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In Situ Room Temperature Synthesis and Characterization of Salicylaldehyde Phenylhydrazone Metal Complexes, Their Cytotoxic Activity on MCF-7 Cell Line, and Their Investigation as Antibacterial and Antifungal Agents

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In Situ Room Temperature Synthesis and Characterization of Salicylaldehyde Phenylhydrazone Metal Complexes, Their Cytotoxic Activity on MCF-7 Cell Line, and Their Investigation as Antibacterial and Antifungal Agents

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In situ synthesis is usually used in industrial plants. As an approach new series of metal complexes of the salicylaldehyde phenylhydrazone, H_2L , have been synthesized and characterized by elemental analysis, IR, UV, ¹H-NMR, ¹³C-NMR and ESR spectra, magnetic susceptibility, and molar conductivity measurements. The spectral data and magnetic measurements of the complexes indicated that the geometries are either square planar or octahedral. All complexes showed low to moderate cytotoxic activity. The antibacterial and antifungal activities of the compounds showed that, all complexes showed higher antifungal activities than antibacterial activities. Nickel and copper complexes showed higher activity than the standard drug.

Keywords: in situ synthesis, room temperature synthesis, metal complexes, Schiff base, thermal analysis, biological study, cytotoxic activity

Introduction

2-Hydroxy Schiff base ligands and their complexes derived from the reaction of derivatives of salicylaldehyde with amines have been extensively studied in great details for their various crystallographic, structural and magnetic features.^[1,2] Numerous biological experiments have demonstrated that DNA is the primary intracellular target of anticancer drugs due to the interaction between small molecules and DNA. which cause DNA damage in cancer cells, blocking the division of cancer cells and resulting in cell death.^[3] Of these studies, the interaction of transition metal complexes containing multidentate aromatic ligands with DNA has gained much attention. This is due to their possible application as new therapeutic agents and their photochemical properties which make them potential probes of DNA structure and conformation.^[4,5] Polydentate Schiff bases with various donor atoms are well known to coordinate with various metal ions.^[6,7] These types of ligands are able to form varieties of complexes with different stoichiometry, structure, and magnetic and spectral properties. These complexes attracted the attention of many authors due to their dioxygen uptake, oxidative catalysis, magnetic behavior, and biological

activities.^[8] In view of the versatile importance of Schiff bases and their transition metal complexes, I report in this article the in situ synthesis and characterization of the Fe(III), Co (II), Cu(II), Zn(II), Mn(II), and Ni(II) metal complexes of salicylaldehyde phenylhydrazone ((E)-2-((2-phenylhydrazono)methyl)phenol). The coordination behavior of the Schiff base ligand toward metal ions was investigated via IR, UV, and ESR as well as conductivity and magnetic moment measurements. All complexes showed low to moderate cytotoxic activity. The antibacterial and antifungal activities of the compounds showed that, some of the metal complexes exhibited a greater inhibitory effect than standard drug.

Experimental

Materials

All the reagents employed for the preparation of the ligand and its complexes were of the best grade available and used without further purification.

Methods

The ligand and its metal complexes were analyzed for C, H, N, Cl, S, and metal contents at the Microanalytical Laboratory, Faculty of Science, Cairo University, Egypt. Analytical and physical data of the ligand and its metal complexes are

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reported. IR spectra of the ligand and its metal complexes were measured using KBr discs with a Jasco FT/IR 300E Fourier transform infrared spectrophotometer covering the range 400–4000 cm⁻¹ and in the 500–100 cm⁻¹ region using polyethylene-sandwiched Nujol mulls on a Perkin Elmer FT-IR 1650 spectrophotometer. Electronic spectra of the ligand and its complexes were obtained in Nujol mulls using a Shimadzu UV-240 UV-Vis recording spectrophotometer. 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.^[9] The magnetic moments were calculated from the equation: $\mu_{\rm eff.} = 2.84 \sqrt{\chi_{\rm M}^{\rm corr.T}}$. Thermal analyses were carried out in air using a Shimadzu DT-30 thermal analyzer. ¹H and ¹³C NMR spectra were obtained on Bruker Avance 300-DRX or Avance 400-DRX spectrometers. Chemical shifts (ppm) are reported relative to TMS. Molar conductances were measured on a Tacussel type CD₆NG conductivity bridge using 10⁻³M DMF solutions. ESR measurements of solid complexes at room temperature were made using a Varian E-109 spectrophotometer, with DPPH as a standard material.

