IJPSR (2012), Vol. 3, Issue 07 **(Research Article)**

INTERNATIONAL JOURNAL
OF
PHARMACEUTICAL SCIENCES
AND
RESEARCH

Received on 15 March, 2012; received in revised form 01 May, 2012; accepted 22 June, 2012

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF BINUCLEAR Fe(III), Co(II), Ni(II), Cu(II) AND Zn(II) COMPLEXES WITH SCHIFF BASE (E)-4-[(HYDROXYL PHENYLIMINO)METHYL]BENZENE-1, 2-DIOL

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Keywords:
Schiff base complexes,
Synthesis,
PCA,
Spectra and Biological Evaluation

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ABSTRACT

Schiff base ligand (E)-4-[(hydroxyl phenylimino)methyl]benzene-1, 2-diol (H_3L) was prepared from the condensation reaction of Protochatechu aldehyde (3, 4-dihydroxybenzaldhyde) with 2-amino phenol. From the direct reaction of the ligand (H_3L) with Co(II), Ni(II) and Cu(II) chlorides and Fe(III) and Zn(II) nitrates in 2M:1L molar ratio, the five new neutral complexes were prepared. The characterization of the newly formed compounds was done by ^{1}HNMR, UV-Vis and IR spectroscopy and elemental analysis. The *in-vitro* antibacterial activity and antifungal activity of the metal complexes were studied and compared with that of free ligand. The Cupper complex shows the higher biological activity.

INTRODUCTION: Some Schiff bases were tested for fungicidal activity, which is related to their chemical structure [1], there metal complexes are important in biochemical process. For example, the transamination reactions are catalyzed by metals ions through the formation of intermediate Schiff bases containing vitamin B6 [2].

In the area of bioinorganic chemistry, interest in Schiff base complexes has centered on the role of such complexes in providing synthetic models for the metal containing sites in metallo-proteins and enzymes [3]. Schiff base ligands are potential anticancer drugs [4] and the anticancer activity of this metal complex is enhanced in comparison to the free ligand [5].

3, 4-dihydroxybenzaldehyde, (Protocatechuaaldehyde, PCA) derivatives were evaluated and showed inhibition for bacteria growth [6], antioxidants [7], antitumor [8], anticorrosion [9] and reagent in simple, rapid and highly sensitive analysis of Cr(VI) and (V) [10].

In the present work, new Schiff base derived from condensation of PCA and 2-amino phenol and its complexes are prepared and investigated using the elemental analysis and UV-Vis, IR, ^{1}HNMR spectra as well as TGA and the biological activities also are studied.

EXPERIMENTAL:

Materials and reagents: The analytical reagent grade (AR) 3, 4-dihydroxybenzaldehyde, 2-amino phenol, $CoCl_2.6H_2O$, $NiCl_2.6H_2O$,$CuCl_2.2H_2O$, $Fe(NO_3)_3$. $9H_2O$, $Zn(NO_3)_2.6H_2O$ are Merk or Aldrich was used and Organic solvents used (methanol, ethanol, diethyl ether and acetone) were HPLC or extra pure grades and were used without further purification.

Instruments: Percentages of C, H and N were determined in the Mirco analytical Laboratory, Cairo University, Giza. IR spectra were recorded using KBr pellets on a Perkin-Elmer 1430 Spectrometer for the region (200-4000 cm^{-1}) at the Faculty of Science, Tanta University.

Electronic spectra were measured in UV- Vis range (195- 1100 nm) using a Perkin-Elmer lambda 35 UV/Vis Spectrometer at the Faculty of Science, Al-Azhar University. The NMR spectra were record on DEITAZ NMR 500 MHZ Spectrometer at the National Research Centre, Dokki, Giza. The mass spectra were recorded on GC- MSA- QP 5050A Shimadzu at Cairo University, Giza. Magnetic susceptibility measurements were carried out at room temperature on a Sherwood Scientific Magnetic Balance at El-Mansoura University, Egypt. Antimicrobial activity experiments were carried out at Fermentation Biotechnology and Applied Microbiology Centre, Al-Azhar University, Cairo, Egypt.

Synthesis of Schiff base ligand (H_3L) (1): The Schiff base ligand (H3L) was prepared by dropwise addition of hot ethanolic solution (25ml)of 3,4-dihydroxy benzaldehyde(0.6905 g, 0.005mole) to hot ethanolic solution of 2-amino phenol (0.5455g, 0.005mole), The reaction mixture was heated under reflux for 3 hr. , evaporation of solvent at r.t. allowed to appear of fine dark orange crystals, filtered, washed with ethanol, acetone and diethyl ether and air dried. M.p. 160°C; M.wt. 229.0; Anal.Calc. for $C_{13}H_{11}N_1O_3$: C,68.1 ; H, 4.8; N, 5.96%, Found: C, 67.8; H, 4.65; N, 5.96%; Main IR Peaks (KBr,Cm^{-1}): ν(OH)3318, ν(C=N)1627.

General procedure for the Preparation of complexes: The solid complexes were prepared by dropwise addition of an ethanolic solution of metal salts to an ethanolic solution of the ligand in 2:1 molar ratio metal salt: ligand, the reaction mixture refluxed for 3hr., the obtained precipitate was filtered and washed with ethanol, acetone and diethyl ether and air dried.

