

Synthesis, Characterization And Biological Studies of Metal Complexes of Schiff Base Ligand Derived From 4-Acetyl-5,6-Diphenyl-3(2H)-Pyridazinone And Ethylenediamine

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Abstract: New metal complexes of Fe(III), Zn(II), Cd(II) and Ce(III) with Schiff base ligand were synthesized. The ligand was synthesized by the reaction of 4-acetyl-5,6-diphenyl-3(2H)-pyridazinone with ethylenediamine. The structures of the Schiff base and its metal complexes were characterized by elemental and thermal analyses, IR, electronic, mass, ^1H NMR as well as conductivity and magnetic susceptibility measurements. The obtained complexes include binuclear as well mononuclear complexes. All metal complexes exhibited octahedral except Ce(III) which gave octa-coordinated arrangements. The antimicrobial activity of the Schiff base and its metal complexes was screened against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), Gram-negative bacteria (*Salmonella typhimurium* and *Escherichia coli*), yeast (*Candida albicans*) and fungus (*Aspergillus fumigatus*).

Keywords: Schiff base ligand, 4-acetyl-5,6-diphenyl-3(2H)-pyridazinone; Antimicrobial activity.

1 Introduction

Schiff-base complexes are important stereochemical models in coordination chemistry due to their preparative accessibility and structural diversity [1–3]. Schiff bases offer a versatile and flexible series of ligands capable to bind with transition, non-transition, lanthanide metal ions to give complexes with suitable properties for theoretical studies and/or practical applications [4–6]. Also, Schiff bases and their metal complexes have been used as anticancer, antitubercular, antibacterial, antifungal, antihypertensive and hypothermic reagents [7–9]. 3-Pyridazinone derivatives possess antibacterial [10,11], antifungal [12,13], anticancer [14,15], antitubercular [13], anti-inflammatory and analgesic [16,17].

The present study aims to study the chelating behavior of the new Schiff base, N,N'-bis[5,6-diphenyl-3-oxo-2H-pyridazin-3-yl-ethylidene]ethane-1,2-diamine towards metal ions. Metal complexes have been synthesized and characterized by elemental and thermal analyses, IR, electronic and mass spectra as well as conductivity and magnetic susceptibility measurements at room temperature. The biological activity of the ligand and its complexes was screened against selected kinds of bacteria and fungi.

2 Experimental

2.1 Measurements

Elemental analyses (C, H and N) were carried out using Vario El-Elementar at the Ministry of Defense, Chemical War Department. Analysis of metal ions followed the dissolution of the solid complex in concentrated HNO_3 , neutralizing the diluted aqueous solutions with ammonia and titrate the metal solutions with EDTA. Melting points of the complexes were determined using a Stuart SMP3 melting point apparatus. IR spectra were recorded using KBr discs on FT IR Nicolet IS10 spectrometer. The electronic spectra were recorded at room temperature on a Jasco model V-550 UV/Vis spectrophotometer as Nujol mulls and/or solutions in DMF. ^1H NMR spectra were recorded at room temperature on a Bruker WP 200 SY spectrometer. Dimethylsulfoxide, DMSO- d_6 , was used as a solvent and tetramethylsilane as an internal reference. Mass spectra were recorded on GC-2010 Shimadzu Gas chromatography instrument mass spectrometer. Samples were introduced directly to the probe, and the fragmentations were carried out at 300 oC and 70 eV. The magnetic susceptibility measurements were carried out at room temperature using a magnetic susceptibility balance of the type Johnson Matthey, Alfa product, Model No.

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(MKI). Effective magnetic moments were calculated and corrected using Pascal's constants for the diamagnetism of all atoms in the compounds [18]. Molar conductivities of 10^{-3} M solutions of the solid complexes in DMF were measured on the Corning conductivity meter NY 14831 model 441. TGA-measurements were carried out from room temperature up to 800 °C at a heating rate of 10 °C/min on a Shimadzu-50 thermal analyzer. The biological activity of the ligand and its metal complexes was studied using the disc diffusion method.