The Ligand, H_2L^1

Ethanol solution (10 mL) of 2-hydroxybenzaldehyde (1.00 g, 8.19 mmol) was added dropwise to ethanol solution (10 mL) of phenylhydrazine (0.89 g, 8.19 mmol) over 15 min with stirring and continue stirring for 0.5 h. The yellow precipitate (see Figure 1) was then filtered off, washed with methanol, and dried in a vacuum desiccator over P_4O_{10} (1.23 g, 71%) yield). ¹H NMR (400 MHz, DMSO): d = 10.61 ppm [s, 1H, H(8)], 10.40 ppm [s, 1H, H(10)], 820 ppm [s, 1H, H(7)], 7.55 ppm [d, 1H, H(6)], 7.28 ppm [pst, 1H, H(2)], 720 ppm [t, 2H, J = 7.6, H(12) and H(16)], 7.01 ppm [t, 2H, J = 7.6, H (13) and H(15)], 690 ppm [m, 2H, H(1) and H(3)], 6.80 [t, 1H, J = 7.6, H(14)]. ¹³C NMR (300 MHz, DMSO, 300 K): 155.67 C(8), 144.70 C(7) and C(11), 137.36 C(2) and C(5), 129.35 C(6), 129.26 C(15) and C(13), 120.41 C(14), 119.35 C (1), 115.98 C(3), 111.70 C(12) and C(16). IR (KBr): v(OH) 3291 (br), ν (NH) 3281(Sh), ν (C=N) 1622(s), ν (C-O) 1250 (m). Elemental analysis for $C_{13}H_{12}N_2O$ (212.25): Anal. Calcd. C 73.56, H 5.70, N 13.20; Found C 73.61, H 5.92, N 13.09.

Metal Complexes

$[H_2LFeCl_3(H_2O)]$.3 H_2O , complex 2

Ethanol solution (10 mL) of 2-hydroxybenzaldehyde (0.25 g, 2.05 mmol) was added dropwise to ethanol solution (10 mL) of phenylhydrazine (0. 22 g, 2.05 mmol). After 5 min a methanol solution (20 mL) of FeCl₃.6H₂O (0.55 g, 2.05 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P₄O₁₀ (0.68 g, 74% yield). Conductance $\Lambda_{\rm m}$: 16 Ω^{-1} cm²mol⁻¹ UV (Nujol mul (nm)): $\lambda = 540, 660$ and 854 nm. Magnetic moment: 5.87 B. M. IR (KBr): v(H₂O) 3455(br), v(OH) 3285 (sh), v(NH) 3280(s), v(C=N) 1614(m), v(C-O) 1255 (m), n(M-N) 435, n(M-O) 560, v(M-Cl) 341, v(M-Cl) 365. TGA (Found (calcd., temp.): 3 H₂O 13.06 (13.18, 75°C), 1 H₂O 4.46 (4.39, 128°C), 3 Cl atoms 25.81 (25.94, 210°C), ¹/₂ Fe₂O₃ 19.25 (19.47, 595°C). Elemental analysis for C₂₆H₂₂CuN₄O₇ (410.05): Anal. Calcd. C 38.08, H 4.67, N 6.83, Fe 13.62; Found C 37.88, H 4.85, N 6.92, Fe 13.47.

$[HLFeSO_4(H_2O)_2].4H_2O$, complex 3

Ethanol solution (9 mL) of 2-hydroxybenzaldehyde (0.20 g, 1.64 mmol) was added dropwise to ethanol solution (9 mL) of phenylhydrazine (0. 18 g, 1.64 mmol). After 5 min a methanol solution (20 mL) of FeSO₄·7H₂O (0.46 g, 1.64 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P_4O_{10} (0.66 g, 85% yield). Conductance $\Lambda_{\rm m}$: 10 Ω⁻¹cm²mol⁻¹ UV (Nujol mul (nm)): $\lambda = 543, 650$ and 834 nm Magnetic moment: 5.94 B. M. IR (KBr): v(H₂O) 3435(br), ν (NH) 3279(s), ν (C=N) 1611(m), ν (C-O) 1260 (m), $\nu(SO_4)$ 1224, 1156, 1068, 965, n(M-N) 430, n(M-O) 565. TGA (Found (calcd., temp.): 4 H₂O 15.45 (15.30, 70°C), 2 H₂O 7.49 (7.65, 127°C), 1 H₂SO₄ 20.60 (20.81, 310°C), ¹/₂ Fe₂O₃ 16.64 (16.94, 590°C). Elemental analysis for C₁₃H₂₃FeN₂O₁₁S (471.24): Anal. Calcd. C 33.13, H 4.92, N 5.94, Fe 11.85, S, 6.80; Found C 32.97, H 5.02, N 6.03, Fe 11.79, S, 6.78

$[H_2LNiCl_2(H_2O)_2].H_2O$, complex 4

Ethanol solution (12 mL) of 2-hydroxybenzaldehyde (0.27 g, 2.29 mmol) was added dropwise to ethanol solution (12 mL) of phenylhydrazine (0.25 g, 2.29 mmol). After 5 min a methanol solution (20 mL) of NiCl₂.6H₂O (0.55 g, 2.29 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P_4O_{10} (0.72 g, 73% yield). Conductance Λ_m : 13 Ω^{-1} cm²mol⁻¹ UV (Nujol mul (nm)): $\lambda = 530$ and 1150 nm. Magnetic moment: 4.78 B. M. IR (KBr): v(H₂O) 3458(br), v(OH) 3286 (m), v(NH) 3279(s), v(C=N) 1609(m), v(C-O) 1254 (m), n(M-N) 440, n(M-O) 562, v(M-Cl) 356. TGA (Found (calcd., temp.): H₂O 4.44 (4.55, 68°C), 2 H₂O 9.23 (9.10, 129°C), 2 Cl atoms 17.78 (17.91, 220°C), NiO 18.64 (18.87, 515°C). Elemental analysis for $C_{13}H_{18}Cl_2N_2NiO_4$ (395.89): Anal. Calcd. C, 39.44; H, 4.58; Cl, 17.91; N, 7.08;

Fig. 1. Preparation of the ligand H_2L .



