Research Article

Synthesis, Characterization, and Anticancer Activity of New Metal Complexes Derived from 2-Hydroxy-3-(hydroxyimino)-4-oxopentan-2-ylidene)benzohydrazide

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Novel metal(II) complexes derived from 2-hydroxy-N-(Z)-3-(hydroxyimino)-4-oxopentan-2-ylidene)benzohydrazide ligand (H2L) were synthesized and characterized by elemental and thermal analyses (DTA and TGA), IR, UV-VIS, 1H-NMR, ESR and mass spectroscopy, magnetic susceptibilities, and conductivities measurements. The complexes adopt distorted octahedral geometry. The ESR spectra of the solid copper(II) complexes are characteristic to d9 configuration and have an axial symmetry type of a d(2-\(x^2-y^2\))^0 ground state. The \(g\) values confirmed the tetragonal octahedral geometry with a considerably ionic or covalent environment. The cytotoxic activity of the ligand and its metal complexes showed potent cytotoxicity effect against growth of human liver cancer HepG2 cell lines compared to the clinically used Sorafenib (Nexavar).

1. Introduction

There is a growing interest in oxime-hydrazone and their coordination compounds caused by their biological activity [1, 2]. Many clinically successful anticancer drugs were either naturally occurring molecules or have been developed from their synthetic analogs. Metal complexes have unique properties enhancing their role as antitumor agents. An important property is the ability of metals to form positively charged ions in an aqueous solution that can bind to negatively charged biological molecules [3, 4]. The high electron affinity of metal ions can significantly polarize groups that are coordinated to them, leading to the generation of hydrolysis reactions [4]. Furthermore, metal ions also have the ability to coordinate ligands in a three dimensional configuration, thus allowing functionalization of groups that can be tailored to defined molecular targets [5, 6]. Recently, considerable attention has been drawn to oximes, hydrazones, and their coordinated compounds due to their biological activities as fungicides [7, 8], bactericides [9], analgesic and anti-inflammatory [10], antioxidant [11, 12], antitumor [13–15], and insecticidal [16]. Metal complexes of bis-hydrazone derived from isatin monohydrazone and 2-hydroxy-1-naphthaldehyde have been reported and they demonstrated interesting biological properties [17]. Oxovanadium(IV) complexes derived from 2-thiophene carboxylic acid hydrazide showed a great cytotoxicity towards Artemia salina [18]. Homo- and heteronuclear copper(II) and nickel(II) complexes derived from oxime-type ligands have been also reported; the observed IC\(_{50}\) values indicated that they are potential antioxidant [19]. Cytotoxicity of a series of cobalt(II) complexes of 2-furaldehyde oximes was compared with copper complexes of furan oximes to determine whether the type of metal is important to the cytotoxicity and mode of action of the complexes. It was shown that varying the type of metal produces differences in both cytotoxicity and mode of action [20].
Oxime hydrazones can react with metal(II) salts to produce either mono- or binuclear complexes. The keto hydrazone moiety may coordinate to metals in the ketoamide or deprotonated enolimine form. Compounds containing both oxime and hydrazone groups are typically act as tridentate, mono- or bidentic ligands coordinating through the amide oxygen, imine, and oxime nitrogen atom depending on the reaction conditions [21]. Considerable interest has been attracted to synthesize oxime-hydrazide compounds as important target structures and evaluated their biological activities. These observations have been guiding the development of new compounds that possess varied biological activities. In view of interest and importance to determine the metal ion content [23]. FT-IR spectra of the ligand and its complexes were obtained on Perkin-Elmer R32-90-MHz spectrophotometer. Chemical shifts (ppm) were reported relative to TMS. ESR measurements of solid complexes at room temperature were made using a Varian E-109 spectrophotometer, using DPPH as a standard material. Mass spectra were recorded using JEULJMS-AX-500 mass spectrometer.

2. Experimental

2.1. Instrumentation. All reagents employed for the preparation of the ligand and its complexes were of the analytical grade available and used without further purification. Metal salts and salicylic hydrazide were provided from SIGMA-ALDRICH company; diacetylmonoxime was prepared by a published method [22]. The purity of all compounds was confirmed by TLC. The ligand and its metal complexes were analyzed for C, H, and N at the Microanalytical center, Cairo University, Egypt. Standard analytical methods were used to determine the metal ion content [23]. FT-IR spectra of the ligand and its metal complexes were measured using KBr discs by a Jasco FT/IR 300E Fourier transform infrared spectrophotometer covering the range 400–4000 cm\(^{-1}\). Electronic spectra in the 200–900 nm regions were recorded on a Perkin-Elmer 550 spectrophotometer. The thermal analyses (DTA and TGA) were carried out on a Shimadzu DT-30 thermal analyzer from room temperature to 800°C at a heating rate of 10°C/min. Magnetic susceptibilities were measured at 25°C by the Gouy method using mercuric tetrathiocyanatocobaltate(II) as the magnetic susceptibility standard. Diamagnetic corrections were estimated from Pascal’s constant [24]. The magnetic moments were calculated from the equation

\[
\mu_{\text{eff}} = 2.84 \sqrt{\frac{\Lambda^\text{corr}}{M_w}} \cdot T.
\]

The molar conductance of 10\(^{-3}\) M solution of the complexes in DMSO was measured at 25°C with a Bibby conductometer type MCl. The resistance measured in ohms and the molar conductivities were calculated according to the equation

\[
\Lambda_M = V \cdot K \cdot \frac{g}{M_w} \cdot \frac{\Omega_w}{\Omega},
\]

where \(\Lambda_M\) = molar conductivity (Ω\(^{-1}\) cm\(^2\) mol\(^{-1}\)), \(V\) = volume of the complex solution (mL), \(K\) = cell constant (0.92/cm\(^{-1}\)), \(M_w\) = molecular weight of the complex, \(g\) = weight of the complex (g), \(\Omega\) = resistance (Ω). \(^1\)H-NMR spectra of the ligand, and its Zn(II), Cd(II), and Hg(II) complexes were obtained on Perkin-Elmer R32-90-MHz spectrophotometer. Chemical shifts (ppm) were reported relative to TMS. ESR measurements of solid complexes at room temperature were made using a Varian E-109 spectrophotometer, using DPPH as a standard material. Mass spectra were recorded using JEULJMS-AX-500 mass spectrometer.