2.2 Materials

4-Acetyl-5,6-diphenyl-3(2H)-pyridazinone was prepared according to literature [19]. EDTA disodium salt, ammonium thiocyanate, ErochromeblakeT and nitric acid were Aldrich, BDH or Merck products. Organic solvents (ethanol, diethylether, dimethylformamide (DMF) and dimethylsulfoxide (DMSO)) were reagent grade chemicals were used without further purification.

2.3 Synthesis Of The Schiff Base Ligand

The Schiff base ligand (Scheme 1) was synthesized by adding ethylenediamine (0.1 g, 1.66 mmol) dissolved in absolute ethanol (10 ml) to 4-acetyl-5,6-diphenyl-3(2H)-pyridazinone (1 g, 3.448 mmol) in absolute ethanol (20 ml). The reaction mixture was heated to reflux for 2h. The obtained yellow product was filtered off and washed with few amounts of ethanol then diethylether, air-dried and recrystallized from ethanol. The crystalline ligand was kept in a desiccator until used. The yield was 0.8 g (38 %) and m.p. above 300°C.

2.4 Synthesis Of The Metal Complexes

The metal salt and the ligand, both dissolved in ethanol, were mixed in the molar ratio 1:2 (L:M) and heated under reflux for 4 h. The resulting precipitates were filtered, washed with ethanol then ether and finally air-dried. The complexes were kept in a desiccator over anhydrous calcium chloride. As representative examples, the following synthetic methods are provided in details.

2.4.1 Synthesis of $[(L)Fe_2(NO_3)_4(H_2O)_4](NO_3)_2$ (1)

0.534 g (1.32 mmol) of $Fe(NO_3)_3 \cdot 9H_2O$ dissolved in 30 ml ethanol was added gradually to 0.4 g (0.66 mmol) of the ligand suspended in 30 ml ethanol. The reaction mixture was heated under reflux for 4 h which resulted brown precipitate and was filtered off, washed several times with ethanol, diethylether and finally air-dried. The yield was 57%.

2.4.2. Synthesis of $[(L)_2Ce](NO_3)_3 \cdot 2H_2O$ (4)

0.432 g (1.00 mmol) of $Ce(NO_3)_2 \cdot 6H_2O$ dissolved in 40 ml ethanol was added gradually to 1 g (1.65 mmol) of the ligand suspended in 40 ml ethanol. The resulting mixture was heated under reflux 7 h which resulted yellow precipitate and was filtered off, washed several times with ethanol, diethylether and finally air-dried. The yield was 15%.

2.5 Antimicrobial Activity

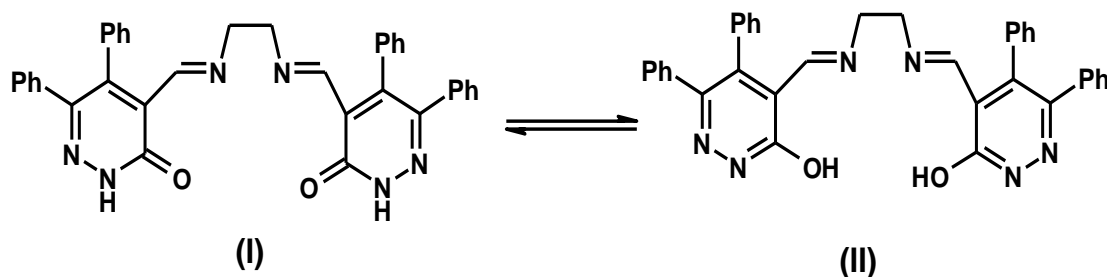
The standardized disc-agar diffusion method [20,21] was followed to determine the activity of the synthesized compounds against the sensitive organisms *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (ATCC 6635) as Gram positive bacteria, *Salmonella typhimurium* (ATCC 14028) and *Escherichia coli* (ATCC 25922) as Gram negative bacteria and *Candida albicans* (ATCC 10231) and *Aspergillus fumigatus* as fungus strain. The antibiotic chloramphenicol was used as reference in the case of Gram-positive bacteria, cephalothin in the case of Gram-negative bacteria and cycloheximide in the case of fungi.

