



## Comparative Study for Synthesis of Novel Mn (II), Co (II), Ni (II), Cu (II), Zn (II) and Zr (IV) Complexes under Conventional Methods and Microwave Irradiation and Evaluation of their Antimicrobial and Anticancer Activity



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A NOVEL Schiff base ligand derived from o-Vanillin, N, N-Diethyl-p-phenylenediamine in 1:1 molar ratio, and its metal complexes of Mn (II), Co (II), Ni (II), Cu (II), Zn (II) and Zr (IV) were synthesized by microwave and conventional methods. The ligand and its complexes were characterized by elemental analysis, FT-IR, UV-Vis, <sup>1</sup>HNMR, mass spectroscopy as well as Thermo-Gravimetric Analysis (TGA). The geometry of the proposed Structures of the chelates based on their Electronic spectra, Electron spin resonance (ESR) and magnetic moment. The thermal dehydration and decomposition of the complexes were studied kinetically using the integral method applying the Coats-Redfern and Horowitz Metzger equation. Study the Variation of magnetic susceptibility at Different temperature for Mn (II) and Co (II) complexes. Surface morphologies were analyzed by Scanning electron microscopy (SEM). The ligand and its metal complexes were screened for antimicrobial activity against Gram-positive, Gram-negative bacteria as well as fungi. Cu (II) complex achieved a brilliant inhibition zone diameter against *E. coli* almost reached to the inhibition zone diameter record by standard positive control Cephalothin making it eligible for treatment of *E. coli*. Also, Cytotoxicity Evaluation was applied against two cell lines; human colon carcinoma (HCT) and liver cancer cells (HepG-2).

**Keywords:** Microwave synthesis, metal complexes, Schiff base, o-vanillin, human colon carcinoma (HCT), HepG-2, Thermal analysis, FT-IR, <sup>1</sup>HNMR, Scanning electron microscopy.

### Introduction

Infectious diseases are the major cause of morbidity in the world. The number of multiple drug resistant strains and the appearance of strains with reduced susceptibility to antibiotics is continuously increasing. This situation had provided the impetus to the search for new antimicrobial substances. Schiff bases are compounds containing C=N group. They are often synthesized from amine and aldehyde or ketone.

Schiff bases have gained importance due to their application in many pharmacological activities like antibacterial [1-2], antifungal [3], anti-proliferative [4], antitumor [5], and antipyretic properties. Schiff bases with aryl substituents are more stable and readily synthesized. o-Vanillin is also the most prominent principal flavor and aroma compound in vanilla which is used as a food flavoring agent in foods, beverages, and pharmaceuticals [6]. Because of

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its numerous biological activities such as anti-inflammatory, analgesic, antiviral activities, it is extensively studied in the medicinal field [7-10]. In addition, it also can be used as an efficient herbicide, pesticide bactericides [11] and Schiff bases containing *o*-vanillin moiety form stable complexes with various metal ions. [12-14] Hence, *o*-Vanillin is an optimal candidate for synthesizing various aromatic Schiff bases with significant bioactivities.

## Experimental

### Materials and instrumentation

All purchased chemicals were of Annular AR grade. *o*-vanillin, *N,N*-Diethyl-phenylenediamine sulfate was obtained from Sigma Aldrich and all Metals salts were purchased from ADWIC except Zirconyl oxychloride purchased from Acros organic. The Microwave-assisted synthesis was carried out in a domestic microwave energy output 900 W. Purity of Schiff base ligand and its complexes were detected by using thin-layer chromatography (TLC) [15] technique. Melting points were recorded in open capillaries with Barnstead Thermolyne Mel-temp 1001D Electrothermal Melting Point. Elemental analysis was done on a Perkin Elmer PE 2400 CHN Elemental Analyzer, at the Regional Center for Microbiology and Biotechnology, Al-Azhar University. Metals content were determined by complexometric titration using xylenol orange (XO) as indicator and hexamine as a buffer (pH = 6) [16]. The UV-Vis range (9091-52631 cm<sup>-1</sup>) using Jenway 6715 UV/Vis spectrophotometer at holding company for water and wastewater, all of the compounds dissolved in DMSO before measurements. The FT-IR spectra samples were ground with potassium bromide (KBr) powder. then pressed into a disk and recorded on Agilent Cary 630 FTIR spectrometer at Faculty of Science, Al-Azhar University. <sup>1</sup>HNMR spectra for Schiff base ligand was recorded in deuterated chloroform (CDCl<sub>3</sub>) solution using Bruker's high-performance Avance III NMR spectrometer 400 MHz, Microanalytical Unit - FOPCU - NMR laboratory, Faculty of Pharmacy - Cairo University. Electron impact mass spectrometric spectrum for Zn (II) complex was carried out using a direct inlet unit (DI-50) in the Shimadzu QP-5050 GC-MS at the Regional Center for Mycology and Biotechnology, Al-Azhar University. Magnetic susceptibility of complexes at different temperature were carried out at Faculty of Science, Al-Azhar University. Thermal

analysis measurements (TGA) were carried out with Shimadzu thermal analyzer model 50 at Microanalytical Center, Cairo University. The calculated the Thermodynamics parameter by two methods (Hawetezmetzegar and Coats Redfern). The EPR spectra of the powdered Cu (II) complex recorded at room temperature by X-band EMX spectrometer (Bruker, Germany) using a standard rectangular cavity of ER 4102 with 100 KHz frequency, at National Center for Radiation Research and Technology, Egyptian Atomic Energy Authority. The morphology of the complexes was examined using JEOL-JSM-6390 OLA Analytical scanning electron microscopy (SEM) at holding company for water and wastewater. Schiff base ligand and their metal complexes were screened for in-vitro antibacterial activity against two species of Gram-positive bacteria and two species of Gram-negative bacteria as well as two species of fungi. Also, Cytotoxicity evaluation was applied against two cell lines; human colon carcinoma (HCT) and liver cancer cells (HepG-2).

*Synthesis of Schiff base ligand. (E)-2-(((4-(diethylamino) phenyl) imino) methyl)-6-methoxy phenol sulfate (OV-DPD).*

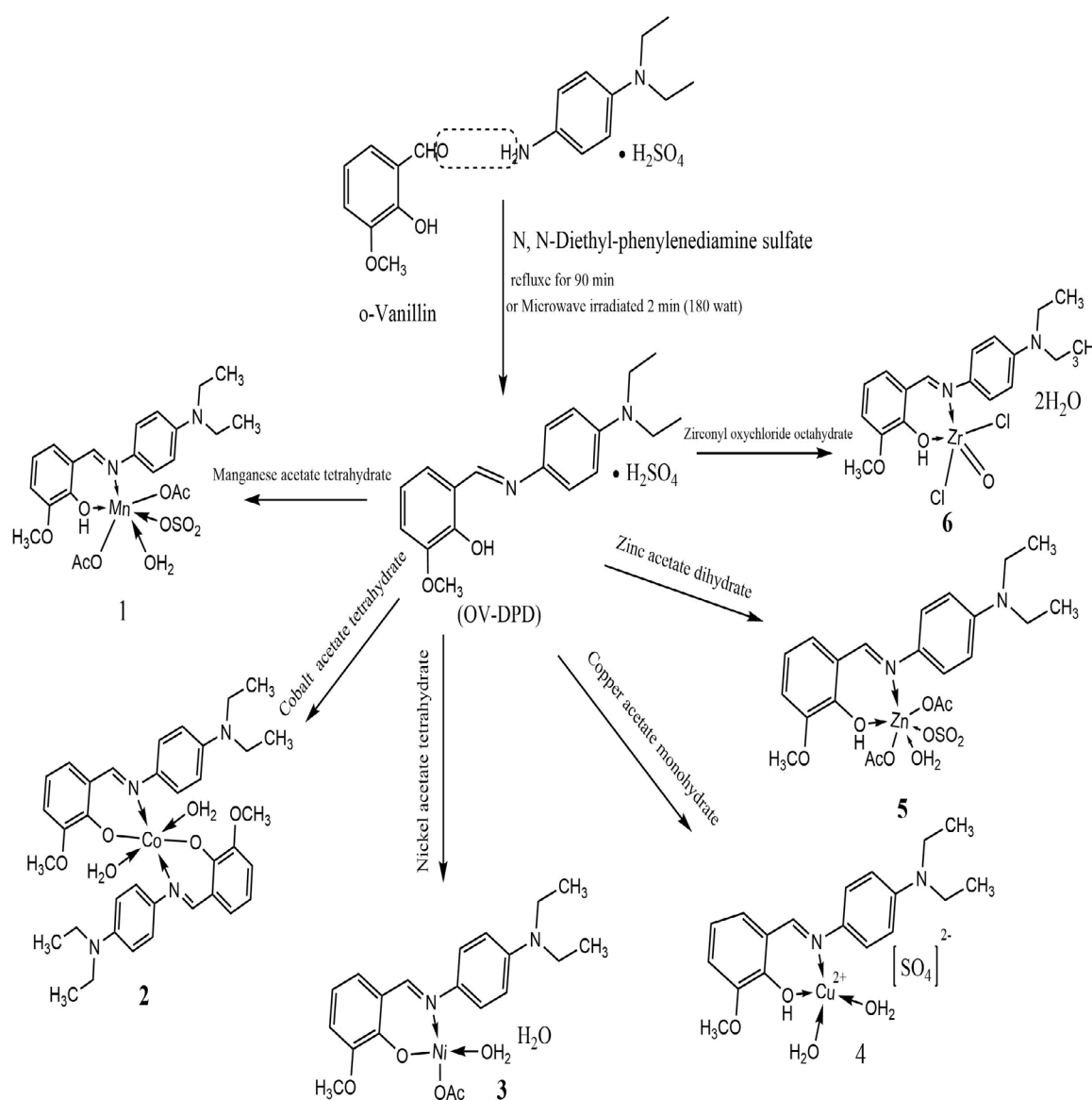
Conventional preparation of Schiff base was carried out from *N,N*-Diethyl-*p*-phenylenediamine sulfate salt (2.62 g, 10 mmol) was dissolved in 20 mL of absolute methanol before mixing it with 20 mL of methanolic solution of ortho-vanillin (1.52 g, 10 mmole). Then, 2 - 3 drops of glacial acetic acid was added in the reaction mixture. The mixture was heated and stirred under reflux for 90 min. The solution was allowed to cool to room temperature for 30 minutes. Let the solution dry in room temperature, precipitates will appear after solvent dry, the precipitates obtained were purified by recrystallization from hot methanol and 1 ml of diethyl ether.