Ni, 14.83; Found C, 39.25; H, 4.71; Cl, 18.07; N, 7.18; Ni, 14.62

$[H_2LCoCl_2(H_2O)_2].3H_2O$, complex 5

Ethanol solution (13 mL) of 2-hydroxybenzaldehyde (0.28 g, 2.29 mmol) was added dropwise to ethanol solution (13 mL) of phenylhydrazine (0.25 g, 2.29 mmol). After 5 min a methanol solution (22 mL) of CoCl₂.6H₂O (0.55 g, 2.29 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P₄O₁₀ (0.72 g, 73% yield). Conductance $\Lambda_{\rm m}$: 18 Ω^{-1} cm²mol⁻¹ UV (Nujol mul (nm)): $\lambda = 530$ and 1150 nm. Magnetic moment: 4.78 B. M. IR (KBr): ν (H₂O) 3465(br), v(OH) 3282 (sh), v(NH) 3278(s), v(C=N) 1615(m), ν (C-O) 1261 (m), n(M-N) 443, n(M-O) 556, ν (M-Cl) 368. TGA (Found (calcd., temp.): 3 H₂O 12.39 (12.51, 74°C), 2 $H_2O 8.46 (8.34, 135^{\circ}C)$, 2 Cl atoms 16.48 (16.40, 210°C), $\frac{1}{2}$ Co₂O₃ 19.06 (19.19, 584°C). Elemental analysis for C₁₃H₂₂Cl₂CoN₂O₆ (432.16): Anal. Calcd. C, 36.13; H, 5.13; Cl, 16.41; Co, 13.64; N, 6.48; Found C, 35.99; H, 5.24; Cl, 16.55; Co, 13.50; N, 6.61

$[HLCu(NO_3)(H_2O)].2H_2O$, complex 6

Ethanol solution (14 mL) of 2-hydroxybenzaldehyde (0.30 g, 2.46 mmol) was added dropwise to ethanol solution (14 mL) of phenylhydrazine (0.27 g, 2.46 mmol). After 5 min a methanol solution (20 mL) of $Cu(NO_3)_2.3H_2O$ (0.59 g, 2.46 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P_4O_{10} (0.73 g, 84% yield). Conductance Λ_m : 9 Ω^{-1} cm²mol⁻¹. UV (Nujol mul (nm)): λ = 550 nm. Magnetic moment: 1.87 B. M. ESR: g_{\parallel} 2.31, g_{\perp} 2.06, g///A// 125, G 5.33, giso 2.14. IR (KBr): v(H₂O) 3430 (br), ν (NH) 3282(s), ν (C=N) 1612(m), ν (C-O) 1257 (m), NO₃: (ν 1) 1465 cm⁻¹; (ν 2) 1055 cm⁻¹; (ν 4) 1377 cm⁻¹ and (v5) 705 cm⁻¹, n(M–N) 438, n(M–O) 573. TGA (Found (calcd., temp.): 2 H₂O 10.09 (10.16, 77°C), 1 H₂O 5.19 (5.08, 133°C), 1 HNO₃ 17.59 (17.76, 295°C), CuO 22.29 (22.42, 530°C). Elemental analysis for $C_{13}H_{22}Cl_2CoN_2O_6$ (432.16): Anal. Calcd. C, 36.13; H, 5.13; Cl, 16.41; Co, 13.64; N, 6.48; Found C, 35.99; H, 5.24; Cl, 16.55; Co, 13.50; N, 6.61

$[H_2LFe(NO_3)_3(H_2O)].4H_2O$, complex 7

Ethanol solution (13 mL) of 2-hydroxybenzaldehyde (0.29 g, 2.37 mmol) was added dropwise to ethanol solution (13 mL) of phenylhydrazine (0.26 g, 2.37 mmol). After 5 min a methanol solution (22 mL) of Fe(NO₃)₃.9H₂O (0.96 g, 2.37 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P₄O₁₀ (0.93 g, 72% yield). Conductance Λ_m : 25 Ω^{-1} cm²mol⁻¹ UV (Nujol mul (nm)): λ = 556, 672 and 860 nm Magnetic moment: 5.90 B. M. IR (KBr): ν (H₂O) 3440(br), ν (OH) 3285 (w), ν (NH) 3280(s), ν (C=N) 1610(m), ν (C—O) 1258 (m), NO₃: (ν 1) 1460 cm⁻¹;

(ν 2) 1043 cm⁻¹; (ν 4) 1372 cm⁻¹ and (ν 5) 715 cm⁻¹, n (M–N) 455, n(M–O) 571. TGA (Found (calcd., temp.): 4 H₂O 13.13 (13.25, 65°C), 1 H₂O 3.33 (3.31, 124°C), 3 HNO₃ 34.57 (34.74, 350°C), $^{1}/_{2}$ Fe₂O₃ 14.77 (14.67, 589°C). Elemental analysis for C₁₃H₂₂FeN₅O₁₅ (544.18): Anal. Calcd. C, 28.69; H, 4.07; Fe, 10.26; N, 12.87; Found C, 28.57; H, 4.23; Fe, 10.41; N, 12.64