2.2. Preparation of the Ligand and Its Metal Complexes

2.2.1 Preparation of the Ligand \([H_2L]\) (I). The ligand \((H_2L)\) was prepared by dropwise addition of equimolar amounts of salyclic hydrazide (2-hydroxy-benzohydrazide) (1.52 g, 0.01 mol) dissolved in 20 mL of absolute ethanol to an ethanolic solution of diacetyl monoxime (1.29 g, 0.01 mol) (Figure 1). The mixture was refluxed with stirring for 4 hrs. A dark green precipitate was obtained, filtered off, washed with ethanol, and dried under vacuum over P\(_2\)O\(_5\). Analytical data of the ligand are given in (Table 1).

2.2.2 Preparation of Metal Complexes, (2)–(17). Complexes (2)–(17) were synthesized by refluxing 25 mL of ethanoic solution of the ligand with 25 mL of ethanoic solution of 3.79 g,
Table 1: Analytical and physical data of the ligand \([\text{H}_2\text{L}]\) (1) and its metal complexes.

| Comp. number | Molecular formula | Color       | FW  | M.P (°C) | Yield (%) | Anal./found (calc.)(%) | Molar conductance* | M | Cl |
|--------------|-------------------|-------------|-----|----------|-----------|------------------------|--------------------|---|----|
| (1)          | \([\text{H}_2\text{L}]\) | Dark green  | 263 | >300     | 80        | 55.01 (54.75)          | 5.48 (4.98)        | 16.01 (15.96)   | —  | —  |
| (2)          | \([(\text{HL})\text{Cu}(\text{OAc})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | Green       | 439 | >300     | 85        | 39.02 (38.31)          | 4.61 (4.82)        | 9.33 (9.57)    | 14.50 (14.48) | —  | 10.12 |
| (3)          | \([(\text{HL})\text{Cu}_2(\text{OAc})_3(\text{H}_2\text{O})_3]\) ⋅ \text{H}_2\text{O} | Greenish brown | 658.56 | >300     | 90        | 33.00 (32.83)          | 5.11 (5.05)        | 6.51 (6.38)    | 19.81 (19.30) | —  | 13.15 |
| (4)          | \([(\text{H}_2\text{L})\text{Cu}(\text{OAc})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | Yellowish green | 762 | >300     | 90        | 44.47 (44.12)          | 4.39 (5.03)        | 11.22 (11.03)  | 8.52 (8.34)   | —  | 11.30 |
| (5)          | \([(\text{H}_2\text{L})\text{Cu}_2(\text{OAc})_3(\text{H}_2\text{O})_3]\) ⋅ \text{H}_2\text{O} | Yellowish green | 452 | >300     | 85        | 32.10 (31.90)          | 4.23 (4.42)        | 9.52 (9.30)    | 14.30 (14.07) | 16.00 (15.70) | 14.10 |
| (6)          | \([(\text{HL})\text{Ni}(\text{OAc})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | Pale brown  | 452 | >300     | 70        | 37.59 (37.20)          | 4.71 (5.13)        | 9.82 (9.30)    | 13.21 (12.98) | —  | 10.87 |
| (7)          | \([(\text{HL})\text{Co}(\text{OAc})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | Dark brown  | 470 | >300     | 78        | 35.98 (35.75)          | 5.51 (5.36)        | 9.12 (8.93)    | 13.00 (12.53) | —  | 11.81 |
| (8)          | \([(\text{HL})\text{Mn}(\text{OAc})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | Pale white  | 523 | >300     | 70        | 30.12 (29.83)          | 5.31 (5.01)        | 8.52 (8.03)    | 11.82 (11.26) | —  | 15.87 |
| (9)          | \([(\text{HL})\text{Zn}(\text{OAc})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | Reddish brown | 515 | >300     | 70        | 28.33 (28.01)          | 4.62 (4.50)        | 8.51 (8.16)    | 13.11 (12.70) | —  | 15.72 |
| (10)         | \([(\text{HL})\text{Cd}(\text{OAc})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | White       | 506 | >300     | 80        | 33.72 (33.25)          | 4.72 (4.58)        | 8.71 (8.31)    | 22.87 (22.23) | —  | 12.11 |
| (11)         | \([(\text{HL})\text{Hg}(\text{OAc})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | Yellowish white | 544 | >300     | 85        | 27.01 (26.50)          | 3.95 (3.89)        | 8.11 (7.73)    | 21.10 (20.67) | —  | 17.11 |
| (12)         | \([(\text{HL})\text{Fe}(\text{Cl})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | Yellowish green | 540 | >300     | 70        | 31.52 (31.15)          | 3.32 (3.17)        | 8.11 (7.78)    | 37.52 (37.15) | —  | 9.82  |
| (13)         | \([(\text{HL})\text{Cr}(\text{Cl})(\text{H}_2\text{O})_2]\) ⋅ \text{H}_2\text{O} | Black       | 461 | >300     | 75        | 31.65 (31.26)          | 4.72 (4.37)        | 9.35 (9.11)    | 12.45 (12.11) | 15.87 (15.38) | 14.87 |