2.5.1 Preparation Of The Tested Compound

The tested compounds were dissolved in dimethylformamide and prepared in two concentrations; 100 and 50 mg/ml and then 10 µl of each preparation was dropped on disk of 6 mm in diameter and the concentrations became 1 and 0.5 mg/disk respectively. In the case of insoluble compounds, the compounds were suspended in DMF and vortexed then processed.

2.5.2 Testing For Anti-Bacterial And Yeast Activity

Bacterial cultures were grown in nutrient broth medium at 30 °C. After 16 h of growth, each microorganism, at a concentration of 10⁸ cells/mL, was inoculated on the surface of Mueller-Hinton agar plates using sterile cotton swab. Subsequently, uniform size filter paper disks (6 mm in diameter) were impregnated by equal volume (10 µl) from the specific concentration of dissolved compounds and carefully placed on surface of each inoculated plate. The plates were incubated in the upright position at 36 °C for 24 hours. Three replicates were carried out for each extract against each of the test organism. Simultaneously, addition of the respective solvent instead of dissolved compound was carried out as negative controls. After incubation, the diameters of the growth inhibition zones formed around the disc were measured with transparent ruler in millimeter, averaged and the mean values were tabulated.

Scheme 1: Tautomeric structures of the Schiff base ligand (H_2L)

2.5.3 Testing For Anti-Fungal Activity

Active inoculum for experiments was prepared by transferring many lapfuls of spores from the stock cultures to test tubes of sterile distilled water (SDW) that were agitated and diluted with sterile distilled water to achieve optical density corresponding to 2.0×10^5 spore/ml. Inoculum of 0.1 % suspension was swabbed uniformly and the inoculum was allowed to dry for 5 minutes then the same procedure was followed as described above.

3 Results And Discussion

3.1 The Schiff Base Ligand

Table 1 lists the analytical and physical data of the Schiff base ligand and its metal complexes. The results of the elemental analyses are in a good agreement with the proposed formula. The characteristic infrared spectral data of the Schiff base ligand and its metal complexes are listed in Table 2. The IR spectrum of the ligand showed four bands at 3289, 1665, 1572 and 1537 cm^{-1} that may be assigned to $\nu(NH)$, $\nu(C=O)$, $\nu(C=N)$ and $\nu(C=C)$, respectively.

The electronic spectral data of the ligand in DMF (Table 3) showed two bands at 271 and 328 nm. The higher energy band may be assigned to $\pi-\pi^*$ transitions of the azomethine linkage and the aromatic benzene ring. The lower energy band may be assigned to the $n-\pi^*$ transition which is overlapped with charge transfer transitions within the molecule.

1H NMR spectral data (δ ppm) of the ligand relative to TMS (0 ppm) in $DMSO-d_6$ are listed in Table 4.

The signals observed at 12.58 ppm may be assigned to the NH protons. The signals due to aromatic protons are detected in the range 7.00-7.28 ppm. Finally, signals observed at 2.84 and 1.78 ppm may be assigned to the CH_2 and CH_3 protons, respectively.

The mass spectrum of the Schiff base showed the molecular ion peak at m/z 605, confirming its formula weight (F.W. 604.72).

3.2 Metal Complexes

The ligand was allowed to react with Fe(III), Zn(II), Cd(II) and Ce(III) ions to give metal complexes. The prepared complexes are stable at room temperature, non-hygroscopic and insoluble in water and common organic solvents. The obtained complexes are characterized by elemental and thermal analyses, IR, electronic and mass spectra as well as conductivity and magnetic measurements. The analytical data of the complexes are listed in Table 1.