- **The complex, $Fe_2L(H_2O)_5(NO3)_3.2H_2O$, (2)** Black solid. M.p. >300°C; M.wt. 649.6; Anal.Calc. for $C_{13}H_{22}Fe_2N_4O_{19}$: C,24.0; H,3.3; N,8.65; Fe,17.17%; Found: C,24.25;H,3.39;N,8.2;Fe,17.00; Main IR Peaks (KBr,Cm^{-1}) : ν(C=N)1590.
- **The complex, $Co_2L(H_2O)_3(Cl).2H_2O$, (3):** Dark brown solid. M.p.180°C; M.wt. 465.8; Anal.Calc for $C_{13}H_{18}Co_2N_1O_8Cl_1$: C, 33.5; H, 3.85; N, 3.0; Co, 25.28%; Found: C, 33.24; H, 3.5; N, 2.8; Co, 25.10%; Main IR Peaks (KBr, cm^{-1}): ν(C=N)1593.
- **The complex, $Ni_2L(H_2O)_3(Cl).2H_2O$, (4):** Dark brown solid, M.p. 175°C;M.wt.465.4; Anal. Calc. for $C_{13}H_{18}Ni_2N_1O_8Cl_1$: C,33.5; H,3.85; N,3.0; Ni, 25.20%; Found: C, 33.4; H,3.75; N,2.85; Ni,25.10%; Main IR Peaks (KBr,Cm^{-1}) : ν(C=N)1592.
- **The complex, $Cu_2L(H_2O)_3(Cl). H_2O$, (5):** Black solid. M.p. 300°C; M.wt. 457.0; Anal.Calc. for $C_{13}H_{16}Cu_2N_1O_7Cl_1$: C, 34.1; H,3.5; N,3.1; Cu, 27.78%; Found: C, 33.80; H, 3.4; N, 2.87; Cu,27.65%; Main IR Peaks (KBr, cm^{-1}): ν(C=N)1604.
- **The complex, $Zn_2L(H_2O)_3(NO_3). 3H_2O$, (6):** Brown solid. M.p. 185°C; M.wt. 526.8; Anal.Calc. for $C_{13}H_{20}Zn_2N_2O_{12}$: C, 29.6; H, 3.8; N, 8.6; Zn, 24.82%; Found: C, 29.5; H, 3.6; N, 8.4; Zn, 24.70; Main IR Peaks (KBr, cm^{-1}): ν(C=N)1596.

RESULTS AND DISCUSSION: The present Schiff base H_3L, (**Fig. 1)** was prepared by refluxing in ethanol an equimolar mixture of PCA and 2-aminophenol. The structure of formed Schiff base was established by IR, ^{1}HNMR, mass and U.V-vis spectra as well as elemental analysis. All complexes were prepared by direct reaction between Schiff base ligand H_3L and corresponding salts. The obtained complexes are stable in air and have melting points above 150°C. They are insoluble in organic solvents such as diethyl ether and acetone, but soluble in DMF and DMSO. The elemental analysis data of the Schiff base and complexes **(Section 2)** are in well agreement with the expected structure.

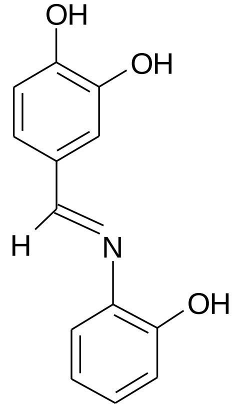


FIGURE 1: PROPOSED STRUCTURE OF (H_3L)

The molar conductance values of the synthesized complexes was determined using 10^{-3} M concentration in DMF as solvent, are in the range of 0.83 -1.65 Ω^{-1} cm^2 mol^{-1} These values suggest non-electrolyte nature for these complexes [11].

Characterization of ligand (H_3l): The infrared spectrum of the Schiff base ligand (H_3L) in the region 200-4000 cm^{-1} shows a medium absorption band at 1627 cm^{-1} assigned to the C=N stretching vibrations, indicating the formation of the Schiff base linkage. Furthermore, the absence of C=O and $-NH_2$ stretching vibration in the spectra of the ligand related to aldehyde and amine, respectively. Indicate the occurrence of Schiff base condensation [12].

The spectrum shows a broad medium intensity band occurs at 3318cm^{-1} due to νOH, the phenolic νC-OH stretching vibration is observed at 1270 cm^{-1}. The two weak intensity bands at 3090 and 2860 cm^{-1} corresponding to ν(C-H)ar. and ν(C-H)aliph stretching vibration. νPh-N gives medium intensity band at 1169cm^{-1} .

The ^{1}HNMR spectrum of the Schiff base ligand (**Fig. 2a, b)** shows signals lying at rang 8.5-9.5ppm are due to the resonance hydroxyl groups, the signals of OH groups lying at higher field side can be attribute to the contribution of the OH group intramolecular and intermolecular hydrogen bonds, addition of D_2O to the pervious solution results in diminishing the signal due to proton exchange. The resonance of imine proton dowenfield shifted to (9.6 ppm) due to the strong shielding effect of the hydroxyl groups. Also the multiple signals lying in range 6.7-8.4 ppm are due to resonance of aromatic protons.