Microwave preparation of Schiff base was carried out by equimolar (1:1) ratio (0.262g, 1 mmol) *N,N*-Diethyl-*p*-phenylenediamine sulfate salt with (0.152 g, 1 mmole) 2-hydroxy-3-methoxy benzaldehyde was mixed thoroughly in a grinder. The reaction mixture was then irradiated by the microwave oven by taking drops of Methanol, the reaction was completed in a short time 2 minutes at 180W with higher yield 93%. The products were then recrystallized with hot methanol and finally dried under reduced pressure over anhydrous CaCl<sub>2</sub> in a desiccator. The progress of the reaction and purity of the product was monitored by TLC

technique. mp: 109 - 111°C. The prepared Schiff base is then characterized IR (KBr,  $\text{cm}^{-1}$ ): 1604 (C=N), 1255 (C-O methoxy), 1462 (Ar-N-(Eth)<sub>2</sub>, methyl group of N aromatic amine), 1118, 616 (SO<sub>4</sub> ion) [17]. 3060(C-H, aromatic), 2974(C-H, aliphatic). <sup>1</sup>HNMR (CDCl<sub>3</sub>,  $\delta$ , ppm) Fig.3: 1.27 (t, 6H, CH<sub>3</sub> adjacent to CH<sub>2</sub>), 8.64 (m, 2H, sulphuric proton)[21], 3.47 (w, 2H, CH<sub>2</sub> adjacent to CH<sub>3</sub>), 3.95 (s, 3H, O-CH<sub>3</sub>), 6.92 -7.32 (aromatic C-H), 11.13 (w, 1H, phenolic proton -OH), 9.94 (m, 1H, azomethine CH=N) [18,22] Elemental analysis; C% (found=53.89, calc.=54.5), H% (found=6.07, calc.=6.1), N% (found=6.78, calc.=7.07), Anal. Calcd. for (C<sub>18</sub>H<sub>24</sub>O<sub>6</sub>N<sub>2</sub>S, MWt. = 396.46).

*General procedure for synthesis of metal complexes using conventional and Microwave-assisted Irradiation.*

Conventional preparation of complexes was carried out by 50 ml of Methanolic solution of 10 mmole of M(CH<sub>3</sub>CO<sub>2</sub>)<sub>2</sub>·nH<sub>2</sub>O, where M= Mn (II), Co (II), Ni (II), Cu (II) and Zn (II), and 10 mmole Zr (IV) oxychloride octahydrate was added to a 50 ml of methanolic solution of the Schiff base ligand (3.96 g, 10 mmole). The mixture was heated and stirred under reflux for 120 min. On standing overnight, the precipitated product was obtained which was filtered, washed with methanol, then with diethyl ether and recrystallized from hot methanolic solution.



**Scheme 1.** The proposed structures of the prepared ligand OV-DPD and its metal complexes.

Microwave preparation of complexes was carried out by the equimolar (1:1) ratio (1.98 g, 5 mmole) of Schiff base ligand (OV-DPD) with 5 mmole of  $M(\text{CH}_3\text{CO}_2)_2 \cdot n\text{H}_2\text{O}$  where  $M=\text{Mn}$  (II),  $\text{Co}$  (II),  $\text{Ni}$  (II),  $\text{Cu}$  (II) and  $\text{Zn}$  (II), and 5 mmole  $\text{Zr}$  (IV) oxychloride octahydrate was mixed thoroughly in a grinder. The reaction mixture was then irradiated by the microwave oven by taking 1-2 ml of Methanol, the reaction

was completed in a short time with higher yields, power and time are enlisted in Table 4, The products were then recrystallized with hot methanol and finally dried under reduced pressure over anhydrous  $\text{CaCl}_2$  in a desiccator. The progress of the reaction and purity of the product was monitored by TLC technique. Physical, analytical and spectral data are given in Tables 1,2.

**TABLE 1. physical, elemental, magnetic, Eg, ESR, and mass spectroscopy of the ligand and its Complexes.**

Molecular Formula	Symbol	Conventional		Microwave		M.P. °C	Color	Elemental Analysis Calc. / (Found) %				$\mu_{\text{eff}}$	M <sup>+</sup> Calc./ (Found)	ESR	
		Time	Yield	Time	Yield			C	H	N	M			g $\perp$	g $\parallel$
$\text{C}_{18}\text{H}_{24}\text{O}_6$ $\text{N}_2\text{S}$	L	90 min	85%	2 min	93%	111	Bloody orange	54.50 (53.89)	6.10 (6.07)	7.07 (6.78)	-	-	396.46 396.99	-	-
$\text{C}_{22}\text{H}_{30}\text{O}_{10}$ $\text{N}_2\text{S Mn}$	1	120 min	65%	4 min	91%	263	Greenish yellow	46.4 (46.68)	5.31 (5.31)	4.92 (5.75)	9.65 (10.2)	3.5	569.1	-	-
$\text{C}_{36}\text{H}_{46}\text{O}_5\text{N}_4$ <b>Co</b>	2	120 min	79%	4 min	91%	132	Black	62.69 (62.75)	6.72 (6.41)	8.12 (8.94)	8.54 (8.63)	3.4	689.71	-	-
$\text{C}_{20}\text{H}_{28}\text{O}_6$ $\text{N}_2\text{Ni}$	3	120 min	83%	5 min	94%	126	Brown	53.25 (55.5)	6.26 (6.73)	6.21 (7.06)	13.01 (12.91)	3.1	450.13	-	-
$\text{C}_{18}\text{H}_{26}\text{O}_8$ $\text{N}_2\text{S Cu}$	4	120 min	88%	4 min	94%	118	Black	43.76 (43.73)	5.3 (5.02)	5.67 (5.49)	11.96 (12.86)	1.81	494.02	2.27	2.17
$\text{C}_{22}\text{H}_{30}\text{O}_{10}$ $\text{N}_2\text{S Zn}$	5	120 min	85%	2 min	91%	226	Orange	45.56 (45.04)	5.21 (5.41)	4.83 (4.89)	11.28 (11.4)	D	579.93 578.66	-	-
$\text{C}_{18}\text{H}_{26}\text{O}_5$ $\text{N}_2\text{Cl}_2\text{Zr}$	6	120 min	54%	9 min	85%	104	Orange	42.18 (42.24)	5.11 (4.99)	5.47 (4.5)	17.8 (17.17)	D	512.54	-	-