3.2.1 IR Spectra

The IR spectral data of the complexes are listed in Table 2. Comparison of the IR spectra of the metal complexes with that of the free ligand revealed that all complexes showed a broad band in the range 3382-3444 cm^{-1} assignable to $\nu(OH)$ of the coordinated or uncoordinated water and/or ethanol molecules associated with the complexes which are confirmed by elemental and thermal analyses. The band observed in the range 3181-3285 cm^{-1} may be assigned to $\nu(NH)$. Also, the bands at 1665 and 1572 cm^{-1} assigned to $\nu(C=O)$ and $\nu(C=N)$, respectively in the free ligand were shifted to lower wave number in all complexes, indicating the participation of these groups in chelation [22]. The appearance of $\nu(NH)$ and $\nu(C=O)$ bands suggests the presence of the ligand in the pyridazinone form (tautomer I, Scheme 1) in the solid state. In complexes 2 and 3, the new bands observed in the ranges (1486, 1457) and (1218, 1217) cm^{-1} may be due to $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$, respectively of the acetate group [23]. The separation of the two bands, $\Delta\nu = (\nu_{as}-\nu_s) = 268-240$ cm^{-1} , is comparable to the values cited for the monodentate character of the acetate group [24-27]. The complex 1 and 4 showed new bands at (1383 and 1387) and (833 and 821) cm^{-1} , indicating the monodentate character of NO_3^- group [28-33]. Also, complex 1 showed bands at (1383 and 1113) cm^{-1} indicating the ionic nature of the NO_3^- group. The previous interpretation is further supported by the appearance of weak to medium intensity absorption bands which are absent in the free ligand at: 516- 622 and 418-428 cm^{-1} that may be attributed to $\nu(M-O)$ and $\nu(M-N)$; respectively [25,26].

Table 1. Analytical and physical data of the pyridazinone Schiff base and its complexes

No	Complex	M. F. [F. Wt]	Color	Yield (%)	M.P. °C	Elemental analysis, % Found/(Calc.)			M
						C	H	N	
	L	C ₃₈ H ₃₂ N ₆ O ₂ [604.72]	Yellow	38	>300	75.30 (75.48)	5.12 (5.33)	13.80 (13.90)	---
1	[(L)Fe ₂ (NO ₃) ₄ (H ₂ O) ₄] (NO ₃) ₂	C ₃₈ H ₄₀ N ₁₂ O ₂₄ Fe ₂ [1160.80]	Brown	57	>300	39.04 (39.32)	4.11 (3.47)	14.46 (14.48)	9.28 (9.65)
2	[(L)Zn(OAc) ₂].3H ₂ O	C ₄₂ H ₄₄ N ₆ O ₉ Zn [841]	White	40	272	59.30 (59.92)	5.90 (5.23)	9.80 (9.98)	7.45 (7.72)
3	[(L)Cd(OAc) ₂]	C ₄₂ H ₃₈ N ₆ O ₆ Cd [835.20]	White	52	>300	60.00 (60.40)	4.90 (4.58)	10.50 (10.06)	13.58 (13.45)
4	[(L) ₂ Ce](NO ₃) ₃ .2H ₂ O	C ₇₆ H ₆₈ N ₁₅ O ₁₅ Ce [1570]	Yellow	15	216	58.46 (58.14)	4.36 (4.30)	13.30 (13.38)	a (8.90)

^a not determined**Table 2.** Characteristic IR spectral data of the pyridazinone Schiff base and its metal complexes

No	Complex	v(O-H)	v(NH)	v(C=O)	v(C=N)	v(C=C)	v(M-O)	v(M-N)	Other bands
	L	----	3289	1665	1572	1537	----	----	---
1	[(L)Fe ₂ (NO ₃) ₄ (H ₂ O) ₄] (NO ₃) ₂	3444	3272, 3181	1640	1575	1530, 1492	530	418	1383, 833; v(NO ₃ ⁻) (ionic), 1383, 1113; v(NO ₃ ⁻)
2	[(L)Zn(OAc) ₂].3H ₂ O	3414	3285, 3186	1645	1571	1494	622	428	1457vas(COO ⁻), 1217vs(COO ⁻); (mondentate OAc ⁻)
3	[(L)Cd(OAc) ₂]	3382	3245, 3186	1645	1566	1501, 1486	516	428	1486 vas (COO ⁻), 1218vs(COO ⁻); (mondentate OAc ⁻)
4	[(L) ₂ Ce](NO ₃) ₃ .2H ₂ O	3410	3283, 3186	1641	1571	1507, 1471	521	422	1387, 821; v(NO ₃ ⁻) (ionic)

