the best activities against *E.coli* and *P.aeruginosa* whereas Zn(II) recorded moderately activities against *E.coli* and *P.aeruginosa*. The relation between the inhibition mean zone of compounds (1), (2), (5), (8) against *Streptococcus pneumoniae*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli* are showed in Figure (4).

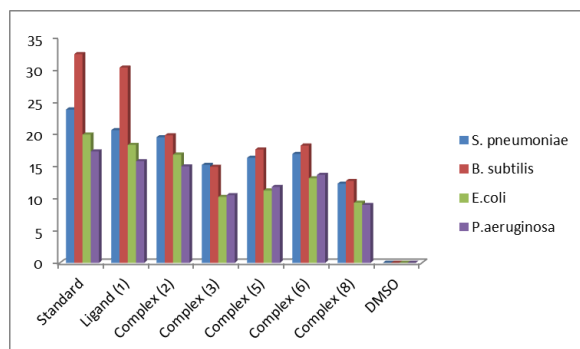


Figure (4): Inhibition mean zone of complexes (2), (3), (5), (6) and (8) against *Streptococcus pneumoniae*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli*

6. Conflicts of interest

The authors have declared no conflict of interest

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