*Λ (Ω⁻¹ cm² mol⁻¹).
0.02 mol of Cu(OAc)$_2$·H$_2$O (1L:1M), complex (2); 7.58 g, 0.04 mol of Cu(OAc)$_2$·H$_2$O (1L:2M), complex (3); 1.89 g, 0.01 mol of Cu(OAc)$_2$·H$_2$O (2L:1M), complex (4); 1.88 g, 0.02 mol of CuCl$_2$·2H$_2$O (1L:1M), complex (5); 3.03 g, 0.02 mol of CuSO$_4$·5H$_2$O (1L:1M), complex (6); 4.73 g, 0.02 mol of Ni(OAc)$_2$·4H$_2$O (1L:1M), complex (7); 4.99 g, 0.02 mol of NiSO$_4$·6H$_2$O (1L:1M), complex (8); 4.73 g, 0.02 mol of Co(OAc)$_2$·4H$_2$O (1L:1M), complex (9); 2.94 g, 0.02 mol of CoSO$_4$·4H$_2$O (1L:1M), complex (10); 5.86 g, 0.02 mol of 4.65 g, 0.02 mol of Mn(OAc)$_2$·4H$_2$O (1L:1M), complex (11); 4.17 g, 0.02 mol of Zn(OAc)$_2$·2H$_2$O (1L:1M), complex (12); 3.41 g, 0.02 mol of ZnSO$_4$·4H$_2$O (1L:1M), complex (13); 5.06 g, 0.02 mol of Cd(OAc)$_2$·2H$_2$O (1L:1M), complex (14); 4.87 g, 0.02 mol of CdSO$_4$·6H$_2$O (1L:1M), complex (15); 6.05 g, 0.02 mol of Hg(OAc)$_2$·4H$_2$O (1L:1M), complex (16); 5.13 g, 0.02 mol of FeCl$_3$·6H$_2$O (1L:1M), complex (17). The reaction mixtures were refluxed with stirring for 2–4 hrs range, depending on the nature of the metal ion and the anion. The precipitates so formed were filtrated off, washed with ethanol, and dried in vacuum over P$_2$O$_5$. Analytical data of the metal complexes are given in (Table 1).

### 3. Results and Discussion

All complexes are colored, stable at room temperature, non-hygrosopic, partially soluble in common organic solvents such as CHCl$_3$, and appreciably soluble in DMF and DMSO. The analytical and physical data (Table 1) and spectral data (Tables 2–4) are compatible with the proposed structures (Figure 2). Many attempts have been made to grow up single crystal but no diffractable crystals have been grown till now. The molar conductances of the complexes in 10$^{-3}$ M DMF at 25°C are in the 13.0–33.4 ohm$^{-1}$ cm$^2$ mol$^{-1}$ range, indicating a nonelectrolytic nature [26, 27]. The relative high values for some complexes suggest partial dissociation in DMF. The elemental analyses indicated that, all complexes were formed in 1 L: 1 M molar ratio, except complex (3) which is found to be formed in 1 L: 2 M molar ratio.

#### 3.1. Mass Spectra of the Ligand.

The mass spectrum of the [H$_2$L]$_2$ ligand showed the molecular ion peak at m/e 263 amu, confirming its formula weight (FW, 363). The mass fragmentation patterns observed at m/z = 76, 93, 109, 123, 137, 180, 215, and 263 amu correspond to C$_5$H$_4$OH, C$_6$H$_5$O$_2$, C$_2$H$_4$O$_2$, C$_2$H$_2$O$_2$, C$_2$H$_2$NO$_2$, C$_6$H$_4$N$_2$O$_3$, C$_6$H$_3$N$_2$O$_4$, and C$_2$H$_2$N$_2$O$_4$ moieties, respectively, supported the suggested structure of the ligand.

#### 3.2. $^1$H-NMR Spectra

The $^1$H-NMR spectrum of the ligand indicated the presence of two peaks at $\delta$ = 11.83 and 12.07 ppm assigned to proton of anti- and syn-oxime NOH protons, respectively; these two bands disappeared in the presence of D$_2$O, indicating that these protons are acidic and the hydroxyl group can participate in the coordination with the metal ions. The syn : anti ratio was found to be 1:1, indicating that the percentages of free and hydrogen bonded OHs are identical [28, 29]. Signals at $\delta$ = 9.73 and $\delta$ = 10.90 ppm were assigned to the NH protons [28, 30]. The spectrum showed a set of peaks as multiplets in the (7.94–6.81 ppm) range, which were assigned to aromatic protons ring [31]. Peaks which appeared at 2.50 and 2.21 ppm were assigned to acetyl and methyl groups respectively [17, 32]. These signals disappeared upon adding D$_2$O.

Zn(II), Cd(II), and Hg(II) complexes (12), (14), and (16) showed similar spectra. The peaks assigned to the oxime protons disappeared, indicating its participation in the metal coordination. A set of multiple peaks corresponding to the aromatic protons were observed in the 6.88–7.50 ppm range. Signals corresponding to acetyl and methyl protons appeared at 2.50 and 1.91 ppm, respectively [17, 32]; these signals were disappeared upon adding D$_2$O. A new signal was observed around 1.87 ppm, which may be assigned to protons of the coordinated acetate group [33].