Table 3. Electronic spectra, magnetic moments and molar conductivity data of the pyridazinone Schiff base and its metal complexes

No	Complex	Electronic spectral bands ^a (nm) λ_{\max}^a (nm)/(ϵ_{\max} L cm ⁻¹ mol ⁻¹)	$\mu_{\text{eff.}}^e$ B.M	μ_{compl}^d B.M.	Conductance ^a (Ω^{-1} cm ² mol ⁻¹)
	L	271,328	-	-	-
1	[(L)Fe ₂ (NO ₃) ₄ (H ₂ O) ₄] (NO ₃) ₂	(428,541) ^b ,(408,526) ^c	4.28	6.07	149
2	[(L)Zn(OAc) ₂].3H ₂ O	(337,430) ^c	-	-	2.66
3	[(L)Cd(OAc) ₂]	(346,439) ^c	-	-	2.48
4	[(L) ₂ Ce](NO ₃) ₃ .2H ₂ O	(327,487) ^b	2.13	-	150

^aSolutions in DMF (10⁻³ M).

^bNujol mull.

^cconcentrated solutions.

^d μ_{compl} . is the total magnetic moments of all cations in the complex.

^e $\mu_{\text{eff.}}$ is the magnetic moment of one cationic species in the complex.

Table 4. ¹H NMR spectral data of the ligand and Cd(II) and Zn(II) complexes

H ₂ L	Zn(II) 2	Cd(II) 3	Assignment
1.78	2.2	2.3	(s, 6H, 2CH ₃)
2.84	2.5	2.5	(s, 4H, 2CH ₂)
7.00-7.28	7.09-7.26	7.11-7.28	(m, 20H, Ar-H)
12.58	13.63	13.20	(bs, 2H, 2NH exchangeable with D ₂ O)

3.2.2. Conductivity Measurements

The molar conductance values of the complexes (Table 3) showed that complexes **2** and **3** have non electrolytic nature while complexes **1** and **4** gave molar conductance values at 149 and 150 Ω^{-1} cm² mol⁻¹, respectively, suggesting their 1:2 electrolytic nature [34].

3.2.3. Magnetic Measurements And Electronic Spectra

The electronic spectra of the Fe(III) complex **1** in DMF is dominated by two absorption bands observed at 408 and 526 nm. The first band is assigned to a charge transfer band (MLCT) and the second band could be assigned to $d \rightarrow d((G)^6A_1 \rightarrow (S)^4T_2)$ electronic transition provides evidence for octahedral arrangement around the Fe(III) ion [25,35,36]. The d-d bands could be assigned to ${}^4A_1E(G) \leftarrow {}^6A_1(S)$ and ${}^4E(D) \leftarrow {}^6A_1(S)$ transitions. The magnetic

moment values 4.28, this value is lower may be due to antiferromagnetic interaction [37]. The white Zn(II) **2** and Cd(II) **3** complexes, are diamagnetic as expected and their geometries are most probably octahedral. The ¹H-NMR spectra of Zn(II) **2** (Figure 1) and Cd(II) **3** complexes in DMSO-d₆. The chemical shifts of the proton signals in the spectrum and their assignments are listed in Table 4. The signals observed at 13.20 and 13.63 ppm may be assigned to the NH protons suggests the presence of the ligand in the pyridazinone form (tautomer I, Scheme 1) in the complexes. The mass spectra of complex **2** and **3** (Figures 2 and 3) showed the molecular ion peaks at m/z 787 and 835 confirming its formula weight with the calculated formula weight of the non-hydrated or solvated complex. The magnetic moment of the present Ce(III) complex **4** are found to be 2.13 B.M This is close to the experimental range of 2.14–2.46 B.M. [38,39]. The electronic spectra of the Ce(III) complex **4** showed a new absorption band at 487 which may be related to MLCT transition [40].