$[H_2LMnSO_4(H_2O)_2].3H_2O$, complex 8

Ethanol solution (9 mL) of 2-hydroxybenzaldehyde (0.24 g, 1.97 mmol) was added dropwise to ethanol solution (9 mL) of phenylhydrazine (0.21 g, 1.97 mmol). After 5 min a methanol solution (18 mL) of MnSO₄.H₂O (0.33 g, 1.97 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P_4O_{10} (0.72 g, 84% yield). Conductance $Λ_{\rm m}$: 15 $Ω^{-1}$ cm²mol⁻¹ UV (Nujol mul (nm)): λ = 554 nm Magnetic moment: 5.14 B. M. IR (KBr): $v(H_2O)$ 3429(br), $\nu(OH)$ 3286 (m), $\nu(NH)$ 3281(s), $\nu(C=N)$ 1613(w), $\nu(C-O)$ 1259 (m), v(SO₄) 1208, 1154, 1072, 972, n(M-N) 440, n (M-O) 568. TGA (Found (calcd., temp.): 3 H₂O 12.11 (11.93, 72°C), 2 H₂O 7.78 (7.95, 131°C), 1 H₂SO₄ 21.52 (21.64, 315°C), $\frac{1}{2}$ Mn₂O₃ 17.53 (17.41, 590°C). Elemental analysis for C13H22MnN2O10S (453.32): Anal. Calcd. C, 34.44; H, 4.89; Mn, 12.12; N, 6.18; S, 7.07; Found C, 34.28; H, 5.03; Mn, 12.18; N, 6.31; S, 6.93.

$[H_2LZnSO_4]$.5 H_2O , complex 9

Ethanol solution (14 mL) of 2-hydroxybenzaldehyde (0.32 g, 2.62 mmol) was added dropwise to ethanol solution (14 mL) of phenylhydrazine (0.28 g, 2.62 mmol). After 5 min a methanol solution (24 mL) of ZnSO₄.7H₂O (0.75 g, 2.62 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P₄O₁₀ (0.85 g, 70% yield). Conductance $\Lambda_{\rm m}$: 17 Ω⁻¹cm²mol⁻¹ IR (KBr): ν(H₂O) 3437(br), ν(OH) 3284 (sh), v(NH) 3280(s), v(C=N) 1616(w), v(C-O) 1263 (m), $\nu(SO_4)$ 1204, 1168, 1054, 984, n(M-N) 457, n(M-O) 569. TGA (Found (calcd., temp.): 5 H₂O 19.49 (19.43, 71°C), 1 H₂SO₄ 21.27 (21.15, 323°C), ZnO 17.42 (17.55, 590°C). Elemental analysis for C₁₃H₂₂N₂O₁₀SZn (463.77): Anal. Calcd. C, 33.67; H, 4.78; N, 6.04; S, 6.91; Zn, 14.10; Found C, 33.54; H, 4.92; N, 6.14; S, 7.02; Zn, 14.00.

$[H_2LZn(NO_3)_2]$.3 H_2O , complex 10

Ethanol solution (12 mL) of 2-hydroxybenzaldehyde (0.26 g, 2.13 mmol) was added dropwise to ethanol solution (12 mL) of phenylhydrazine (0.23 g, 2.13 mmol). After 5 min a methanol solution (22 mL) of Zn((NO₃)₂.6H₂O (0.63 g, 2.13 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P₄O₁₀ (0.65 g, 67% yield). Conductance Λ_m : 19 Ω^{-1} cm²mol⁻¹ IR (KBr): ν (H₂O) 3444(br), ν (OH) 3287 (w), ν (NH) 3281(s), ν (C=N) 1613(m), ν (C–O) 1259 (m), NO₃: (ν) 1470 cm⁻¹; (ν 2) 1037 cm⁻¹; (ν 4) 1382 cm⁻¹ and (ν 5)

720 cm⁻¹, n(M-N) 438, n(M-O) 539. TGA (Found (calcd., temp.): 3 H₂O 12.11 (11.86, 68°C), 1 HNO₃ 13.97 (13.83, 330°C), ZnO 17.83 (17.86, 510°C). Elemental analysis for $C_{13}H_{18}N_4O_{10}Zn$ (455.68): Anal. Calcd. C, 34.26; H, 3.98; N, 12.30; Zn, 14.35; Found C, 34.22; H, 4.09; N, 12.42; Zn, 14.26.

$[(HL)_2Co(H_2O)_2].2H_2O$, complex 11

Ethanol solution (16 mL) of 2-hydroxybenzaldehyde (0.39 g, 3.19 mmol) was added dropwise to ethanol solution (16 mL) of phenylhydrazine (0.35 g, 3.19 mmol). After 5 min a methanol solution (22 mL) of CoCl₂.6H₂O (0.38 g, 1.60 mmol) was added dropwise with stirring. A two drops of trimethyl amine were added to increase precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P₄O₁₀ (0.70 g, 79% yield). Conductance $\Lambda_{\rm m}$: 11 Ω^{-1} cm²mol⁻¹ UV (Nujol mul (nm)): $\lambda = 562$ and 1110 nm Magnetic moment: 4.65 B. M. IR (KBr): $\nu(H_2O)$ 3467(br), $\nu(NH)$ 3282(s), $\nu(C=N)$ 1609(m), $\nu(C-O)$ 1257 (m), n(M-N) 453, n(M-O) 559. TGA (Found (calcd., temp.): 2 H₂O 6.41 (6.51, 68°C), 2 H₂O 6.63 (6.51, 128°C), $^{1}/_{2}$ Co₂O₃ 15.12 (14.98, 582°C). Elemental analysis for C₂₆H₃₀CoN₄O₆ (553.47): Anal. Calcd. C, 56.42; H, 5.46; Co, 10.65; N, 10.12; Found C, 56.29; H, 5.55; Co, 10.51; N, 10.23.