**TABLE 2. Significant FT-IR and electronic absorption data of the ligand and its metal complexes.**

Symbol	$\nu$ (OH)	$\nu$ (C-H) aliphatic aromatic	$\nu$ (C=N)	$\nu$ (Ar-N-(Eth)) <sup>†</sup>	$\nu$ (OAc)	$\nu$ (C-O-C)	$\nu$ (SO <sub>4</sub> ) <sup>2-</sup> ion	$\nu$ (M-N)	$\nu$ (M-O) Transition and Assignment	$\lambda_{\text{max}} \cdot 10^3 (\text{cm}^{-1})$	Suggested structure
L	3404	2974 3060	1604	1462	-	1255	1118 vs 618 s	-	-	25.641 (n- $\pi^*$ C=N), 28.653 ( $\pi$ - $\pi^*$ C=N), 33.670 ( $\pi$ - $\pi^*$ Phenyl), 49.751 (n- $\sigma^*$ , phenolic)	-
Mn-L (1)	3414	2970 3063	1611	1465	1406	1258	-	519	479	39.062 ( $\pi$ - $\pi^*$ ), 25.706 (n- $\pi^*$ ), 25.000 LMCT	Octahedral
Co-L (2)	3412	2971 3060	1604	1469	-	1260	-	517	479	36.232 ( $\pi$ - $\pi^*$ ), 31.056 (n- $\pi^*$ ), 17.605 $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{T}_{1g}(\text{P})(\nu_3)$	Octahedral
Ni-L (3)	3342	2972 3060	1612	1465	1406	1258	-	519	479	37.453 ( $\pi$ - $\pi^*$ ), 26.178 (n- $\pi^*$ ), 25.062 LMCT, 17.605 $3\text{A}_{2g} \rightarrow ^3\text{T}_{1g}(\text{F})(\nu_2)$	Tetrahedral
Cu-L (4)	3404	2974 3060	1607	1468	-	1256	1118 vs 618 s	518	479	36.232 ( $\pi$ - $\pi^*$ ), 31.056 (n- $\pi^*$ ), 16.667 $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$	Tetrahedral
Zn-L (5)	3446	2973 3061	1611	1462	1404	1254	-	519	479	34.602 ( $\pi$ - $\pi^*$ ), 30.488 (n- $\pi^*$ ), 24.875 LMCT	Octahedral

### Antimicrobial activity

The obtained metal complexes were screened for their activities as antibacterial, against Gram-positive of *Staphylococcus aureus* (ATCC25923), *Bacillus subtilis* (ATCC6635); Gram-negative species of *Escherichia coli* (ATCC 25922), *Salmonella typhimurium* (ATCC 14028) as well as anti-fungal of *Candida albicans* (ATCC 10231) and Fungus: *Aspergillus fumigatus*. Antimicrobial activity was tested by the disc diffusion method [23]. Cephalothin, chloramphenicol, and cycloheximide were used as standard references for Gram-positive, Gram-negative bacteria and fungi respectively. Nutrient agar was prepared then autoclaved at 121 °C for 15 min, cooled and finally poured in Petri dishes. The tested compounds were dissolved in Dimethyl sulfoxide (DMSO) solvent and prepared in two concentrations; 100 and 50 mg/ml and then 10 µL of each preparation was dropped on disk of 6 mm in diameter and the concentrations became 1 and 0.5 mg/disk respectively, Bacterial cultures were grown in nutrient broth medium at 30 °C. After 16 h of growth, each microorganism, at a concentration of 10<sup>8</sup> cells/mL, was inoculated on the surface of Mueller-Hinton agar plates using a sterile cotton swab. Subsequently, uniform size filter paper disks (6 mm in diameter) were impregnated by equal volume (10 µl) from the specific concentration of dissolved compounds and carefully placed on the surface of each inoculated plate. The plates were incubated in the upright position at 36°C for 24 hours. Three replicates were carried out for each extract against each of the test organisms. Simultaneously, the addition of the respective solvent instead of dissolved compound was carried out as negative controls. After incubation, the diameters of the growth inhibition zones formed around the disc were measured with a transparent ruler in millimeter, averaged and the mean values were recorded in table 5.

### Cytotoxic activity

Cytotoxic activity test (*In vitro* bioassay on human tumor cell lines) was conducted and determined. It was performed on human hepatocellular carcinoma cell line (HepG2) based on the method suggested by Mosmann [24] and human colon carcinoma cell line according to the protocol suggested by Vichai and Kirtikara [25]. All the tumor cells were purchased from CSIR-National Chemical Laboratory, Pune, India. An MTT colorimetric assay was used to plot a dose-response curve required to kill 50% of the cell population (IC<sub>50</sub>). The results are shown in Table 6.

### Results and Discussion

The Schiff base ligand was prepared by the condensation reaction of 2-hydroxy 3-methoxy benzaldehyde "o-vanillin" with N, N-Diethyl-p-phenylenediamine sulfate "DPD" under microwave irradiation and conventional synthesis as shown in Scheme 1. Schiff base ligand and their metal complexes obtaining from microwave assisted preparation have the same physical properties (color, shape, melting point) comparing with those synthesized by conventional preparation. ligand and their metal complexes isolated from both methods exhibited one spot in TLC chart indicating the high purity of these compounds. The comparison between productivity and time spent on the preparation of Schiff base ligand and its complexes are shown in Table 1. The results show that microwave preparation is faster and more productive and consumes less solvent, making it more suitable for principles of green chemistry. The synthesized Schiff base ligand was soluble in Methanol, Acetone, Acetonitrile, Chloroform, DMF and DMSO at room temperature, also soluble in hot Ethanol. All of the newly synthesized Schiff base ligand and its metal complexes (1–6) were air and moisture stable are shown in (Table 1) at room temperature. They were prepared by the stoichiometric reaction of the corresponding metal salts and the respective ligand in the molar ratio M:L of 1:1 for all complexes except Co (II) complex in the molar ratio M:L of 1:2. Physical measurements and analytical data of the complexes 1–6 are given in Tables (1,2). The potential sites (N and O) of the prepared Schiff base ligand coordinate with the metal ions of Mn (II), Co (II), Ni (II), Cu (II), Zn (II) and Zr (IV) producing metal complexes. Characterization of the prepared metal complexes helps in more understanding of the mode of chelation of the ligand towards metals.

### Infrared spectra

The infrared spectrum of Schiff base ligand and its metal complexes Fig. (1,2) and Table 2 shows that azomethine symmetric stretching frequency strong bands between 1604-1638 cm<sup>-1</sup> are assigned to the imine, ν (C=N) group [27], there are two strong bands at 1118 cm<sup>-1</sup> and 618 cm<sup>-1</sup> assigned to ν (SO<sub>4</sub><sup>2-</sup>) ion appears in ligand and Cu (II) complex [17], the phenolic ν (C-O) frequencies for the ligand and its complexes were observed at 1254-1261 cm<sup>-1</sup> [26], the methyl group of N Aromatic amine ν (Ar-N-Et<sub>2</sub>) of ligand and its complexes shows M-S bands between 1462-1474 cm<sup>-1</sup> [27], The appearance of a weak band at



*<sup>1</sup>H NMR spectra*

The <sup>1</sup>H NMR spectra of ligand (OV-DPD) have been recorded in CDCl<sub>3</sub>, the characteristic absorption <sup>1</sup>H NMR signals are represented in Fig.3. Chemical shifts of methyl and -CH<sub>2</sub> group protons were observed as a single peak at δ 1.27, δ 3.47 ppm respectively [18]. The peak at δ 2.12 ppm was attributed to water impurity with sulphuric acid [19]. the protons of methoxy group (-OCH<sub>3</sub>) as a singlet at δ 3.95 ppm [20]. Chemical shifts of the sulphuric acid protons were observed at δ 8.64 [21]. A broad multiple was observed at δ 6.99-7.88 ppm were assigned to aromatic protons [22]. Chemical shifts of the Azomethine proton -CH=N and Phenolic proton -OH were appeared at δ 9.94 and δ 11.13 ppm respectively [18,22].

*UV-Vis spectra and magnetic susceptibility of complexes.*

Electronic spectra and magnetic moment (B.M) of Schiff base ligand and its metal complexes of Mn (II), Co (II), Ni (II), Cu (II), Zn (II) and Zr (IV) in DMSO are shown in Table 2, were scanned in the region 9091-52631 cm<sup>-1</sup> at concentrations between 50 μM and 1 mM at room temperature. The electronic data of the studied exhibited absorption bands at λ<sub>max</sub> equals 24875-25062 cm<sup>-1</sup> (n-π\*, C=N), 28653-31056 cm<sup>-1</sup> (π-π\*, C=N), n-π\* of C=N band showed either a blue shift with a reduction of intensity or disappeared as Co, Cu and Zr complexes. This is due to a donation of the lone pair of electrons to the metal and hence the coordination of the azomethine group [29]. and shows a band at 35715- 39062 cm<sup>-1</sup> (π-π\*, aromatic ring), 42918-46512 cm<sup>-1</sup> (n-σ\*, phenolic group). [30] Acetate group associated with complexes of Mn,