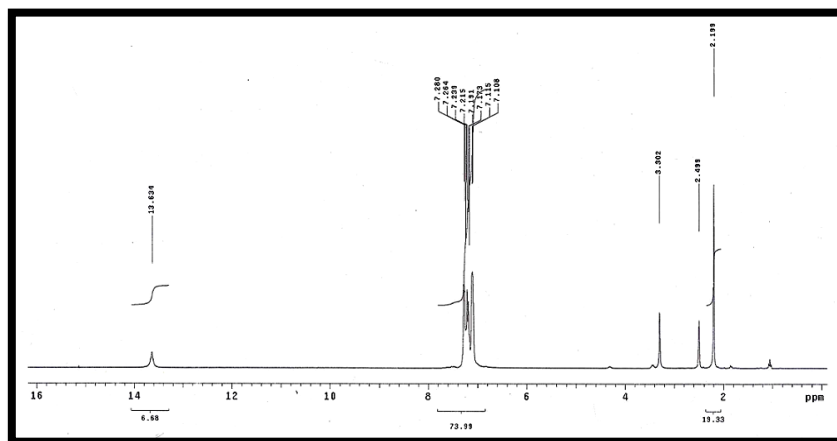


Figure 1. ^1H NMR spectrum of $[(\text{L})\text{Zn}(\text{OAc})_2]\cdot 3\text{H}_2\text{O}$ (**2**)

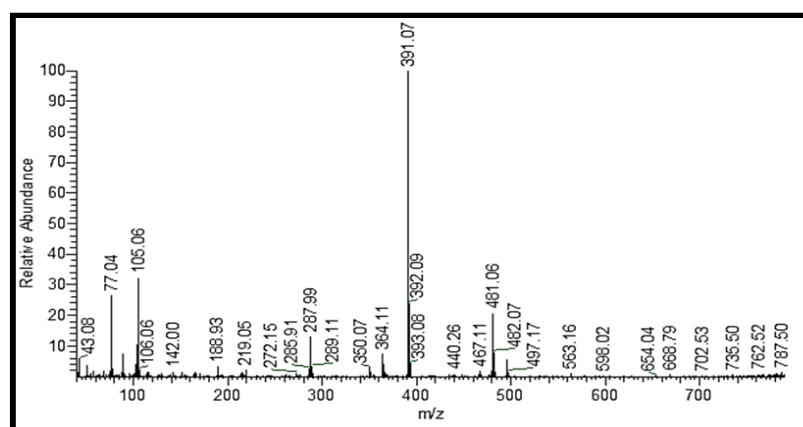


Figure 2. The mass spectrum of $[(\text{L})\text{Zn}(\text{OAc})_2]\cdot 3\text{H}_2\text{O}$ (**2**)

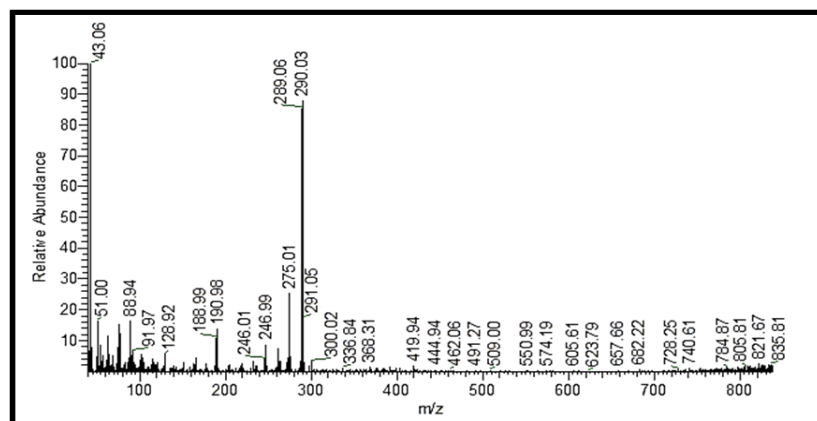


Figure 3. The mass spectrum of $[(\text{L})\text{Cd}(\text{OAc})_2]$ (**3**)

3.2.4 Thermal Analysis

Thermal gravimetric analysis (TGA) was used to proof the associated water or solvent molecules to be in the coordination sphere or in the outer sphere of the complex. Complexes **1** and **4** were taken as representative examples for thermal analysis.