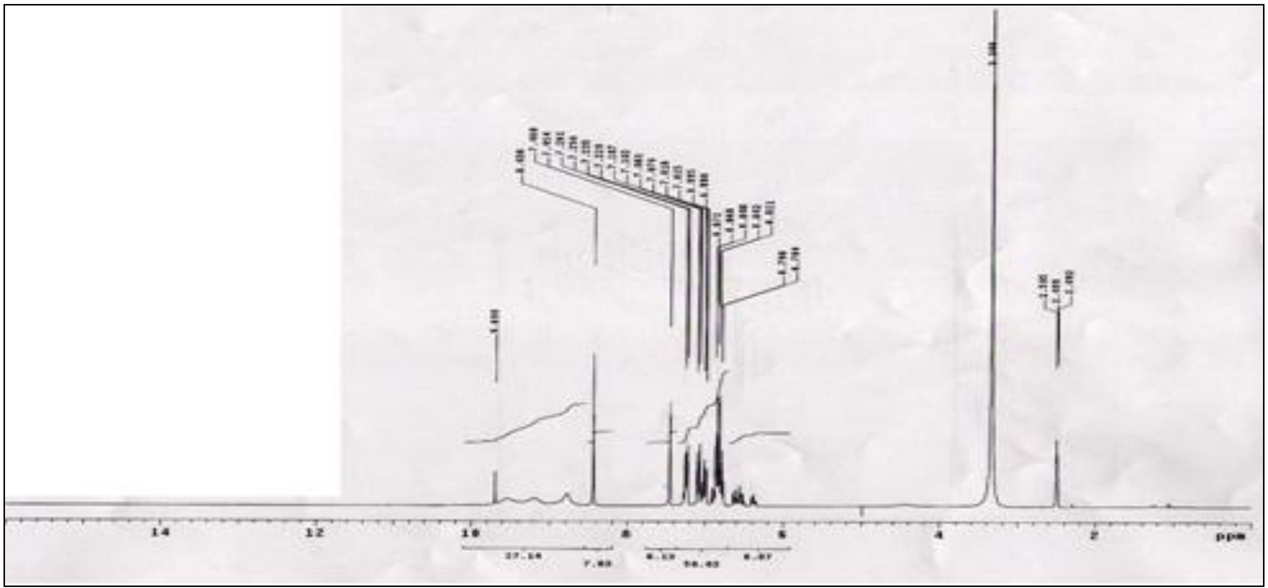


FIGURE (2-A): THE ^{1}HNMR SPECTRUM FOR (H3L) IN (DMSO)

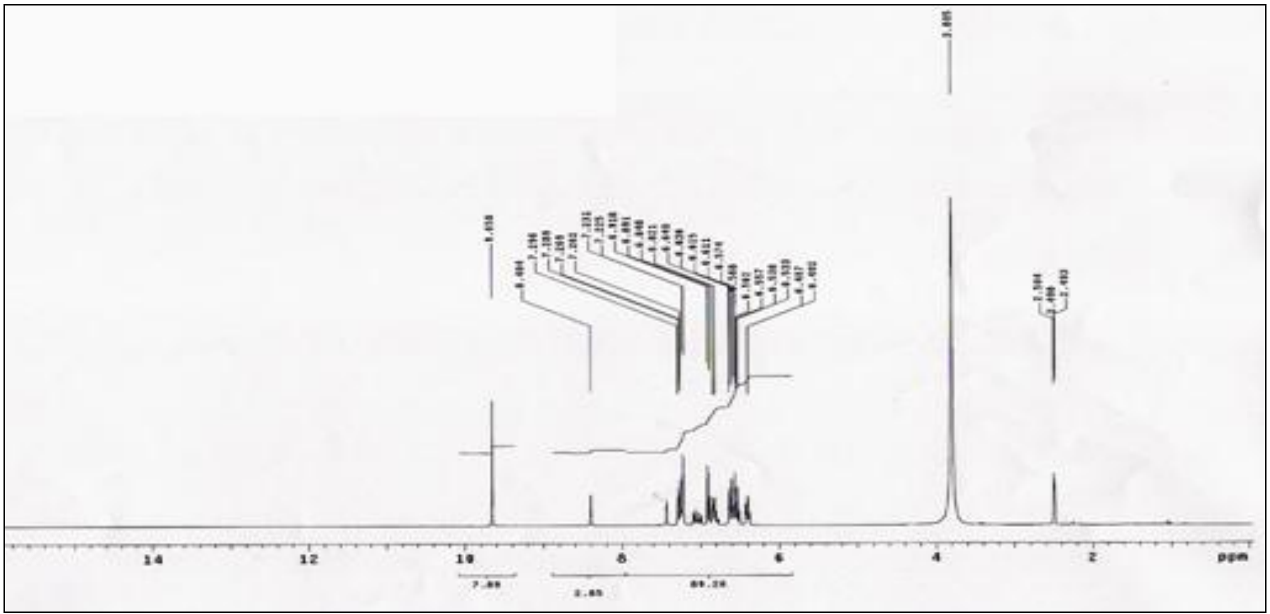


FIGURE (2-B): THE ^{1}HNMR SPECTRUM FOR (H3L) IN (DMSO+D_2O)

The electronic spectrum of the ligand in DMF displays bands below 330nm are attribute to intraligand Π-Π* and n-Π* transitions of the benzene ring and azomethine group. The mass spectrum of the free Schiff base ligand **(Fig. 3)** shows its molecular ion peak at m/e=229 which coincides with formula weight.