#### 3.3. IR Spectra

The characteristic infrared spectral data of ligand H$_2$L (1) and its metal complexes are listed in Table 2. The spectrum of the ligand showed characteristics absorption broad bands in 3360–3315 cm$^{-1}$ range, which are due to intra- and intermolecular hydrogen bonding of OH of the oxime groups with the imino nitrogen and carbonyl oxygen atoms [22, 30]. The medium band at 3215 cm$^{-1}$ was assigned to (NH) group [29]. The band appearing at 1700 cm$^{-1}$ was assigned to v(C=O) band, which is less than the expected value. It is deduced, therefore, that the carbonyl group is involved in hydrogen bondings in the ligand. On the other hand, the v(C=O) band of the amide group appeared at 1664 cm$^{-1}$ [29]. The v(C=N) vibrations (imine and oxime groups) appeared at 1613 and 1587 cm$^{-1}$, respectively [29, 32]. Two strong bands observed at 1147 and 1000 cm$^{-1}$ which were assigned to v(N–O) [22, 34]. The splitting of the v(N–O) vibration into two bands confirmed the presence of two nonequivalent hydrogen bonding formations whereby the intramolecular type is stronger than the intermolecular type. The bonding mode of the ligand in the metal complexes has been deduced by comparing the IR spectra of the complexes with that of the free ligand. IR spectra showed that the ligand coordinated through the nitrogen atoms of the imine and
Figure 2: Proposed structures of the ligand $[H_2L]$ and its metal complexes.
| Comp. number | Molecular formula | \( \nu(H_2O/OH) \) | \( \nu(NH) \) | \( \nu(C=O)_{acetyl} \) | \( \nu(C=O)_{amide} \) | \( \nu(C=N)_{imine} \) | \( \nu(C=N)_{imine} \) | \( \nu(N-O) \) | \( \nu(\text{OAc})/\text{SO}_4 \) | \( \nu(M-O) \) | \( \nu(M-N) \) | \( \nu(M-\text{Cl}) \) |
|-------------|------------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|----------------|-----------------|----------------|----------------|----------------|
| (1) | \([H_2L]C_{12}H_{14}N_3O_4\) | 3360, 3315 | 3215 | 1700 | 1664 | 1613 | 1587 | 1147, 1000, 931 | — | — | — | — |
| (2) | \([HL]Cu(\text{OAc})_2(H_2O)_2\cdot H_2O\) | 3430 | 3260 | 1680 | 1650 | 1605 | 1575 | 1155, 1040, 925 | 1443, 1342 | 600 | 575 | — |
| (3) | \([HL]Cu_2(\text{OAc})_3(H_2O)_5\cdot H_2O\) | 3421 | 3217 | 1712 | 1669 | 1601 | 1564 | 1163, 1068, 925 | 1483, 1382 | 679 | 580 | — |
| (4) | \([H_2L]Cu_2(\text{OAc})_3(H_2O)_5\cdot H_2O\) | 3434–3380 | 341 | 1695 | 1659 | 1606 | 1538 | 1154, 1128, 1013, 954 | — | 662 | 575 | 443 |
| (5) | \([HL]CuCl_2(H_2O)\cdot 2H_2O\) | 3500 | 3202 | 1717 | 1667 | 1611 | 1529 | 1190, 1104, 1075, 977, 915 | 1260, 1071, 867, 650 | 618 | 522 | — |
| (6) | \([HL]Ni(\text{OAc})_2H_2O\) | 3464 | 3217 | 1760 | 1674 | 1605 | 1565 | 1150 | 1024, 909 | 1456, 1339 | 682 | 620 | — |
| (7) | \([HL]Ni(\text{OAc})_2H_2O\) | 3428 | 3165 | 1700 | 1670 | 1609 | 1531 | 1160, 1102, 1043, 925 | 1240, 1102, 850, 690 | 592 | 528 | — |
| (8) | \([HL]Co(\text{OAc})_2H_2O\) | 3495 | 3198 | 1719 | 1671 | 1609 | 1526 | 1150, 1065, 1022, 920 | 1465, 1326 | 624 | 535 | — |
| (9) | \([HL]Co(\text{OAc})_2H_2O\) | 3300 | 3215 | 1700 | 1652 | 1610 | 1553 | 1152, 1030, 956 | 1232, 1092, 858, 650 | 605 | 545 | — |
| (10) | \([HL]Mn(\text{OAc})_2H_2O\) | 3408 | 3217 | 1695 | 1600 | 1595 | 1565 | 1170, 1149, 1029, 920 | 1460, 1338 | 654 | 587 | — |
| (11) | \([HL]Zn(\text{OAc})_2H_2O\) | 3315 | 3217 | 1700 | 1673 | 1601 | 1566 | 1154, 1039, 985 | 1523, 1391 | 597 | 535 | — |
| (12) | \([HL]Zn(\text{OAc})_2H_2O\) | 3380 | 3285 | 1717 | 1653 | 1603 | 1552 | 1154, 1042, 951 | 1501, 1366 | 589 | 537 | — |
| (13) | \([HL]Cd(\text{OAc})_2H_2O\) | 3380 | 3206 | 1705 | 1675 | 1613 | 1534 | 1155, 1044, 979 | 1237, 1115, 1060, 885, 650 | 616 | 526 | — |
| (14) | \([HL]Cd(\text{OAc})_2H_2O\) | 3428 | 3217 | 1710 | 1652 | 1587 | 1565 | 1160, 1014, 956 | 1500, 1376 | 612 | 588 | — |
| (15) | \([HL]Hg(\text{OAc})_2H_2O\) | 3365 | 3200 | 1710 | 1644 | 1609 | 1543 | 1151, 1008, 936 | — | 665 | 524 | 482 |
| (16) | \([HL]Fe(Cl)(\text{H}_2O)\cdot 3H_2O\) | 3365 | 3200 | 1710 | 1644 | 1609 | 1543 | 1151, 1008, 936 | — | 665 | 524 | 482 |
| (17) | \([HL]Fe(Cl)(\text{H}_2O)\cdot 3H_2O\) | 3365 | 3200 | 1710 | 1644 | 1609 | 1543 | 1151, 1008, 936 | — | 665 | 524 | 482 | — |
Table 3: Electronic spectra (nm) and magnetic moments (BM) for the ligand (1) and metal complexes.