Ni, Zn showing two bands at 35714 -37453 cm<sup>-1</sup> (π-π\*, C=O), 25706-26178 cm<sup>-1</sup> (n-π\*, C=O). [31]. The electronic spectra of Mn (II) complex exhibited bands at 39062, 25706, 25000 cm<sup>-1</sup> are assigned to π-π\*, n-π\*, ligand to metal transfer (LMCT) transitions respectively suggesting an octahedral geometry around Mn (II) ion with magnetic moment value 3.5 B.M [2,3]. for Co (II) complex exhibited bands at 36232, 31056, 17605 cm<sup>-1</sup> are refers to π-π\*, n-π\*, <sup>4</sup>T<sub>1g</sub>(F)→<sup>4</sup>T<sub>1g</sub>(P)(v<sub>3</sub>) transitions respectively suggesting an octahedral geometry with magnetic moment value 3.4 B.M [2,3,20] the electronic spectra of Ni (II) complex shows four bands of appreciable intensity at 37453, 26178, 25062, 17605 cm<sup>-1</sup> these transitions have tentatively been assigned to π-π\*, n-π\*, ligand to metal transfer (LMCT), 3A<sub>2g</sub> → 3T<sub>1g</sub>(F)(v<sub>2</sub>) transitions respectively suggesting a tetrahedral geometry with magnetic moment value 3.1 B.M [22]. for Cu (II) complex shows three bands at 36232, 31056, 16.667 cm<sup>-1</sup> are assigned to π-π\*, n-π\*, <sup>2</sup>B<sub>1g</sub> → <sup>2</sup>A<sub>1g</sub> transitions respectively. The magnetic moment is 1.81 B.M. Thus, the tetrahedral geometry [22,31] has been suggested for Cu (II) complex, the electronic spectra of Zn (II) complex shows bands at 34602, 30488, 24875 cm<sup>-1</sup> are assigned to π-π\*, n-π\*, ligand to metal transfer (LMCT) transitions respectively with diamagnetic properties suggesting an octahedral geometry around Zn (II) ion [2,22]. for Zr (IV) complex shows three bands at 35714, 31056, 25000 cm<sup>-1</sup> are assigned to π-π\*, n-π\*, ligand to metal transfer (LMCT) transitions respectively with diamagnetic properties suggesting a distorted trigonal bipyramidal geometry around Zr (IV) ion [32-34].

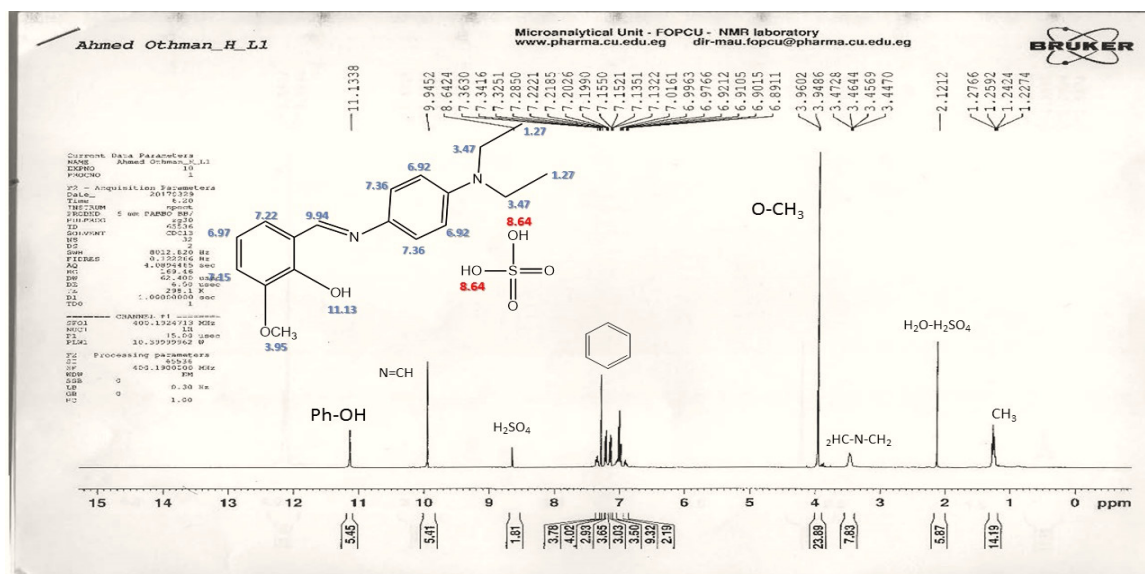
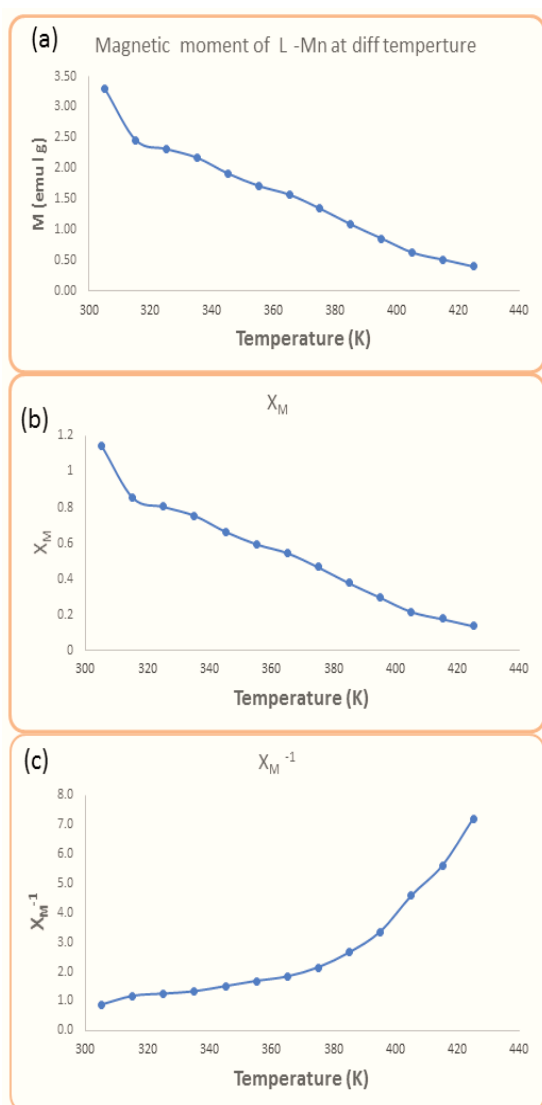


Fig. 3. <sup>1</sup>H NMR spectra of Schiff base ligand .

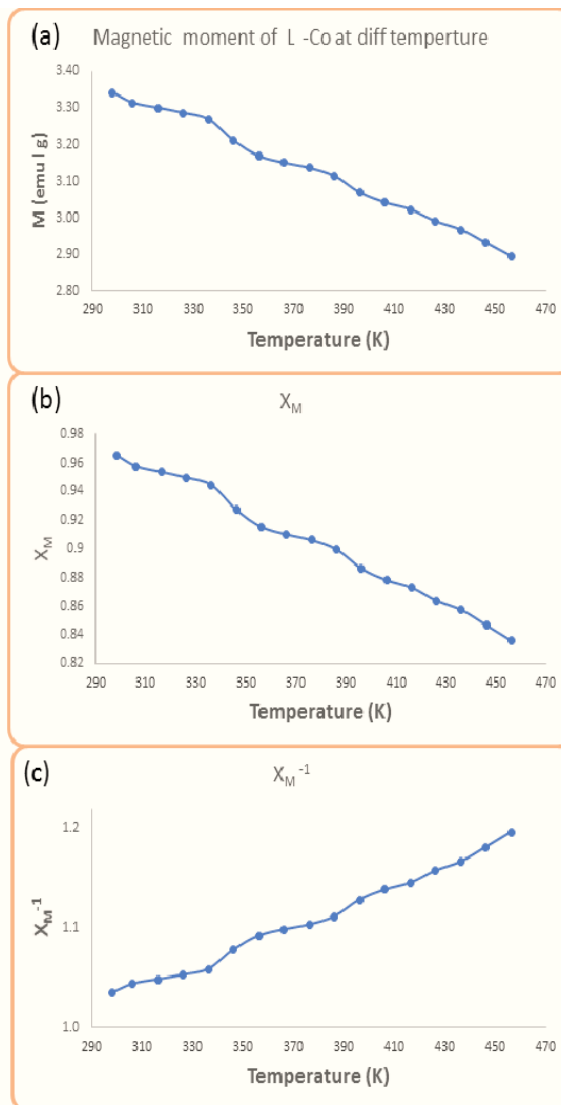
### Variation of magnetic susceptibility with temperature

Variation of magnetic susceptibility with temperature in the case of Mn (II) and Co (II) complexes of OV-DPD ligand has been studied. The  $\chi_M$ ,  $\chi_M^{-1}$  and  $\mu_{\text{eff}}$  versus T plots for Mn (II) and Co (II) complexes are illustrated in Fig. (4,5) Indeed, change of magnetism with increasing temperatures for Mn (II) and Co (II) complexes may be taken as conclusive evidence for the formation of high spin octahedral complexes. Effective magnetic moment ( $\mu_{\text{eff}}$ ) of the octahedral Mn (II) and Co (II) complexes is independent of temperature. The molar magnetic susceptibility ( $\chi_M$ ) for these complexes decreases slowly with increasing the temperature until

approaching zero value of susceptibility ( $\chi_M$ ). Such behavior is suggested to be characteristic of “normal” paramagnetic behavior of Mn (II) and Co (II) complexes and can be elucidated as follows. Upon enhancing the temperature from 300 to 450 K, some molecules of high spin octahedral Mn (II) and Co (II) complexes changed their spin state gradually from ( $t_{2g}^{-5}e_g^2$ ) to ( $t_{2g}^{-6}e_g^0$ ) assigning to low spin Mn (II) and Co (II) octahedral complexes. This modification was prolonged until all the metal complexes were oxidized completely by heat into analogous Mn (III) and Co (III) complexes, subsequently, the magnetism becomes zero where all the complexes molecules accepted diamagnetic nature.