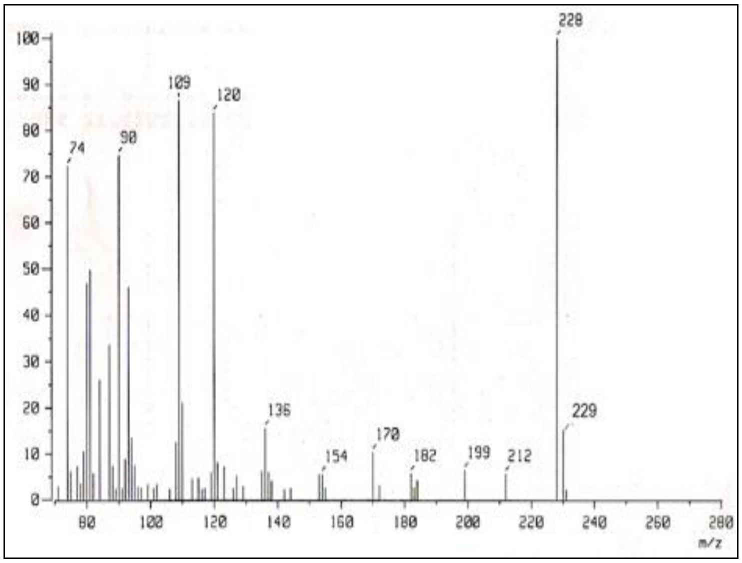


FIGURE 3: THE MASS SPECTRUM FOR (H3L)

Characterization of the complexes:

1. **Infrared spectra:** The infrared spectra (**table 1**) of the complexes provide some information about the bonding in the complexes. The band in the ir spectrum of the ligand at 1627cm^{-1} is found to be shifted to lower frequencies (1590-1604cm^{-1}) in the spectra of the complexes, indicating coordination via the azomethine nitrogen [13], the new bands in the far infrared spectra of the complexes in the range (450-509)cm^{-1} assigned to the νM-N.

Deprotonation of of all phenolic functions is confirmed by the lack of phenolic O-H stretching bands at 3318 indicating the Participation with the metal ion as –O$^-$,on the other hand very broad bands observed in the spectra of the complexes in the range (3389-3448) cm^{-1}considerable support the presence of water molecules in the complexes [14]. The band at 1270cm^{-1} in the free ligand ascribed to the phenolic C-O stretching vibration, this band is shifted to lower frequencies (1165-1196cm^{-1}) due to O- metal coordination **[15]**. The weak bands appeared in the far IR spectra between (540-590cm^{-1}) attributed to νM-O.

The infrared spectra of complexes **(2)** and **(6)** exhibit bands around 1543, 1289 and 1125 cm^{-1} due to ν(N=O), $\nu_{asym}(NO_2)$ and, $\nu_{sym}(NO_2)$, respectively which are corresponding to nature of coordinated monodentate nitrate group [16]. The far infrared spetra of the complexes **(3, 4 and 5)** show weak bands in the range (370-390cm^{-1}) ascribable to νM-Cl.

TABLE 1: THE IR SPECTRA DATA FOR COMPOUNDS (1-6)

Compound No.	ν(H_2O)	ν(OH)	ν(CH)ar.	ν(CH) aliph.	ν(C=N)	ν(C-OH)	ν(Ph-N)	ν(M-O)	ν(M-N)	ν(M- Cl)
1	-	3318	3090	2860	1627	1270	1169	-	-	-
2*	3414	-	3068	2838	1590	1190	1125	***580***	***509***	-
3	3389	-	3050	2886	1593	1196	1114	***581***	***480***	***375***
4	3348	-	3062	2850	1592	***1193***	1116	***590***	***490***	***370***
5	3434	-	3080	2855	1604	1192	1114	***578***	***450***	***390***
6*	3425	-	3065	2845	1599	1165	1118	***540***	***471***	-

*nitrate complexes

2. **Electronic spectra:** The electronic spectrum of Fe^{+3} complex (**2**) in DMF, exhibit two bands at 440 and 320 nm assignable to the spin allowed electronic absorption of T2g(F) ⟶ 5Eg transition in octahedral configuration and charge transfer, respectively. The magnetic moment (5.60 B.M) infers the presence of octahedral geometry around the central Fe^{+3} ion [17]. The electronic spectrum of Co(II) complex **(3)** in DMF shows the low intensity shoulders at 590 and 656. The former bands is probably due to $^4A_2$(F) ⟶ $^4T_1$ (P) and $^4A_2$(F) ⟶ $^4T_1$(F) which indicating tetrahedral geometry of this complex [18]. The magnetic moment of 4.27 BM sustain this configuration. The spectrum of the Ni(II) complex **(4)** in DMF shows a very broad band at 600nm containing the $^3T_1$ ⟶ $^3T_1$(P) corresponding to the tetrahedral configuration of this complex.

The magnetic moment (3.2 BM) indicates the tetrahedral geometry of the ligand around Ni $^{+2}$ ion [19]. The spectrum of Cu(II) complex **(5)** in DMF gave abroad band at 506nm ,hence, the cupper complex appear to be in tetrahedral geometry .The μeff value (1.8 B.M) is corresponding to tetrahedral geometry arrangement of the ligands around the Cu^{+2} ion [20]. The electronic spectroscopy doesn't permit the establish of a clear stereochemistry for the Zn(II) but taking into consideration the tendency of the Zn(II) ion for the tetrahedral geometry in the tetra coordination complexes, we propose this type of stereochemistry. The electronic absorption spectrum of Zn(II) complex **(6)** in DMF showed charge transfer band at 430nm**,**the diamagnetic behavior due to d10 configuration of Zn^{+2} ion [21].