| Comp. number | Molecular formula | $\lambda_{\text{max}}$ (nm) | $\mu_{\text{eff}}$ (BM) | $\nu_2/\nu_1$ |
|--------------|-------------------|----------------------------|-------------------------|--------------|
| (1)          | $[\text{H}_2\text{L}]\text{C}_2\text{H}_3\text{N}_{3}\text{O}_4$ | 275 nm ($e = 5.86 \times 10^{-4}$ L mol$^{-1}$ cm$^{-1}$) | —                       | —            |
|              |                   | 315 nm ($e = 8.45 \times 10^{-4}$ L mol$^{-1}$ cm$^{-1}$) | —                       | —            |
|              |                   | 350 nm ($e = 9.20 \times 10^{-4}$ L mol$^{-1}$ cm$^{-1}$) | —                       | —            |
| (2)          | $[(\text{HL})\text{Cu}\text{(OAc)}(\text{H}_2\text{O})_2]\cdot\text{H}_2\text{O}$ | 265, 302, 380, 495, 550, 625 | 1.79                    | —            |
| (3)          | $[(\text{HL})\text{Cu}\text{(OAc)}(\text{H}_2\text{O})_2]_2$ | 268, 308, 380, 425, 550, 626 | 1.68                    | —            |
| (4)          | $[(\text{H}_2\text{L})\text{Cu}\text{(OAc)}(\text{H}_2\text{O})_2]_3\cdot\text{H}_2\text{O}$ | 270, 370, 390, 450, 370, 610 | 1.81                    | —            |
| (5)          | $[(\text{H}_2\text{L})\text{CuCl}_2(\text{H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 260, 300, 370, 460, 656, 605 | 1.77                    | —            |
| (6)          | $[(\text{H}_2\text{L})\text{Cu}\text{(SO}_4\text{(H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 265, 300, 400, 505, 595, 605 | 1.78                    | —            |
| (7)          | $[(\text{HL})\text{Ni}\text{(OAc)}(\text{H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 272, 303, 420, 525, 617, 687, 749 | 2.85                    | 1.06         |
| (8)          | $[(\text{HL})\text{Ni}\text{(SO}_4\text{(H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 265, 305, 415, 510, 620, 690, 720 | 2.95                    | 1.04         |
| (9)          | $[(\text{HL})\text{Co}\text{(OAc)}(\text{H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 275, 301, 420, 598, 620 | 5.11                    | 1.03         |
| (10)         | $[(\text{HL})\text{Co}\text{(SO}_4\text{(H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 302, 397, 430, 556, 621, 265 | 5.52                    | 1.11         |
| (11)         | $[(\text{HL})\text{Mn}\text{(OAc)}(\text{H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 265, 298, 390, 425, 585, 611 | 6.10                    | —            |
| (12)         | $[(\text{HL})\text{Zn}\text{(OAc)}(\text{H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 270, 305, 365 | Diamagnetic | —            |
| (13)         | $[(\text{HL})\text{Zn}\text{(SO}_4\text{(H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 265, 300, 378 | Diamagnetic | —            |
| (14)         | $[(\text{HL})\text{Cd}\text{(OAc)}(\text{H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 268, 305, 360 | Diamagnetic | —            |
| (15)         | $[(\text{HL})\text{Cd}\text{(SO}_4\text{(H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 265, 302, 370 | Diamagnetic | —            |
| (16)         | $[(\text{HL})\text{Hg}\text{(OAc)}(\text{H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 260, 305, 370 | Diamagnetic | —            |
| (17)         | $[(\text{HL})\text{Fe}\text{(Cl)}(\text{H}_2\text{O})_2]_2\cdot\text{H}_2\text{O}$ | 265, 302, 330, 475, 541, 615 | 6.11                    | —            |

the oximato (C=N → O) groups. This mode of bonding is supported by negative shifts in bands of these groups and simultaneous increasing in (N → O) band, appearing in the 1150–1170 cm$^{-1}$ range [35, 36]. In all complexes except complexes (3) and (4), the strong band assigned to $\nu(C=O)$ amid stretching band was shifted to lower frequency, indicating involvement of amide keto oxygen in the metal coordinating. The appearance of two characteristic bands at 1482, 1483, 1500, and 1345, 1382, 1376 cm$^{-1}$ in spectra of complexes (3), (4), and (16), respectively, were attributed to $\nu_{\text{asym}}(\text{COO}^-)$ and $\nu_{\text{sym}}(\text{COO}^-)$, respectively, indicating the participation of the acetate oxygen in the metal coordination [37]. The mode of coordination of acetate group has often been deduced from the magnitude of the observed separation between the $\nu_{\text{asym}}(\text{COO}^-)$ and $\nu_{\text{sym}}(\text{COO}^-)$. The separation value (Δ) between $\nu_{\text{asym}}(\text{COO}^-)$ and $\nu_{\text{sym}}(\text{COO}^-)$ for these complexes were 137, 101, and 124 cm$^{-1}$ suggesting the coordination of acetate group in a monodentate fashion [38, 39]. In addition, complex (3) showed $\nu(\text{CO}_2\text{})$ at 1560 and 1425 cm$^{-1}$ due to a bridging acetate group. The chloro complexes (5) and (17) showed new bands at 443 and 482 cm$^{-1}$, respectively, this band was assigned to $\nu(\text{M–Cl})$, whereas sulphate complexes (6), (8), (10), (13), and (15) exhibited new bands in the (1232–1260), (1004–1115), (850–885), and (650–690) cm$^{-1}$ ranges, these values indicated that the sulphate ion is coordinated to the metal ion in a unidentate chelating fashion [35, 40]. The mode of coordination is supported by presence of additional bands in 620–528 and 682–592 cm$^{-1}$ regions corresponding to $\nu(\text{M–N})$ and $\nu(\text{M–O})$ bands, respectively [22, 36, 41].