$[(HL)_2FeCl(H_2O)].3H_2O$, complex 12

Ethanol solution (15 mL) of 2-hydroxybenzaldehyde (0.38 g, 3.11 mmol) was added dropwise to ethanol solution (15 mL) of phenylhydrazine (0.34 g, 3.11 mmol). After 5 min a methanol solution (20 mL) of FeCl₃.6H₂O (0.42 g, 1.56 mmol) was added dropwise with stirring. A few drops of trimethyl amine were added to allow precipitation. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P₄O₁₀ (0.69 g, 76% yield). Conductance $\Lambda_{\rm m}$: 14 Ω^{-1} cm²mol⁻¹ UV (Nujol mul (nm)): $\lambda = 558, 667$ and 855 nm. Magnetic moment: 5.98 B. M. IR (KBr): v(H₂O) 3464(br), v(NH) 3281(s), v(C=N) 1615(s), v(C-O) 1257 (m), 1261(m), n(M-N) 432(m), 437(w), n(M-O) 552 (m), ν (M—Cl) 347(w). TGA (Found (calcd., temp.): 3 H₂O 9.41 (9.23, 72°C), 1 H₂O 7.91 (3.08, 125°C), 1 Cl atoms 6.12 $(6.05, 210^{\circ}C)$, $\frac{1}{2}$ Fe₂O₃ 13.49 (13.63, 595°C). Elemental analysis for C₂₆H₃₀ClFeN₄O₆ (585.84): Anal. Calcd. C, 53.30; H, 5.16; Cl, 6.05; Fe, 9.53; N, 9.56; Found C, 53.19; H, 5.24; Cl, 6.13; Fe, 9.41; N, 9.64.

$[(H_2L)_2Cu(CH_3COO)_2].2H_2O$, complex 13

Ethanol solution (18 mL) of 2-hydroxybenzaldehyde (0.45 g, 3.68 mmol) was added dropwise to ethanol solution (16 mL) of phenylhydrazine (0.4 g, 3.68 mmol). After 5 min a methanol solution (22 mL) of Cu(CH₃COO)₂.H₂O (0.37 g, 1.84 mmol) was added dropwise with stirring. The precipitate was then filtered off, washed with methanol, and dried in a vacuum desiccator over P₄O₁₀ (1.03 g, 87% yield). Conductance Λ_m : 11 Ω^{-1} cm²mol⁻¹. UV (Nujol mul (nm)): $\lambda = 540$ and 610 nm. Magnetic moment: 1.95 B. M. ESR: $g_{||}$ 2.19, g_{\perp} 2.04, $g_{//}/A_{//}$ 165, G 5.26, g_{iso} 2.09. IR (KBr): ν (H₂O) 3454 (br), ν (OH) 3285 (w), ν (NH) 3281(s), ν (C=N) 1608(m),

 ν (C—O) 1256 (m), n(M-N) 436, 447, n(M—O) 549, 553. TGA (Found (calcd., temp.): 2 H₂O 5.52 (5.61, 79°C), 2 CH₃COOH 18.54 (18.70, 305°C), CuO 12.44 (12.39, 530°C). Elemental analysis for C₃₀H₃₄CuN₄O₈ (642.16): Anal. Calcd. C, 56.11; H, 5.34; Cu, 9.90; N, 8.72; Found C, 55.99; H, 5.43; Cu, 9.77; N, 8.79

In Vitro Antibacterial and Antifungal Activities

The investigation of the biological activities of the newly synthesized Schiff base ligand, its metal complexes, and their corresponding metal salts were carried out in the Botany Department, Laboratory of Microbiology, Faculty of Science, El-Menoufia University. The antibacterial and antifungal activities were investigated by disc diffusion method.^[10,11] The antibacterial activities were done using Escherichia coli and Aspergillus niger at 2000 ppm concentrations in DMSO. DMSO poured disc was used as negative control. The bacteria was subcultured in nutrient agar medium which was prepared using $(g.L^{-1})$ distilled water) NaCl (5 g), peptone (5 g), beef extract (3 g), and agar (20 g). The fungus was subcultured in Dox's medium, which was prepared using $(g.L^{-1}$ distilled water) yeast extract (1 g), sucrose (30 g), NaNO₃, agar (20 g), KCl (0.5 g), KH₂PO₄ (1 g), MgSO₄.7H₂O (0.5 g), and traces of FeCl₃ .6H₂O. These mediums were then sterilized by autoclaving at 120°C for 15 min. After cooling to 45°C the medium was poured into 90 mm diameter Petri dishes and incubated at 37 or 28°C, respectively. After few hours, Petri dishes were stored at 4°C. Microorganisms were spread over each dish by using sterile bent Loop rod. The test is carried out by placing filter paper disks with a known concentration of the compounds on the surface of agar plates inoculated with a test organism. Standard antibacterial drug (tetracycline), antifungal drug (Amphotericin B), and solution of metal salts were also screened under similar conditions for comparison. The Petri dishes were incubated for 48 h at 37 or 28°C, respectively. The zone of inhibition was measured in millimeters carefully. All determinations were made in duplicated manner for each of the compounds. An average of the two independent readings for each compound was record.