3. **The ^{1}HNMR spectra:** The ^{1}H-NMR spectrum of the zinc complexe (**Fig. 4a**) recorded in DMSO-d6 at room temperature. In the spectrum of the complex the enolic proton signals observed at δ 8.5-9.5 ppm in the spectrum of the free ligand is found to be absent, confirming subsequent involvement of deprotonated hydroxyls in chelation to the metal ions. The strong broad signal appears at δ 4.4 ppm which not found in the spectrum of the free ligand due to resonance of protons of coordinated water molecules. Addition of D_2O to the previous solution shows the absence of the signal due to proton exchange (**Fig. 4b**).

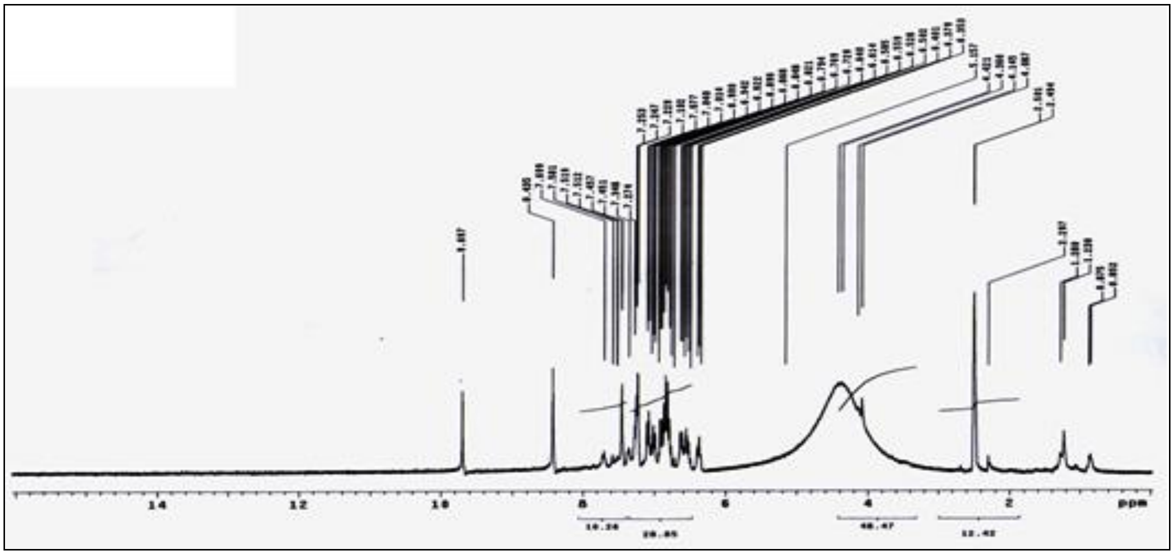


FIGURE (4-A) THE ^{1}HNMR FOR Zn COMPLEX IN (DMSO)

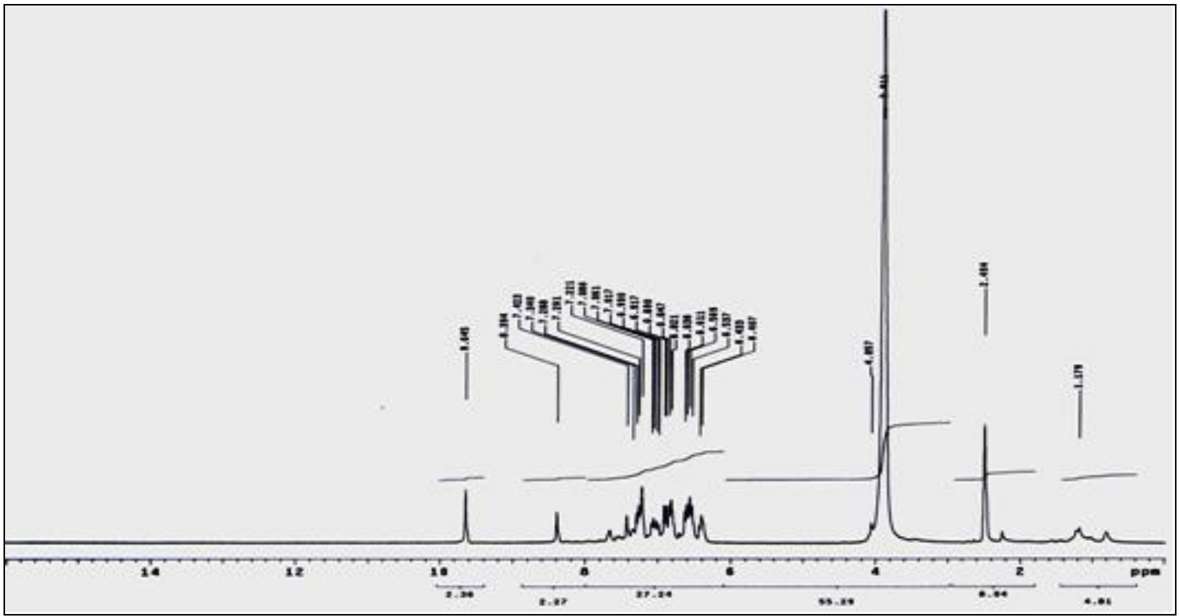


FIGURE (4-B): THE ^{1}HNMR FOR Zn COMPLEX IN (DMSO+D_2O)

4. **Thermal analysis:** The thermogravimetric analysis (TGA) **Figures (5-7)**, curves for complexes (**2, 3 and 4**), respectively were obtained at a heating rate of 10°C/min and flowing nitrogen atmosphere over a temperature range of 20-1000°C and recorded in **table 2**. The decomposition temperature and the weight losses of the complexes were calculated from TGA data.