3.4. Electronic Spectra and Magnetic Moments. The electronic absorption spectral data of the ligand and its metal complexes in DMF are listed in Table 3. The ligand showed three bands at 275 nm (5.86 × 10$^{-4}$ L mol$^{-1}$ cm$^{-1}$) and 315 nm
Table 4: ESR data for metal(II) complexes (2)–(5).

| Complex | $g_\parallel$ | $g_\perp$ | $g_{iso}^{a}$ | $A_1$ (G) | $A_1$ (G) | $A_{iso}^{b}$ (G) | $G^c$ | $\Delta E_{xx}$ (cm$^{-1}$) | $\Delta E_{zz}$ (cm$^{-1}$) | $K_1^{d}$ | $K_2^{d}$ | $K$ | $g_\parallel/A_1$ (cm$^{-1}$) | $\alpha^d$ | $\beta^d$ | $\beta_1^d$ | $2\beta$ | $\alpha_0^{f}$ (%) |
|---------|--------------|--------------|----------------|-----------|-----------|----------------|------|----------------|----------------|-----------|-----------|------|----------------|---------|---------|---------|---------|---------|
| (2)     | –            | –            | 2.18           | –         | –         | –              | –    | –              | –              | –         | –         | –    | –              | –       | –       | –       | –       | –       |
| (3)     | –            | –            | 2.10           | –         | –         | –              | –    | –              | –              | –         | –         | –    | –              | –       | –       | –       | –       | –       |
| (4)     | 2.31         | 2.06         | 2.14           | 135       | 15        | 55             | 5.2  | 18181           | 20202         | 0.7       | 0.84      | 0.86 | 165             | 0.76    | 0.92    | 1.1    | 170     | 72.4    |
| (5)     | 2.25         | 2.05         | 2.12           | 120       | 12        | 48             | 5    | 17857           | 21739         | 0.63      | 0.67      | 0.8  | 173.1           | 0.67    | 0.94    | 1       | 182     | 77.7    |

$^a$ $g_{iso} = (g_\parallel + 2g_\perp)$.

$^b$ $A_{iso} = (A_1 + 2A_1)$.

$^c$ $G = (g_\parallel - 2)/ (g_\perp - 2)$. 

$^d$ $\alpha$, $\beta$, $\beta_1$, $\alpha_0$.
These values are consistent with high spin cobalt(II) ions (d^7) and charge transfer transitions of the azomethine and carbonyl groups [30, 42]. These two bands were shifted to lower energy upon complex formation, indicating participation of these groups in coordination with the metal ions. The electronic spectra of copper(II) complexes (2)–(6) were nearly identical and showing bands centered in the 425–505, 550–595, and 605–626 nm ranges assigned to 2A_{1g} \rightarrow 2A_{1g}, 3B_{1g} \rightarrow 3B_{1g}, and 2E_{g} \rightarrow 2E_{g} transitions, respectively. These transitions indicated that the copper(II) ion has a tetragonally distorted octahedral geometry. This could be due to the Jahn-Teller effect that operates on the d^9 electronic ground state of six coordinate system, elongating one trans pair of coordinate bonds and shortening the remaining four ones [43]. The magnetic moments for copper(II) complexes at room temperature were in the 1.68–1.81 range BM, supporting axial symmetry type of a d_{xz,yz} ground state, which is the most common for copper(II) complexes [22]. Complexes (2) and (3) showed isotropic type with g_{iso} = 2.18 and 2.10, whereas complexes (4) and (5) showed axial type with g_{x} > 2.04, indicating a tetragonal distortion [26, 33], corresponding to elongation along the fold symmetry axis Z. These g-values are related by the expression G = (g_{x} - 2)/(g_{x} - 2). If G > 4.0, then, the local tetragonal axes are aligned parallel or only slightly misaligned; if G < 4.0, the significant exchange coupling is present. Complexes (4) and (5) showed G value ≥ 4.0, indicating that tetragonal axes are present. Also, these complexes showed g_{y} ≤ 2.3, suggesting considerable covalent bond character around the copper(II) ion [49, 50]. Also, the in-plane σ-covalence parameter, α^2(Cu), was calculated by

\[
\alpha^2(Cu) = \left( \frac{A_1}{0.036} \right) + (g_{x} - 2.002) + \frac{3}{7}(g_{z} - 2.002) + 0.04.
\]

The calculated values for (4) and (5) are 0.76 and 0.67 (Table 4), suggesting covalent bond character [26, 51]. The g_{y}/A_1 is taken as an indication for the stereochemistry of the copper(II) complexes. Karlin has suggested that this ratio may be an empirical indication of the stereochemistry of copper(II) complex [52]. The value g_{y}/A_1 quotient in the (165–173 cm^{-1}) range is expected for copper(II) complexes within perfectly square based geometry and those higher than 150 cm^{-1} for tetragonally distorted complexes. The values for copper(II) complexes (4) and (5) are associated with a tetragonally distorted field around copper(II) centers. For copper(II) complexes with 3B_1 ground state, the g-values can be related to the parallel (K_{||}) and perpendicular (K_{\perp}) components of the orbital reduction factor (K) as follows [51]:

\[
K_{||}^2 = \frac{(g_{||} - 2.0023) \Delta E_{xy}}{8\lambda_o},
\]

\[
K_{\perp}^2 = \frac{(g_{\perp} - 2.0023) \Delta E_{xx}}{2\lambda_o},
\]

\[
K^2 = \frac{(K_{||}^2 + 2K_{\perp}^2)}{3},
\]

where \lambda_o is the spinc-orbit coupling of free copper ion (~828 cm^{-1}) and \Delta E_{xy} and \Delta E_{xx} are the electronic transition energies of 2B_1 \rightarrow 2B_2 and 2B_1 \rightarrow 2E, respectively. For the
purpose of calculation, it was assumed that the maximum in the band corresponds to $\Delta E_{xy}$ and $\Delta E_{xz}$ can be taken from the wavelength of these bands. From the above relations, the orbital reduction factors ($K_1, K_1$, and $K$) which are a measure of covalence can be calculated. For an ionic environment, $K = 1$, and for a covalent environment, $K < 1$, the lower the value of $K$, the greater the covalent character. The values of $K$ for (4) and (5) (Table 4) showed considerable covalent bond character. The in-plane and out-of-plane $\pi$-bonding coefficients ($\beta_1^2$ and $\beta_2^2$), respectively, are dependent upon to values of $\Delta E_{xy}$ and $\Delta E_{xz}$ in the following equations [53]:

$$\alpha^2 \beta_1^2 = \frac{(g_1 - 2.002) \Delta E}{2\lambda^0},$$

$$\alpha^2 \beta_2^2 = \frac{(g_1 - 2.002) \Delta E}{8\lambda^0}.$$  \hspace{1cm} (5)