Cytotoxicity Assays

The cell culture cytotoxicity assays were carried out as described previously,^[12] at the National Cancer Institute, Cairo University, Cairo, Egypt.

Results and Discussion

The analytical and physical data, spectral data are compatible with the suggested structures (Figure 2). The complexes are colored, stable in air, and insoluble in H_2O , ethanol and nonpolar solvents such as benzene. However, they dissolve in polar solvents such as DMF and DMSO. All the complexes are nonelectrolytes.

Complex 2, [H₂LFeCl₃(H₂O)].3H₂O, M=Fe, X=Cl Complex 7, [H₂LFe(NO₃)₃(H₂O)].4H₂O, M=Fe, X=NO₃



Complex 8, [H₂LMnSO₄(H₂O)₂].3H₂O, M=Mn, Y=H₂O Complex 9, [H₂LZnSO₄].5H₂O, M=Zn, Y=none





HN

Complex 3, [HLFeSO₄(H₂O)₂].4H₂O, M=Fe, Y=H₂O



 $\begin{array}{l} \mbox{Complex 4, } [H_2LNiCl_2(H_2O)_2].H_2O, \ M=Ni, \ X=Cl, \ Y=H_2O \\ \mbox{Complex 5, } [H_2LCoCl_2(H_2O)_2].3H_2O, \ M=Co, \ X=Cl, \ Y=H_2O \\ \mbox{Complex 10, } [H_2LZn(NO_3)_2].3H_2O, \ M=Ze, \ X=NO_3, \ Y=none \\ \end{array}$



 $\begin{array}{l} Complex \ 11, [({\rm HL})_2 Co({\rm H_2O})_2].2 {\rm H_2O}, \ M=\!{\rm Co}, \ X=\!Y={\rm H_2O} \\ Complex \ 12, [({\rm HL})_2 {\rm FeCl}({\rm H_2O})].3 {\rm H_2O}, \ M=\!{\rm Fe}, \ X=\!{\rm Cl}, \ Y={\rm H_2O} \end{array}$



Fig. 2. The proposed structures of metal complexes of the ligand H_2L .

Complex 13, [(H2L)2Cu(CH3COO)2].2H2O, X=CH3COO

Infrared Spectra

IR spectra of the complexes were recorded to confirm their structures. The assignments of the characteristic vibrational frequencies of the complexes were made by comparison with the vibrational frequencies of the free ligand. The ligand behaved as neutral or monobasic bidentate ligand coordinating through the imine nitrogen and the phenolic oxygen. In all complexes the signal of the imine group was shifted to lower wave number accompanied by a decrease in its intensity while the signal due to phenolic C—O was shifted to higher wave number, indicating they are involved in complex

formation.^[13–17] In complexes **3**, **6**, **11**, and **12** the signal due to hydroxyl group disappeared, indicating the subsequent deprotonation of the phenolic proton prior to coordination. In other complexes this signal was shifted to lower wave number accompanied by a decrease in its intensity indicating it is coordinated to the central metal.^[18] The two new signals in the 430–457 and 539–573 cm⁻¹ ranges may be assigned to n (M–N) and n(M–O) respectively.^[15,19,20] The presence of water molecules in all complexes was supported by the presence of bands in the 3467–3429 cm⁻¹ regions.^[1,21] The spectra of the complexes **2**, **4**, **5**, and **12** showed an assignable, weak intensity ν (M-Cl) band in 347–368 cm⁻¹ range indicating a

terminal chloro ligand.^[22,23] Complexes 6, 7, and 10 showed bands in the $1460-1470 \text{ cm}^{-1}$ ($\nu 1$), $1037-1055 \text{ cm}^{-1}$ ($\nu 2$), $1372-1382 \text{ cm}^{-1}$ (v4), and 705-720 cm⁻¹ (v5) ranges with v - v4 separation of 88 cm⁻¹, characteristic of monodentate nitrato group.^[23,24] The sulfate ion has a regular tetrahedral structure belonging to the point group T_d .^[25] In its ionic state, SO₄ has nine vibrational degrees of freedom, distributed in four normal modes of vibration. Out of these, only two are infrared active.^[25] When SO₄ functions as a monodentate ligand, the oxygen coordinating to a metal atom is no longer symmetrically equivalent to the other three oxygen's and the effective symmetry of SO₄ is lowered to C_3 , C_{3v} .^[25] In C_3 , C_{3v}, symmetry, six infrared absorption bands are observed. When SO₄ functions as a bidentate group, its effective symmetry is further lowered to C2v. In C2v symmetry, eight modes of vibration, out of the total of nine, are infrared active.^[9] The sulfato complexes 3, 8, and 9 showed bands in the 965–984, 1064–1072, 1154–1168, 1205–1224 cm^{-1} regions, indicating a bidentate coordinating sulfato group.^[26] IR spectral studies reported on metal aceto complexes [24] indicated that the acetate ligand may coordinate to a metal center in either a monodentate, bidentate, or bridging manner. The $\nu_{asym.}(CO_2)$ and $\nu_{sym.}(CO_2)$ of the free acetate ions are at 1560 cm⁻¹ and 1416 cm⁻¹, respectively. In monodentate coordination $\nu(C=O)$ is found at higher energy than $v_{asym}(CO_2)$ and v(C-O) is lower than $v_{sym}(CO_2)$. As a result, the separation between the two v(CO) bands is much larger in monodentate complexes than the free ion.^[17] The opposite trend is observed in bidentate aceto coordination; the separation between ν (CO) is smaller than for the free ion. For bridging acetate with both oxygens coordinated as in copper(II) acetate; however, the two ν (CO) bands are close to the free ion values.^[27,28] Complex 13 showed two new bands at 1554 cm⁻¹ and 1344 cm⁻¹, which may be attributed to $\nu_{asym.}(COO^{-})$ and $\nu_{sym.}(COO^{-})$, respectively, with D > 210 indicating monodentate acetates.[27] Further, the complex exhibits δ (COO) at 750 cm⁻¹, which is considered diagnostic for monodentate acetates.^[29]