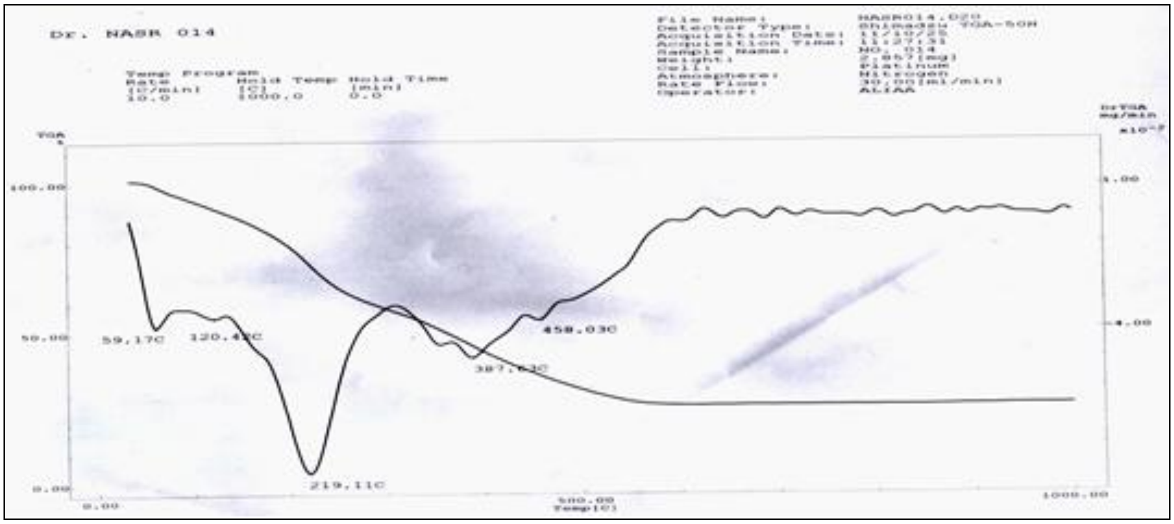


FIG. 5: TG AND DTG OF COMPLEX (2)

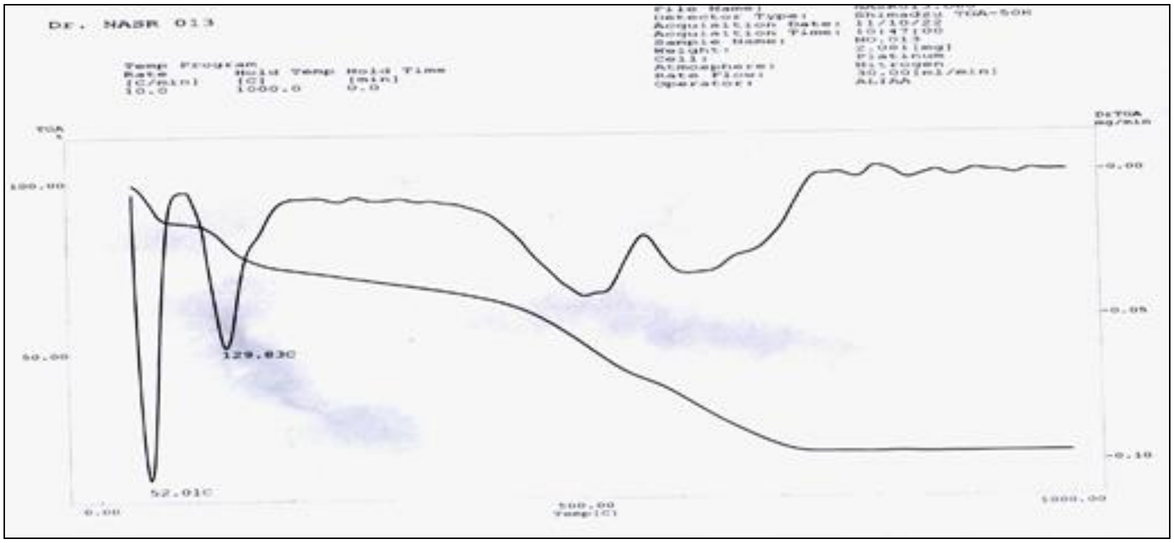


FIG. 6: TG AND DTG OF COMPLEX (3)