Complexes (4) and (5) showed $\beta_1^2$ values 1.1 and 1.0, indicating a moderate degree of ionic character in the in-plane $\pi$-bonding, while $\beta_2^2$ are 0.92 and 0.94, indicating ionic character in the out-of-plane $\pi$-bonding [54]. It is possible to calculate the approximate orbital population for d orbital using the following equations [22]:

$$A_1 = A_{iso} - 2B \left(1 + \frac{7}{4}\right) \Delta g_1,$$

$$a_d^2 = \frac{2B}{2B^o}.$$  \hspace{1cm} (6)

where $2B^o$ is the calculated dipolar coupling for unit occupancy of the d orbital. When the data of complexes (4) and (5) are analyzed, the results suggested an orbital population close to 72.4 and 77.7% d-orbital spin density clearly, the orbit of the unpaired electron is a $d_{xy}$ orbital ground state [22]. The ESR spectral data, for copper(II) complexes are shown in Table 4. Co(II) (9) and Mn(II) (11) complex showed isotropic spectra with $g_{iso} = 2.1$ and 2.003, respectively.

### 3.6. Thermal Analyses (DTA and TGA)

IR spectral data (Table 2) indicates the presence of water molecules; thermal analyses were carried out to ascertain their nature, and to give an insight into the thermal stability of the studied compounds. The results showed that there is a good agreement in the weight loss between the calculated and the proposed formula. The thermal analyses imply that all complexes generally decomposed in several steps (Table 5). The DTA and TGA thermogram of complex (4) showed that the complex decomposed in four steps. The first peak at 120°C with a weight loss of 7.0% (calcd. 7.08%) is assigned to elimination of three hydrated water molecules, which is accompanied by an endothermic peak. The second step appeared as an exothermic peak at 160°C, assigned to loss of two CH$_3$COOH molecules with weight loss 78.1% (calcd. 77.4%). The third step appeared as an exothermic peak at 298°C, referring to melting point of the complex. The fourth step at 475°C with a weight loss of 73.36% (calcd. 74.48) implies completion decomposition of this complex that ended with the formation CuO that is accompanied by an exothermic peak. The TG and DTA thermogram of complex (8) showed that the complex decomposed in four steps. The first peak at 90°C with a weight loss of 3.69% (calcd. 3.60%) assigned to the elimination one hydrated water molecule, which is accompanied by an endothermic peak. The second step at 195°C with a weight loss of 7.48% (calcd. 7.39%) is assigned to elimination of two coordinating water molecules that is accompanied by an endothermic peak. The third step appeared as an exothermic peak at 275°C, assigned to loss of one H$_2$SO$_4$ molecule with weight loss 20.27% (calcd. 20.13%). The fourth step appeared as an exothermic peak at 400°C, referring to melting point of the complex. The fifth step at 460°C with a weight loss of 67.31% (calcd. 68.73) implies the complete decomposition of this complex that ended with the formation NiO that is accompanied by an exothermic peak. The TG and DTA thermogram of complexes (9) and (11) showed that these complexes decomposed in five steps. The first peak appeared at 79 and 90°C with a weight loss of 11.60 and 11.87% (calcd. 11.49 and 11.74%), respectively, is assigned to removal of three hydrated water molecules from each complex; this weight loss is accompanied by an endothermic peak. The second peak at 140 and 170°C with a weight loss of 7.24 and 7.90% (calcd. 7.35 and 7.73%) is assigned to elimination of two coordinated water molecules from each complex; this is accompanied by an endothermic peak. The third step at 170 and 258°C associated a weight loss of 12.46 and 12.86% (calcd. 12.25 and 13.04%) is assigned to the elimination of one acetate ion from each complex, this step accompanied with endothermic peak. The fourth step appeared as an exothermic peak at 325 and 319°C, referring to the melting point of the two complexes, respectively. The fifth step at 450 and 445°C with a weight loss of 51.79 and 64.13% (calcd. 52.98 and 65.18) implies to complete decomposition of these complexes, respectively, leaving metal oxide that is accompanied by an exothermic peak:

\[
\text{[(HL) Cu(OAc) (H$_2$O)$_2$]} \cdot 2\text{H$_2$O} \rightarrow 60^\circ\text{C} \rightarrow \text{[(HL) Cu(OAc) (H$_2$O)$_2$]} \cdot 2\text{H$_2$O}
\]

\[
\text{[(HL) Cu(OAc) (H$_2$O)$_2$]} \rightarrow 150^\circ\text{C} \rightarrow \text{[(HL) Cu(OAc)]} + 2\text{H$_2$O}
\]

\[
\text{[(HL) Cu(OAc)]} \rightarrow 265^\circ\text{C} \rightarrow \text{[(L) Cu]} + \text{CH$_3$COOH}
\]

\[
\text{[(L) Cu]} \rightarrow 570^\circ\text{C} \rightarrow \text{CuO} + \text{organic residues}
\]