Molar Conductivity

The molar conductance of the metal complexes is in the 9–25 Ω^{-1} cm² mol⁻¹ range, indicating their non-electrolytic nature.^[30]

Electronic Spectra

The magnetic moments of the complexes **2**, **3**, **7**, and **12** are in 5.87–598 BM range, which is closer to the spin only value indicating an octahedral structure for the complexes, ^[31] which was further supported by the appearance of very week signals in the 540–556, 650–672, and 834–860 nm ranges which can be assigned to the transitions ${}^{6}A_{1g} \rightarrow {}^{4}T_{2g}(G)$, ${}^{6}A_{1g} \rightarrow {}^{4}T_{2g}(G)$, and ${}^{6}A_{1g} \rightarrow {}^{4}T_{1g}(G)$ in an octahedral geometry. ^[31,32] The magnetic moment of complex **3** was 5.94, indicating five unpaired electron which support that iron is present as Fe(III), this assumption was further supported by the d-d transitions pattern. Complex **4** showed d–d

transitions at 960 and 687 nm assigned to ${}^{3}A_{2g}(F) \rightarrow {}^{3}T_{2g}(F)$ (v1) and ${}^{3}A_{2g}(F) \rightarrow {}^{3}T_{1g}(F)$ (v2) spin allowed electronic transitions, which are characteristic of Ni²⁺ in an octahedral configuration.^[33-35] The 10 Dq = 10410 cm⁻¹ and calculated B $= 771 \text{ cm}^{-1}$ are in good agreement with the predicted values for octahedral complexes of Ni(II). The calculated value for the transition ${}^{3}A_{2g}(F) \rightarrow {}^{3}T_{1g}(P)$ (v3) was found at 508 nm, which is masked with the more intense C. T. The effective magnetic moment value of 3.12 BM of the nickel complex also indicates the octahedral structure of the complex.^[33,36] Complexes 5 and 11 showed signals in 530-562 and 1110-1150 nm ranges, which can be assigned to the transitions ${}^{4}T_{1g}(F) \rightarrow {}^{4}T_{1g}(P)$ and ${}^{4}T_{1g}(F) \rightarrow {}^{4}T_{2g}(F)$ in an octahedral geometry. The magnetic moments were in 465-4.78 B. M. rang, together with the positions of the absorption bands suggest octahedral geometries around the Co(II) ions.^[37-39] The UV–Vis absorption spectrum of the complex 6 showed single d-d transition band at 550 nm as is expected for a square planar copper(II) Schiff base. The magnetic moment (1.87 BM) suggests a square-planar geometry.^[39-42] The Cu(II) complex 13 showed two bands at 540 nm and 610 nm, which can be assigned to the ${}^{2}B_{1g} \rightarrow {}^{2}B_{2g}$ and ${}^{2}B_{1g} \rightarrow {}^{2}E_{g}$ transitions, respectively indicating that copper(II) have tetragonal distorted octahedral geometry.^[43,44] Its magnetic moment was 1.95 B. M., which falls within the range normally observed for octa-hedral copper complexes.^[34] The Mn(II) complex 8 showed broad bands near 554 nm, which were attributed to ${}^{6}A_{1g} \rightarrow {}^{4}T_{1g}(G)$ transition in octahedral structures.^[45,46] The magnetic moment value of 4.14 B.M. indicates a high-spin 3d⁵ system.^[45]

ESR

Further insight about the environment around copper center was provided using X-band ESR spectra of the complexes. The ESR spectra of the solid copper(II) complexes 6 and 13 at room temperature showed the g values: $g_{\parallel} = 2.19-2.31$ and $g_{\perp} = 2.04$ –2.06. These complexes showed an axial shape with $g_{\parallel} > g_{\perp}$, characteristic of complexes with ${}^{2}B_{1}(d_{x2-y2})$ ground state. The average g values were calculated according to the equation $g_{av} = 1/3[g_{\parallel} + 2g_{\perp}]$ (2.09–2.14). Complex 13 exhibits $g_{\parallel} < 2.3$, suggesting covalent characters of the copper-ligand bonding, while complex 6 exhibits $g_{\parallel} >$ 2.3 suggesting ionic characters around the copper. The parameter G = $(g \parallel -2.0023)/(g \perp -2.0023)$ shows the possibility of exchange interaction in the Cu(II) complex. The G values for all complexes (G > 4) indicated that there is no direct copper-copper interaction in the solid state.^[47] The $g_{\|}/A_{\|}$ is taken as an indication for the stereochemistry of the copper(II) complexes. Addison^{[48]} suggested that this ratio may be an empirical indication of the tetrahedral distortion of the square planar geometry. The values lower than 135 cm are observed for square planar structures and those higher than 150 cm⁻¹ for tetragonal distorted complexes. The value of $g \|/A\|$ for complexes 13 lies above 150 indicating tetragonal distorted complex. Complex 6 showed g||/A|| below 135 cm, indicating square planar geometry around copper in this complex.