**Fig.4. Temperature variation of Mn-complex. (a)  $\mu_{\text{eff}}$ , (b)  $\chi_M$  and (c)  $\chi_M^{-1}$  versus T plots.**



**Fig. 5. Temperature variation of Co-complex. (a)  $\mu_{\text{eff}}$ , (b)  $\chi_M$  and (c)  $\chi_M^{-1}$  versus T plots.**



### Mass spectra

The mass spectrum of Zn (II) complex showed an ion peak at  $m/z = 578$  as molecular peak of  $(C_{22}H_{30}N_2O_{10}SZn)$ . The ion peak at  $m/z 577$  is due to  $M^+(C_{22}H_{29}N_2O_{10}SZn)$ , while the

Other characteristic peaks are observed at  $m/z$  values 551, 523, 480, 449, 423, 393, 367, 339, 313, 298, 283, 265, 236, 154 and 57. Suggested structural assignments of fragments are shown in scheme 2.

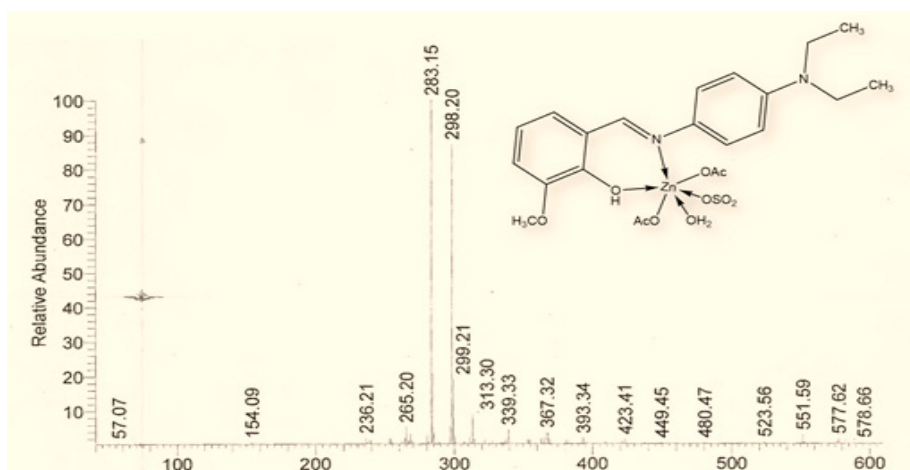
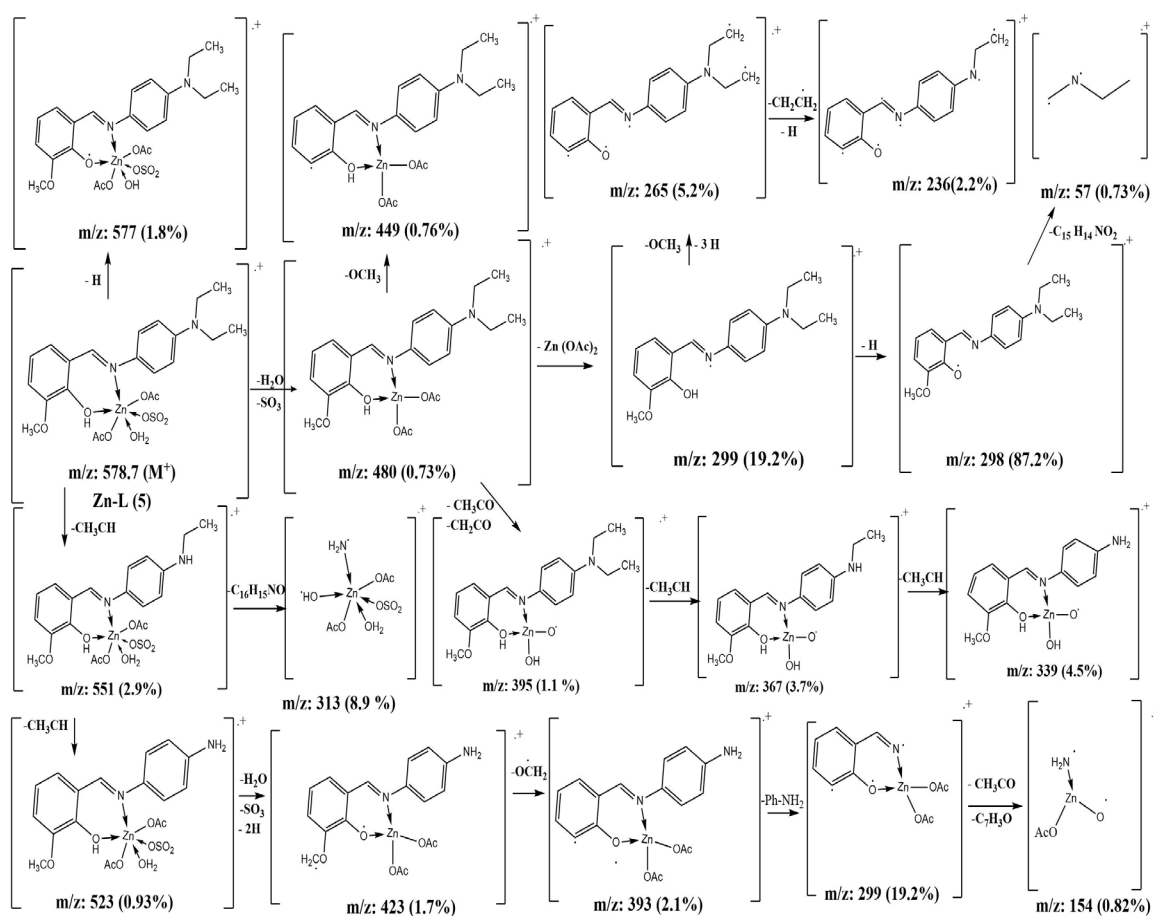


Fig. 6. Mass spectra of Zn (II) complex.



Scheme 2. Mass fragmentation of Zn (II) complex.

### ESR Spectrum

The ESR spectra of Cu (II) complex showed broad signals (Fig 7) with two “g” values ( $g^{\parallel}$ ,  $g^{\perp}$ ) depicted in Table 1, Cu (II) complex exhibited  $g^{\parallel}$  at 2.17 which are less than 2.3, suggesting covalent character of copper – ligand bonds in the present complexes, where,  $g^{\parallel} < 2.3$  concerns ionic metal – ligand bond [35-36]. Fairly high values of g are in conformity with the oxygen, nitrogen coordination in these compounds [36]. This coupling, known as the hyperfine interaction. The above complexes have a tetrahedral structure as indicated by the electronic absorption spectra.

### Thermal analysis for metal complexes

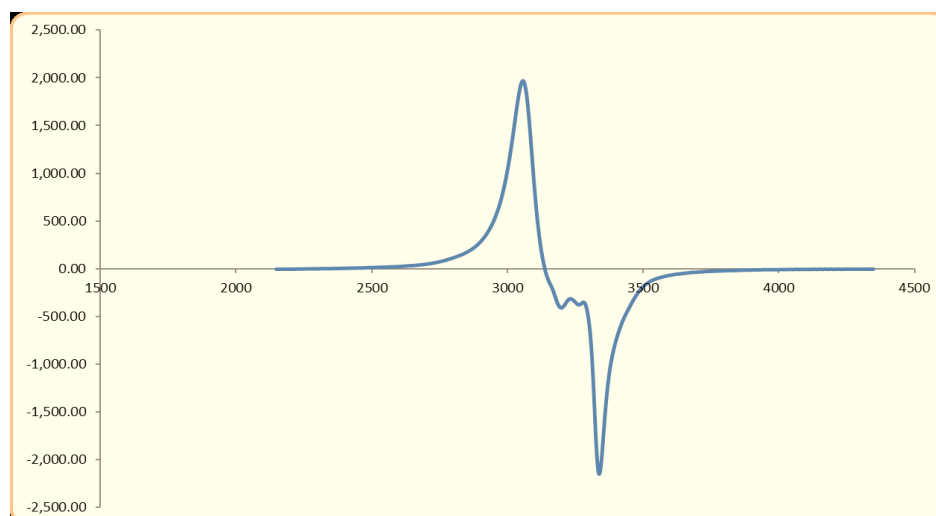
Thermodynamic activation parameters of decomposition of dehydrated complexes mostly enthalpy ( $\Delta H^*$ ), activation energy ( $E^*$ ), entropy ( $\Delta S^*$ ) and Gibbs free energy change of the decomposition ( $\Delta G^*$ ) are evaluated graphically by employing the Coats–Redfern relation [37] and Horowitz-Metzger [38]. Kinetic parameters (The entropy of activation ( $\Delta S^*$ ), enthalpy of activation ( $\Delta H^*$ ) and the free energy change of activation ( $\Delta G^*$ ) were calculated. The data are calculated for the first stages, by employing the Coats-Redfern and Horowitz-Metzger equations, for three complexes for each ligand and summarized in Table 4. The thermogram of Mn (II) complex shows four decomposition steps; The first step at a temperature range of (42–166) °C corresponds to the loss of H<sub>2</sub>O (3.16 %) molecule. The second step at a temperature range of (167–369) °C corresponds to the loss of acetate (CH<sub>3</sub>COO) molecule (10.3 %). The third and fourth steps at temperature ranges of (370–724, 725–999) °C correspond to the loss of acetate