### 3.7. Cytotoxicity Activity

The cytotoxic activity of the oxime hydrzone ligand H$_2$ L (1) and its metal complexes (2), (3), (4), and (9) was evaluated against human liver HepG2 cancer cell, (HepG2 cell line) within 0.1-100 $\mu$g/L concentration range. The IC$_{50}$ values were calculated for each compound and results are presented in Figure 3 and Table 6. As shown, most complexes displayed significantly cytotoxic activities compared to Sorafenib (Nexavar) standard drug. It seems that changing the anion, coordination sites, and the nature of the metal ion has effect on the biological behavior. Cytotoxicity
Table 5: Thermal analyses for metal complexes.

| Comp. number | Molecular formula | Temp. (°C) | DTA (peak) | TGA (Wt. loss %) | Assignments |
|--------------|-------------------|------------|------------|------------------|-------------|
| (4)          | [(H₂L)₂Cu(OAc)₂]⋅3H₂O C₂₈H₃₈N₆O₁₅Cu | 120  Endo     —  7.08  7.00  | Loss of hydrated 3H₂O  |
|              |                   | 160  Endo     —  8.33  8.27  | Loss of CH₃COOH  |
|              |                   | 240  Endo     —  9.09  9.02  | Loss of CH₃COOH  |
|              |                   | 298  Endo     —  —     —     | Melting point  |
|              |                   | 350  —  Exo    —  —     —     |                |
|              |                   | 395  —  Exo    —  —     —     |                |
|              |                   | 475  —  Exo    13.47 13.53 | Decomposition process with the formation of CuO  |
| (8)          | [(H₂L)Ni(SO₄)(H₂O)₂]⋅H₂O CₙH₂₇N₃O₁₁SNi | 92   Endo     —  3.69  3.38  | Loss of hydrated 1H₂O  |
|              |                   | 186  Endo     —  7.67  7.62  | Loss of coordinated 2H₂O  |
|              |                   | 275  Endo     —  22.17 22.03 | Loss of H₂SO₄  |
|              |                   | 314  Endo     —  —     —     | Melting point  |
|              |                   | 400  —  Exo    —  —     —     |                |
|              |                   | 420  —  Exo    —  —     —     |                |
|              |                   | 460  —  Exo    22.16 22.88 | Decomposition process with the formation of NiO  |
| (9)          | [(HL)Co(OAc)(H₂O)₂]⋅3H₂O CₙH₂₅N₃O₁₁CO | 79   Endo     —  11.48 11.01 | Loss of hydrated 3H₂O  |
|              |                   | 140  Endo     —  8.65  8.47  | Loss of coordinated 2H₂O  |
|              |                   | 170  Endo     —  15.52 15.25 | Loss of CH₃COOH  |
|              |                   | 325  Endo     —  —     —     | Melting point  |
|              |                   | 400  —  Exo    —  —     —     |                |
|              |                   | 430  —  Exo    —  —     —     |                |
|              |                   | 450  —  Exo    13.39 13.55 | Decomposition process with the formation of CoO  |
| (11)         | [(HL)Mn(OAc)(H₂O)₂]⋅3H₂O CₙH₂₅N₃O₁₁Mn | 90   Endo     —  11.58 11.86 | Loss of hydrated 3H₂O  |
|              |                   | 170  Endo     —  8.73  8.47  | Loss of coordinated 2H₂O  |
|              |                   | 258  Endo     —  15.65 15.69 | Loss of CH₃COOH  |
|              |                   | 319  Endo     —  —     —     | Melting point  |
|              |                   | 390  —  Exo    —  —     —     |                |
|              |                   | 413  —  Exo    —  —     —     |                |
|              |                   | 445  —  Exo    12.93 12.71 | Decomposition process with the formation of MnO  |

Table 6: Cytotoxic activity (IC₅₀) of the ligand and some metal complexes against human liver HepG2 cancer.

| Number | Compound | IC₅₀ (µM) |
|--------|----------|----------|
| Ligand | H₂L, (1) | 107 ± 5.2 |
| (2)    | [(HL)Cu(OAc)(H₂O)₂]⋅H₂O | 6.49 ± 1.7 |
| (3)    | [(HL)Cu₂(OAc)₃(H₂O)₅] | 2.67 ± 1.2 |
| (4)    | [(H₂L)₂Cu(OAc)₂]⋅3H₂O | 2.24 ± 1.2 |
| (9)    | [(HL)Co(OAc)(H₂O)₂]⋅3H₂O | 36.80 ± 4.0 |
| Standard | Sorafenib (Nexavar) | 11.8 ± 3.2 |

Activity of the complexes may be attributed to the central metal atom which was explained by Tweedy’s chelation theory [55, 56]. Cytotoxicity results indicated that all tested complexes (IC₅₀ = 2.24–6.49 µM) (except complex (9) with IC₅₀ = 36.80 µM) demonstrated potent cytotoxicity against HepG2 cancer cells. Copper complex (4) showed the highest cytotoxicity effect with IC₅₀ value of 2.24 µM, followed by complex (3) with IC₅₀ value 2.67 µM and then complex...
(2) with IC$_{50}$ value 6.49 μM. It was observed also that all complexes are more active than the free ligand. This indicated enhancing of the antitumor activity upon coordination. The enhancement of cytotoxic activity may be assigned to that the positive charge of the metal increased the acidity of coordinated ligand that bears protons, leading to stronger hydrogen bonds which enhanced the biological activity [57, 58]. 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 [59, 60]. 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 [61].

4. Conclusions

New copper(II), Nickel, cobalt(II), manganese(II), zinc(II) and cadmium(II), Mercury(II), and iron(II) metal complexes derived from $\mu^1$-(3-hydroxyiminomethyl)-4-oxopentan-2-ylidene) salicylic hydrazide (H$_2$LY) were synthesized. The analytical and physicochemical data confirmed the composition and structure of the newly obtained compounds. The ligand and tested complexes showed a high potential cytotoxic activity with IC$_{50}$ value 6.49 μM followed by complex 2.67 μM. These compounds are promising candidates as anticancer agents because of their high cytotoxic activity.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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