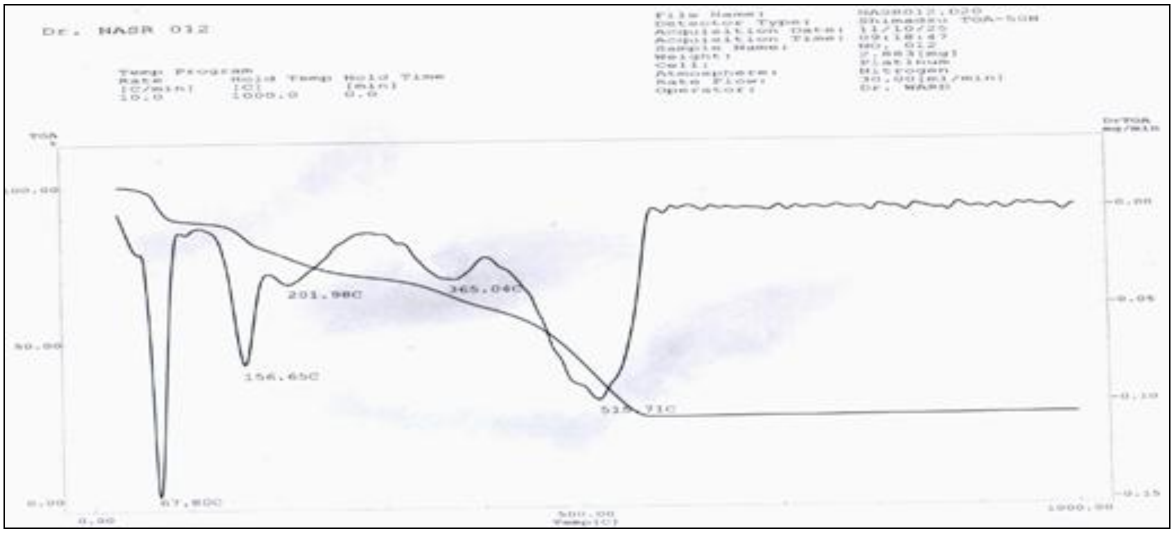


FIG. 7: TG AND DTG OF COMPLEX (4)

TABLE 2: THERMAL GRAVIMETRIC ANALYSIS FOR COMPOUNDS (2, 3 AND 4)

Compound No.	Stages	Calculated	Found	Assignment
2	First Step	***5.50***	***5.53***	Two crystalline H_2O
	Second Step	***16.70***	***16.30***	Five Coordinated H_2O +1H_2O from decomposition of Nitric Acid
	Third Step	***19.00***	***19.07***	1O_2 + 2NO_2 from Decomposition of Nitric Acid
	Fourth Step	***33.70***	***34.20***	1NO_2 from Decomposition of Nitric Acid and Organic part of ligand
	Residue	***24.90***	***24.50***	F_2O_3
3	First Step	11.15	11.22	2 crystalline H_2O + 1Coordinated H_2O
	Second Step	14.87	14.12	2 Coordinated H_2O + 1HCl
	Third ,Fourth and Fifth Step	54.10	54.05	Decomposition of Organic part of ligand
	Residue	***23.97***	***25.50***	1.25CoO
4	First Step	11.15	11.57	3 crystalline H_2O
	Second Step	11.15	11.53	3 Coordinated H_2O
	Third Step	7.73	6.16	1HCl
	Fourth Step	9.66	9.61	1.5NO
	Fifth Step	***35.02***	***35.84***	Decomposition of Organic part of ligand
	Residue	***23.97***	***25.50***	1.5NiO

5. **ESR Spectra:** The ESR spectrum of complex **(5), Fig. 8** exhibit a signal associated to Cu(II) with g*ll* – factor of about 3400. In this case, the electronic fine structure is large compared to the electron Zeeman interaction leading to a single line. The g factor derivates strongly from complex **(5)** because of strong spin-orbit coupling. The ESR spectral parameter of Copper(II) in complex having tetrahedral geometry around Cu^{+2} ion. These data are well consistent with other reported values [22].

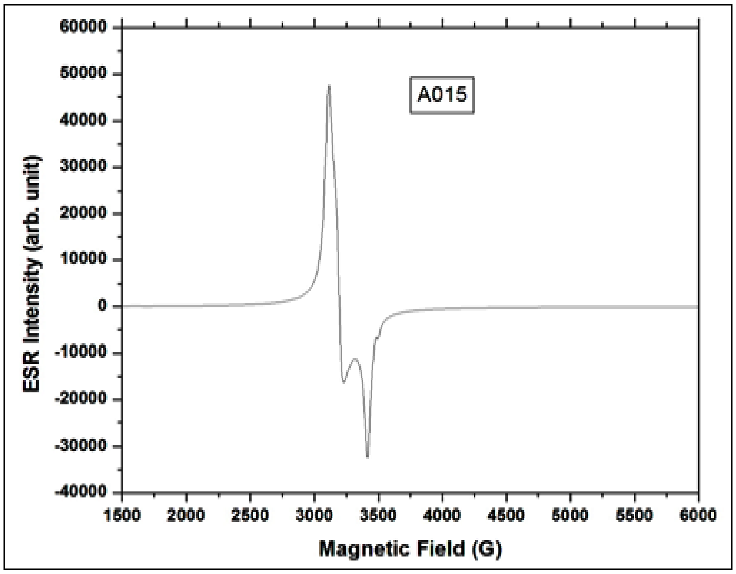
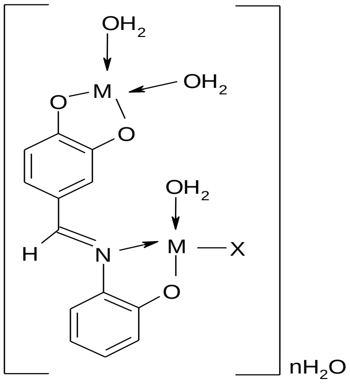