(CH<sub>3</sub>COO) and (SO<sub>3</sub>) and an organic part with MF of (C<sub>18</sub>H<sub>22</sub>ON<sub>2</sub>) (73.8%), leaving (12.5%) MnO as a residue. The thermogram of Ni (II) complex shows four decomposition steps; The first step at a temperature range of (44–282) °C corresponds to the loss of 2.H<sub>2</sub>O (8 %) molecules. The second step at a temperature range of (283–435) °C corresponds to the loss of acetate (CH<sub>3</sub>COO) molecule (13.1 %). The third and fourth steps at temperature ranges of (436–650, 650–999) °C corresponds to the loss of organic part with MF of (C<sub>18</sub>H<sub>21</sub>O<sub>2</sub>N<sub>2</sub>) (65.53%), leaving (16.4 %) NiO as a residue. The thermogram of Zn (II) complex shows Three decomposition steps; The first step at a temperature range of (43–265) °C correspond to the loss of (H<sub>2</sub>O) and two acetate ion (2 CH<sub>3</sub>COO) and (SO<sub>3</sub>) molecules and organic part (CH<sub>3</sub>O) (42.65 %). The second step at a temperature range of (266–393) °C corresponds to the loss of organic part with MF of (C<sub>10</sub>H<sub>14</sub>N) (25.5%). The third step at temperature ranges of (505–669) °C corresponds to the loss of organic part with MF of (C<sub>7</sub>H<sub>5</sub>N) (17.8%), leaving (14 %) ZnO as a residue.

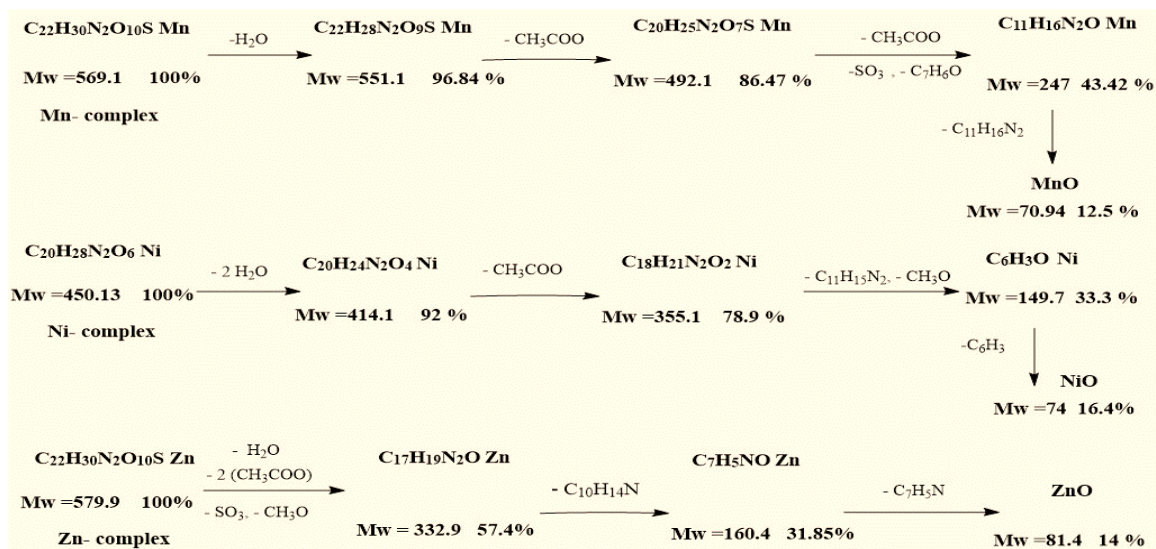
### Scanning Electron Microscope (SEM).

Scanning-electron microscope (SEM) is a type of electron microscope that produces images of a sample by scanning the surface with a focused beam of electrons. The electrons interact with atoms in the sample, producing various signals that contain information about the surface topography and composition of the sample.

The morphology of the OV-DPD ligand and its metals complexes is performed with a scanning-electron microscope and shown in Fig 9.



**Fig.7. ESR: ESR spectra of Cu (II) complex.**



Scheme 3. The sequence of decomposition steps for metal complexes.

TABLE 3. Thermo-gravimetric data of complexes.

Compd.	Molecular Formula	Molecular Weight	Steps	$\Delta T$ °C		mass %		Assignment
				$T_i$	$T_f$	Calc.	Found	
Mn-L (1)	$C_{22}H_{30}N_2O_{10}S$ Mn	569.1	1 <sup>st</sup>	42	166	3.16	3	H <sub>2</sub> O
			2 <sup>nd</sup>	167	369	10.3	9.4	CH <sub>3</sub> COO
			3 <sup>rd</sup>	370	724	43.1	44.4	C <sub>7</sub> H <sub>6</sub> O, CH <sub>3</sub> COO, SO <sub>3</sub>
			4 <sup>th</sup>	725	999	30.7	29.7	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub>
			Residue	-	-	12.5	13.52	MnO
Ni-L (3)	$C_{20}H_{28}N_2O_6$ Ni	450.13	1 <sup>st</sup>	44	282	8.0	8.55	2 H <sub>2</sub> O
			2 <sup>nd</sup>	283	435	13.1	12.44	CH <sub>3</sub> COO
			3 <sup>rd</sup>	436	650	45.33	46.39	C <sub>11</sub> H <sub>15</sub> N <sub>2</sub> , CH <sub>3</sub> O
			4 <sup>th</sup>	650	999	20.2	19.64	C <sub>6</sub> H <sub>3</sub> O
			Residue	-	-	16.4	15.8	NiO
Zn-L (6)	$C_{22}H_{30}N_2O_{10}S$ Zn	579.93	1 <sup>st</sup>	43	265	42.65	45.52	H <sub>2</sub> O, 2*CH <sub>3</sub> COO, SO <sub>3</sub> , CH <sub>3</sub> O
			2 <sup>nd</sup>	266	393	25.5	23.22	C <sub>10</sub> H <sub>14</sub> N,
			3 <sup>rd</sup>	505	669	17.8	18.7	C <sub>7</sub> H <sub>5</sub> N
			Residue	-	-	13.9	12.54	ZnO

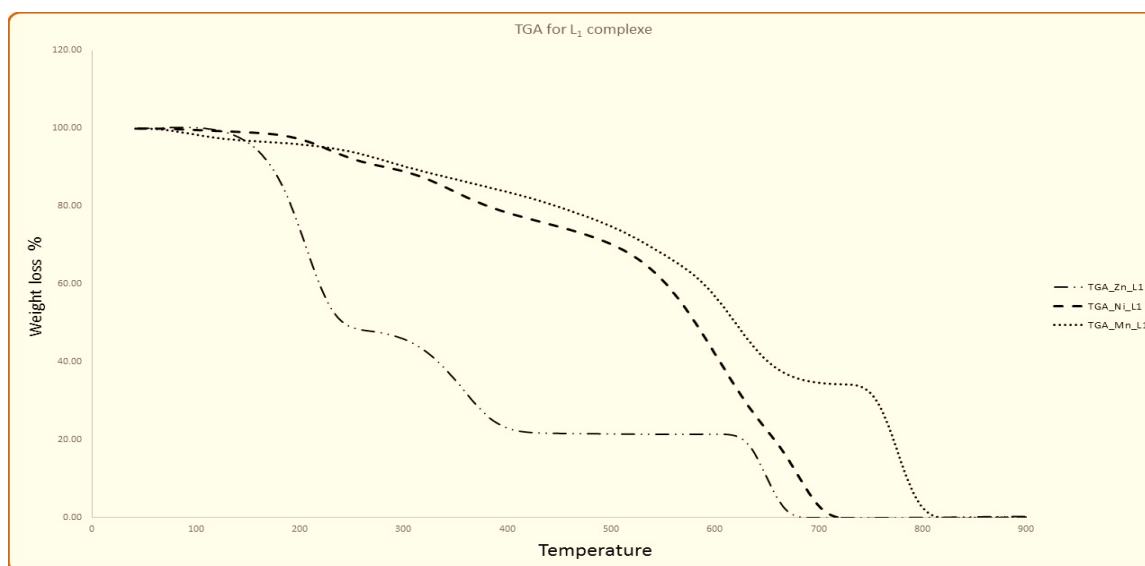


Fig.8. Thermographs of metals complexes of Mn, Ni, and Zn of OV-DPD.