Fig. 3. Antibacterial activity of the ligand and its metal complexes against gram-negative bacterium (E. coli).

Thermal Analysis of Metal Complexes

The results of TGA of complexes were in good agreement with the proposed structures. The thermo-gravimetric analysis (TG) was measured in the 20–800°C temperature range and showed that all complexes are thermally stable up to 50°C, when dehydration begins. The thermal decomposition of the complexes **2–8** and **12** take place in four main stages. These stages are losing lattice water (65–77°C range), losing coordinated water (124–135°C range), losing of the anion

(210–350°C range) then the organic constituents of the complexes start to decompose, finally leaving the metal oxides (515–595°C range), while complex **11** showed only three of these stages eliminating the stag losing the anion from the previous four. The thermal decomposition of the complexes **9**, **10**, and **13** take place in three main stages. These stages lose lattice water (68–79°C range) and the anion (305– 330°C range), then the organic constituents of the complexes start to decompose, finally leaving the metal oxides (510–590°C).



Fig. 4. Antifungal activity of the ligand and its metal complexes against fungus (Aspergillus niger).



Fig. 5. Cytotoxic activities of the ligand and its complexes against human breast cancer cell line (MCF-7).

Antibacterial and Antifungal Screening

The results of biological activity tested for the ligand and its complexes are given in Figures 3 and 4. Diameter of inhibition zone (mm) including the disc diameter was measured for each treatment. The results was in agreement with the previously reported antibacterial and antifungal properties of this class of compounds.^[49–51] All compounds under investigation showed higher antifungal activities than antibacterial activities. Complexes 4 and 6 (nickel and copper, respectively) showed higher activity than the standard drug. The overall results indicated that Ni(II), Cu(II), Zn(II), and Co(II) complexes exhibited the maximum antibacterial and antifungal activities, while Mn(II) and Fe(III) complexes showed



Fig. 6. Ratio of the IC50 of standard drug to that of ligand and its metal complexes against human breast cancer cell line (MCF-7; reactivity ratio).

moderate antibacterial and antifungal activities in this study. The results indicate that the complexes showed more activity than the ligand. This would suggest that the chelation could facilitate the ability of a complex to cross a cell membrane and can be explained by Tweedy's chelation theory.^[28] Chelation considerably reduces the polarity of the metal ion mainly because of partial sharing of its positive charge with the donor groups and possible electron delocalization over the whole chelate ring. Such chelation could also enhance the lipophilic character of the central metal atom, which subsequently favors its permeation through the lipid layer of the cell membrane.^[29]

Cytotoxic Activity

The cytotoxic activities of the ligand and its complexes were evaluated against the human breast cancer cell line (MCF-7). All the tested compounds showed low biological activity, except copper complexes, which showed a moderate activity (Figures 5 and 6). Metal complexes have higher antitumor activity than the ligand. This may be due to the lipophilic character of the central metal atom explained by Tweedy's chelation.^[29] The IC50 value of Cu(II) complexes was significantly smaller than that of the all tested compounds, which means that Cu(II) complexes are more effective than the other complexes and their ligand.^[52] The presence of oxygen coordinating to copper may reduce its activity since it is a hard base that increases the stability of Cu(II) rather than Cu (I). Sulfur is a soft base that stabilizes copper in its low oxidation state, hence in future work it may be used instead of oxy-gen as a coordinating center.^[53,54] It is to be noted that the copper is a redox active metal and the copper based metallocomplexes react with DNA, leading to the production of reactive oxygen species (ROS).[55]

Conclusion

The ligand was synthesized to compare its spectra analysis to that of its metal complexes for their characterization. The ligand and some of its complexes were previously prepared^[56,57] using complicated methods, but in this manuscript the synthesis proceeds in situ at room temperature, which is more convenient for industrial manufacturing. The spectral data and magnetic measurements of the complexes indicate that the ligand behaved as neutral or monobasic bidentate ligand and the geometries are either square planar or octahedral. The metal in complex 3 was oxidized during complex formation (Fe(II) \rightarrow Fe(III)), which is supported by its magnetic moment (5.94) and its UV and IR spectrum. Only copper showed moderate cytotoxic activity, while other complexes showed low cytotoxic activity. The presence of oxygen coordinating to copper may reduce its activity since it is a hard base that increases the stability of Cu(II) rather than Cu(I). Sulfur is a soft base that stabilizes copper in its low oxidation state, and hence in future work it may be used instead of oxygen as a coordinating center. All compounds under investigation showed higher antifungal activities than

antibacterial activities. The results indicate that the complexes showed more activity than the ligand.

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