FIG. 8: ESR SPECTRUM OF COMPLEX 5



M=Co(II), Ni(II) X=Cl n=2
M=Cu(II) X=Cl n=1
M=Zn(II) X=NO_3 n=3

FIG. 9: PROPOSED STRUCTURE OF COMPLEXES 3, 4, 5 AND 6

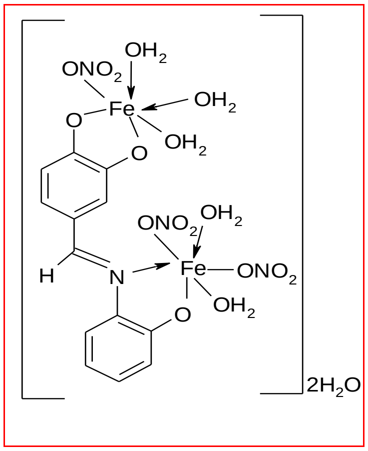


FIG. 10: PROPOSED STRUCTURE OF COMPLEX (2)

Antimicrobial Activity: Screening for the antimicrobial activity of the ligand H_3L and its complexes were tested; the testing was carried out by using the classical agar diffusion method (Cooper, 1972). Antimicrobial disk diffusion was performed as described by the National Committee for Clinical Laboratory Standard [23, 24]. The antimicrobial activity data of the compounds are collected in **table 3** and show that all tested compounds have an appropriate activity against Gram-positive bacteria represented by *Bacillus subtilis* and *Staphylococcus aureus*. The most active of them was compound number **(5)** (recorded 28.5 & 29 mm inhibition zone diameter respectively) followed by compound number **(3)** (recorded 22 & 25 mm inhibition zone diameter respectively). Also, the compound **(5)** showed a good activity against Gram-negative bacteria represented by *Escherichia coli* ande *Pseusdomonas aeruginosa* (recorded 22 & 30 mm inhibition zone diameter respectively).

In turn, compounds **(5)** and **(4)** have a good and highest activity against unicellular fungi represented by *Candida albicans* (compound **(5)** recorded 29.5 mm zone diameter) and filamentous fungi represented by *Aspergillus niger* (compounds **(5, 6** and **4)** showed a good activity and recorded (30, 27.4 and 25.5 mm zone diameter respectively). In sum, the most active compound among the six tested compounds against the six tested microorganisms was compound number **(5)** due to its wide spectrum of activity and good activity against bacteria and fungi as we see from (**Fig. 11**).

TABLE 3: THE ANTIMICROBIAL ACTIVITY OF THE COMPOUNDS (1-6)

Comp No.	Recorded zone diameter (mm) for each test microorganism					
	Bacteria				Fungi	
	Gram +ve		Gram -ve		Unicellular	Filamentous
	B. subtilis **NCTC 10400**	***S. aureus*** **NCTC 7447**	***E. coli*** **NCTC 10416**	***P. aeruginosa*** **ATCC 10145**	***C. albicans*** **IMRU3669**	***A. niger*** **LIV 131**
1	22.50	22.00	17.50	23.00	19.50	24.50
2	15.50	17.50	14.00	16.50	19.00	20.00
3	22.00	25.00	19.5	20.00	20.00	23.50
4	20.5	19.50	18.00	20.00	20.00	25.50
5	28.5	29.00	22.00	30.00	29.50	30.00
6	21.00	21.00	17.00	22.00	16.00	27.4
St.	29.00	31.00	34.00	32.00	25.00	00.00

St. = Standard antibiotic (Amikacin)

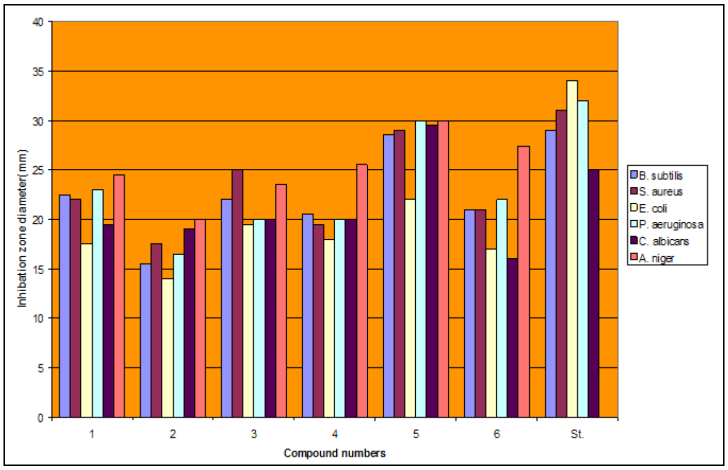


FIGURE 11: BIOLOGICAL EVALUATION OF SCHIFF BASE (H3L) AND ITS COMPLEXES

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How to cite this article:
Hassan A.M., Nassar A.M., Ahmed Y.Z. and Elkmash A.N.: Synthesis, Characterization and Biological Evaluation of Binuclear Fe(III), Co(II), Ni(II), Cu(II) AND Zn(II) complexes with schiff base (e)-4-[(hydroxyl phenylimino)methyl]benzene-1, 2-diol. *Int J Pharm Sci Res*, 2012; Vol. 3(7): 2243-2251.