TABLE 4. Thermodynamic kinetic parameters data of the thermal decomposition of metal complexes.

Compd. No.	Steps	Coats Redfern						Horowitz-Metzger					
		R <sup>2</sup>	E <sub>a</sub> KJ mol <sup>-1</sup>	A S <sup>-1</sup>	ΔS* mol <sup>-1</sup> K <sup>-1</sup>	DH* KJ mol <sup>-1</sup>	DG* KJ mol <sup>-1</sup>	R <sup>2</sup>	E <sub>a</sub> KJ mol <sup>-1</sup>	A S <sup>-1</sup>	ΔS* mol <sup>-1</sup> K <sup>-1</sup>	DH* KJ mol <sup>-1</sup>	DG* KJ mol <sup>-1</sup>
Mn-L (1)	1 <sup>st</sup>	0.99	129	1.9x10 <sup>11</sup>	-31	126	138	0.99	59	9.3x10 <sup>7</sup>	-102	56	94
	2 <sup>nd</sup>	0.99	87	1.7x10 <sup>10</sup>	-144	82	162	0.99	50	9.5x10 <sup>3</sup>	-188	46	151
	3 <sup>rd</sup>	0.97	65	2x10 <sup>7</sup>	-154	58	174	0.97	32	1.2x10 <sup>1</sup>	-242	26	207
Ni-L (3)	1 <sup>st</sup>	0.98	27	5.2x10 <sup>8</sup>	-81	24	58	0.98	15	6.29	-250	11	117
	2 <sup>nd</sup>	0.99	267	7.9x10 <sup>14</sup>	-22	261	275	0.99	130	2.7x10 <sup>10</sup>	-64	125	165
	3 <sup>rd</sup>	0.99	312	2.4x10 <sup>11</sup>	-98	305	382	0.99	147	1.9x10 <sup>9</sup>	-85	141	207
Zn-L (6)	1 <sup>st</sup>	0.998	60	3.7x10 <sup>5</sup>	-141	56	114	0.99	25.7	3.7x10 <sup>2</sup>	-224	22	114
	2 <sup>nd</sup>	0.99	112	2.6x10 <sup>8</sup>	13.5	107	99	0.99	54	8.8x10 <sup>3</sup>	-183	49	159
	3 <sup>rd</sup>	0.99	731	2.5x10 <sup>41</sup>	780	723	21	0.99	323	2.8x10 <sup>18</sup>	90	316	234

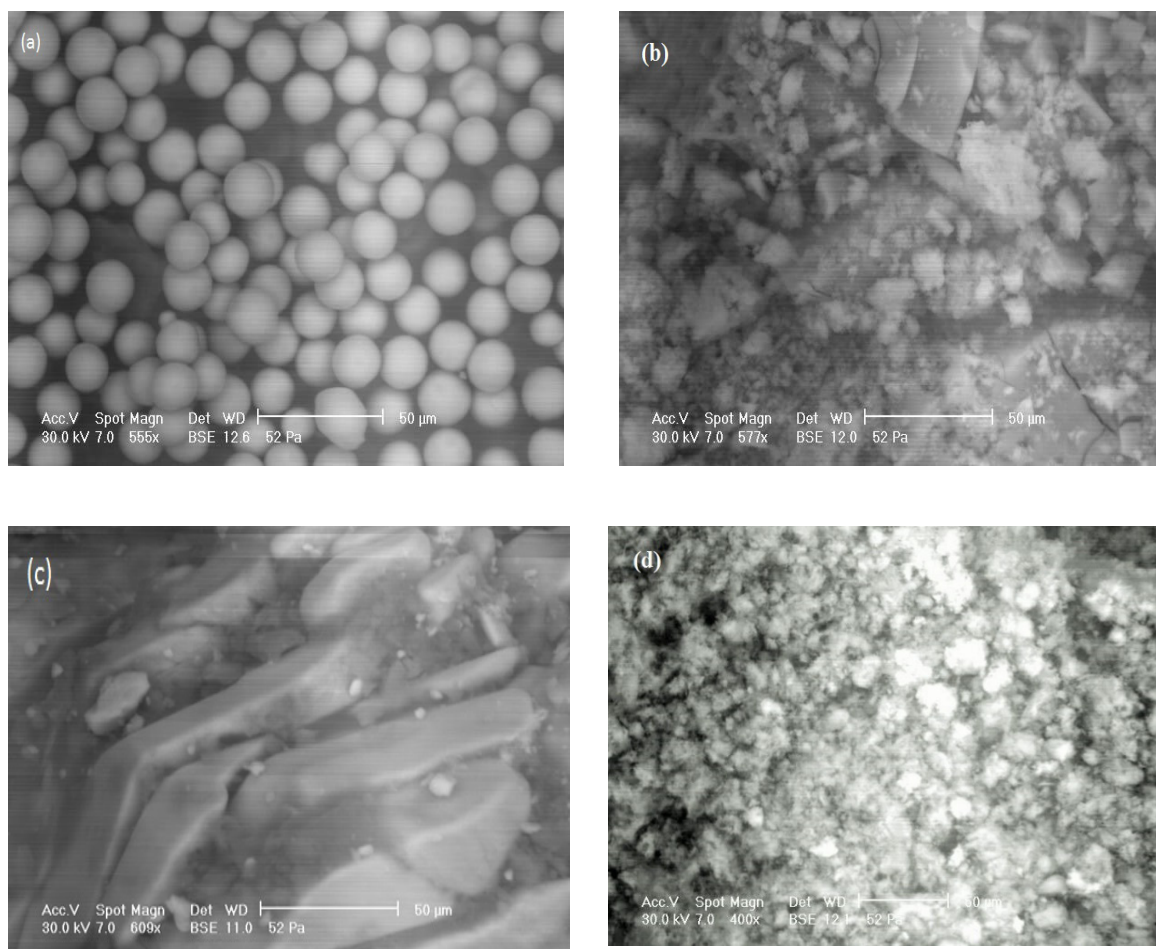


Fig.9. SEM diagrams of complexes: (a) Mn (II), (b) Co (II), (c) Ni (II), and (d) Zn (II).

## Applications

### Anti-microbial activity

Data of the antibacterial and antifungal activity of isolated Schiff base ligand and their metal complexes were recorded in **Table 5** and their antimicrobial activity taken as inhibition zone diameter was depicted graphically in **Fig. 10**. It was found that Schiff base ligand and its Cu and Ni complexes exhibited the highest antibacterial activity against *S. aureus* (ATCC 25923) of Gram-Positive Bacteria and *E. coli* (ATCC25922) of Gram-Negative Bacteria. Furthermore, Schiff base ligand showed the highest anti-fungal activity against *C. albicans* (ATCC10231) and *A. fumigates*. Its Cu complex showed the highest effect against *A. fumigates* while its Ni complex exerted the highest effect against *C. albicans* (ATCC10231). On the other hand, its Mn complex showed no efficiency against all the bacterial or fungal species selected to be under the current study. This was

in accordance with Sekhon [39] and supported recently by Gałczyńska [40] who emphasized that the antibacterial properties of the metal complexes depend on the penetration mechanisms through the bacterial cell membranes (diffusion via calcium or iron channels). The antibacterial activity of Cu (II) ions is explained by the change in permeability of the bacterial membrane due to the interaction between metal ions and outer membrane. Also, it is explained by the interaction between bacteria and generated free radicals [41-42]. Furthermore, the presence of the metal ions in complexes with azomethane derivatives is more effective in membrane destabilization than free ions. This leads to disturbing structural integrity of the cell and hence eradicating the microorganism [43]. Antifungal properties of metals ions and their coordination complexes are connected with several defects in enzymatic steps of ergosterol biosynthesis. This is a major mechanism of metal complexes toxicity against fungal cells [44].

TABLE 5. Antimicrobial result of Free Schiff base ligand and its related metal complexes.

Sample code	Gram - positive bacteria		Gram - negative bacteria		Yeasts and Fungi	
	<i>Staphylococcus aureus</i> (ATCC 25923)	<i>Bacillus subtilis</i> (ATCC 6635)	<i>Salmonella typhimurium</i> (ATCC14028)	<i>Escherichia coli</i> (ATCC25922)	<i>Candida albicans</i> (ATCC10231)	<i>Aspergillus fumigatus**</i>
L	32	17	21	32	29	20
Mn-L (1)	NA	NA	NA	NA	NA	NA
Co-L (2)	9	16	16	13	16	15
Ni-L (3)	29	9	11	32	28	12
Cu-L (4)	30	NA	17	37	18	23
Zn-L (5)	11	21	11	20	23	18
Control	35	35	36	38	35	37
DMSO	0	0	0	0	0	0

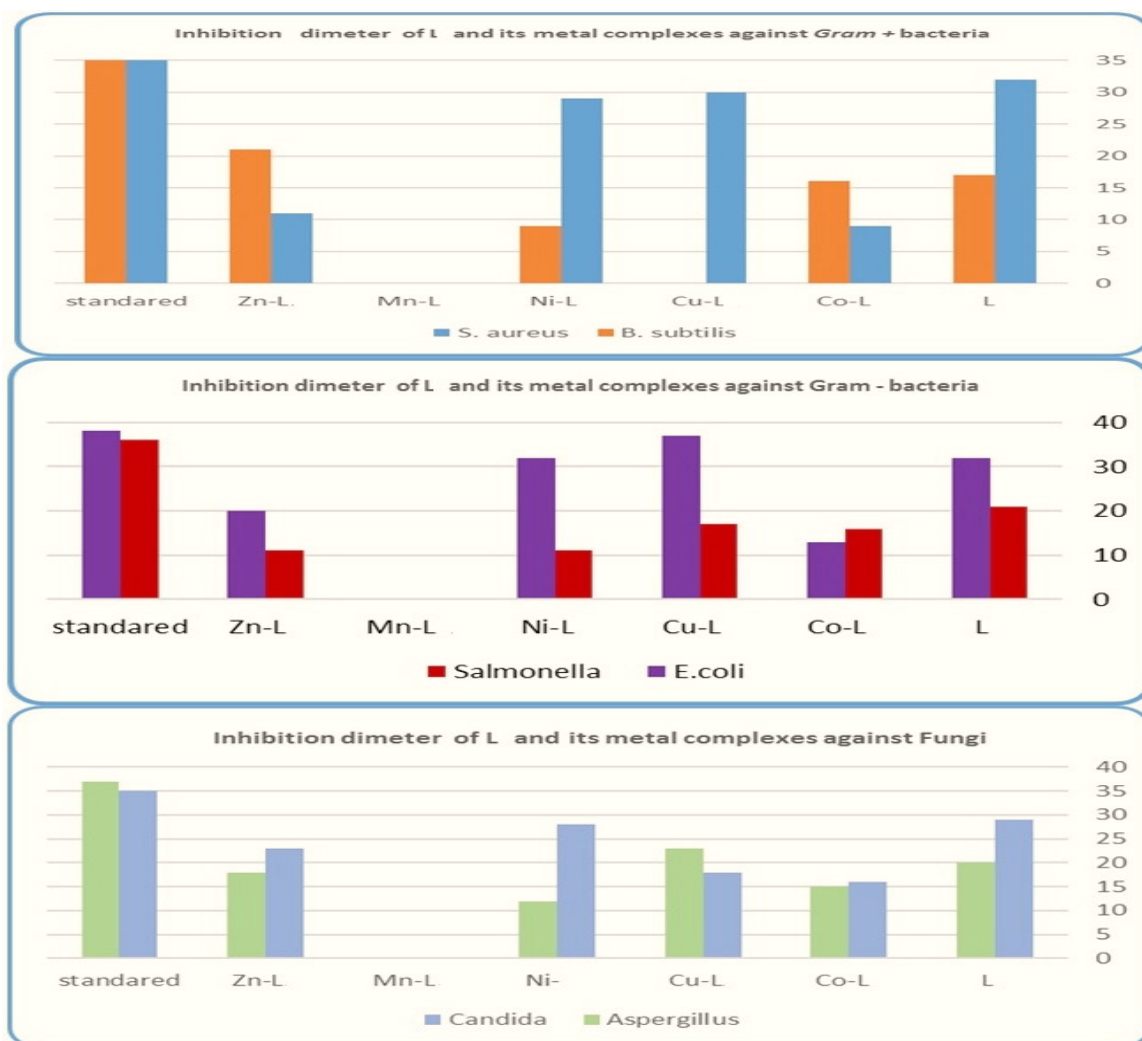


Fig.10. Antimicrobial activity of Schiff base ligand and their metal complexes against different strains.

*Anticancer activity*

It is well known that the substance appears effective and exhibits cytotoxic activity when it is able to inhibit growth of cancer cells at low concentrations. Data compiled in **Table 6** showed that Schiff base ligand and its Zn and Cu complexes exhibited the highest cytotoxic activity against HEPG2 and HCT. This because of lower concentrations of the ligand and these complexes required to decrease viability of these cancer cells. It was found that concentrations of the metal complexes required to inhibit growth of cancer cells are convergent. This was in accordance with [45] who reported that the metal complexes possess higher cytotoxic activity against the selected human cancer cells. They have different antitumor mechanisms and have great potential as metal-based anticancer agents. This might attribute to ability of these complexes to induce S-phase arrest in cancer cells at low concentration with increasing expression of tumor suppressors' genes like p<sup>21</sup>, p<sup>27</sup> and p<sup>53</sup>. In addition, these complexes might exhibit the ability to induce apoptosis, production of ROS followed by increasing intracellular Ca<sup>2+</sup> in cancer cells and finally caused complete apoptosis of cancer cells [46-47].

Furthermore, [40] postulated that there are several potential mechanisms of antitumor activity of metal complexes, especially in the case of Cu-complexes. This type of the activity could be associated with the transport of Cu (II) ions into the cell. The Cu (II) ions are introduced by specific copper transporters in the Cu(I) form. The presence of the natural copper transport system is crucial from the clinical point of view because no additional exogenous drug carriers is needed. Thus, the cellular effects of metal complexes activity might be determined

by their interaction with proteins (e.g. receptors) or nucleic acids. Considering metal complexes activity not only the interactions with DNA but also with proteins should be analyzed as the targeted molecules in antitumor mechanisms. For comparison purposes, the cytotoxicity of cisplatin, as standard drug, was evaluated against HepG-2 and HCT. and produced IC<sub>50</sub> values (8.4µg/ml, 6.9µg/ml) respectively under the same conditions.

**Conclusions**

A novel Schiff bases ligand obtained from condensation of o-vanillin and N, N-Diethyl-p-phenylenediamine using microwave-assisted irradiation and conventional techniques act as bidentate ligand, which coordinated through the azomethine-N and hydroxy -O to the metal ions; Mn (II), Co (II), Ni (II), Cu (II), Zn (II) and Zr (IV). The thermal dehydration and decomposition of Mn (II), Ni (II) and Zn (II) complexes show dehydration of water, and elimination of acetate then organic content and metal oxide MO remained as a residue. The antimicrobial activity of ligand and its metal complexes against the bacterial and fungal strains showed that the activity of the free Schiff base ligand is biologically active and its activity may be arising from the hydroxyl, methoxy, sulphuric groups which may play an important role in the antibacterial activity, Cu (II) complex achieved a brilliant inhibition zone diameter and antimicrobial activity against *E. coli* almost reached the inhibition zone diameter record by standard positive control Cephalothin making it eligible for a treatment of *E. coli*. Although concentrations of the Schiff base ligand and its metal complexes required to inhibit growth of HEPG2 and HCT are convergent, the Schiff base ligand and its Zn and Cu complexes exhibited the highest cytotoxic activity.

**TABLE 6. Cytotoxic activity of free Schiff base ligand and its related metal complexes against human colon carcinoma (HCT) and liver cancer cells (HepG-2).**

	L	Mn-L (1)	Co-L (2)	Ni-L (3)	Cu-L (4)	Zn-L (5)	Zr-L (6)	cisplatin
The median inhibitory concentration (IC <sub>50</sub> ) in µg/ml								
HepG-2	17	21.6	25	22	18.4	18.6	21	8.4
HCT	21	28.3	34.7	25.8	21.7	22	24.2	6.9

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### استخدام الميكروويف والطرق التقليدية في تحضير وتوصيف مترابط لمشتق الارثوفانلين و متراكباته واستخدامها كمضادات للبكتيريا ومضادات للسرطان

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تم استخدام الطرق التقليدية و الميكروويف في تحضير مترابط (مشتق من الارثوفانلين ) وكذلك تحضير متراكبات المنجنيز والكوبلت والنيكل والنحاس والزنك والزركون و تم توصيف المركبات واثباتها باستخدام التحليل العنصرية والقياسات الطيفية الخاصة بالأشعة تحت الحمراء والأشعة فوق البنفسجية والرنين النووي المغناطيسي والرنين البرمي المغناطيسي ومطياف الكتلة و التحليل الحراري كاتم تصوير المتراكبات بالميكروسكوب الالكتروني الماسح . وتم دراسة جميع المتراكبات كمضادات لسرطان الكبد والقولون وجميع المتراكبات كمضادات للبكتريا الموجبة والسالبة والفطريات وقد أظهرت النتائج أن النشاط البيولوجي لمتراكب النحاس مرتفع جدا ضد البكتريا الاشريكية القولونية . وبالرغم من تقارب النتائج فان مترابط شيف الحر و متراكبات الزنك والنحاس قد اظهرت اعلي نشاط سام للخلايا السرطانية القولونية والكبدية.