The results of thermal analysis of these complexes are consistent with elemental analyses.

In case of complex **1** (Figure 4), two decomposition stages were observed in the temperature range 32-313°C. the first step corresponds to the loss of four coordinated water and two HNO₃ molecules (weight loss; Calc./Found%;16.30/17.57 %). The second step correspond to the loss four HNO₃ molecules (weight loss; Calc./Found%; 20.75/19.55 %).

The thermogram of complex **3** (Figure 5) showed two weigh losses in the ranges 136-514 and 514-622 °C which correspond to one CH₃COOH molecule and one CH₃COOH in addition to C₁₆H₂₀N₄ molecules (weight loss; Calc./Found%; 6.14/7.18 and 39.44/39.28 %, respectively). Finally, based on the above interpretation of analytical and spectral techniques, tentative structures of the metal complexes can be summarized in Schemes 2.

3.3 Antimicrobial Studies

The antimicrobial activity of the ligand and its metal

complexes was investigated against the sensitive organisms *Staphylococcus aureus* (ATCC25923) and *Bacillus subtilis* (ATCC6635) as Gram-positive bacteria, *Escherichia coli* (ATCC 25922) and *Salmonella typhimurium* (ATCC 14028) as Gram-negative bacteria, yeast: *Candida albicans* (ATCC 10231) and fungus: *Aspergillus fumigatus*. The results are listed in Table 5.

Inspection of the data given in Table 5 reveals that the ligand is only active towards *Bacillus subtilis*, and revealed

the following findings:

- 1- Complex **1** showed low activity against *Candida albicans*.
- 2- Complex **2** showed intermediate activity against *Bacillus subtilis* and *Candida albicans*.
- 3- Complex **3** showed high activity against *Candida albicans* and intermediate activity against *Staphylococcus aureus* and *Bacillus* and low activity against *Escherichia coli* and *Salmonella typhimurium*.
- 4- Complex **4** showed no activity against antimicrobial activity.

It was reported that the antibacterial activity of the compound is affected by different factors such as nature of the chelating agent and its chelating sites, nature of the metal ion, geometrical structure of the complex, solubility and other factors [41].

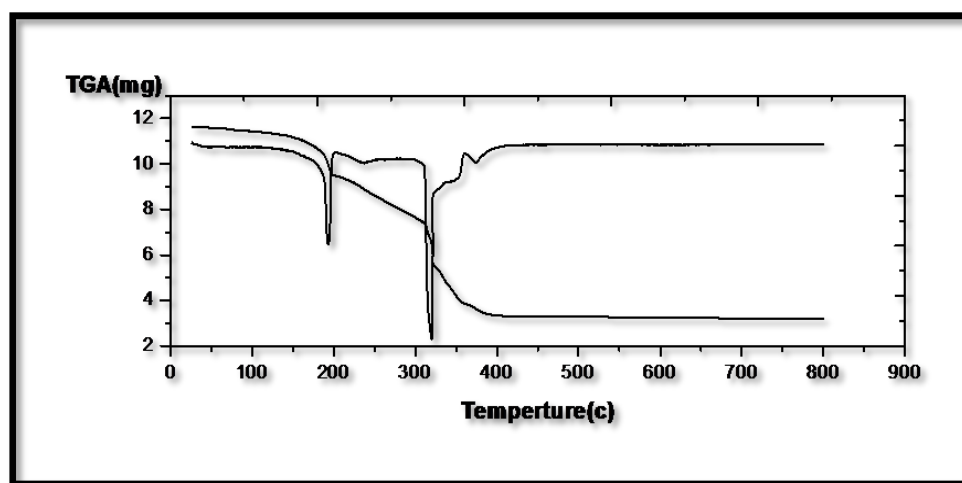


Figure 4. The TGA-DrTGA curves of [(L)Fe₂(NO₃)₄(H₂O)₄](NO₃)₂ (**1**)

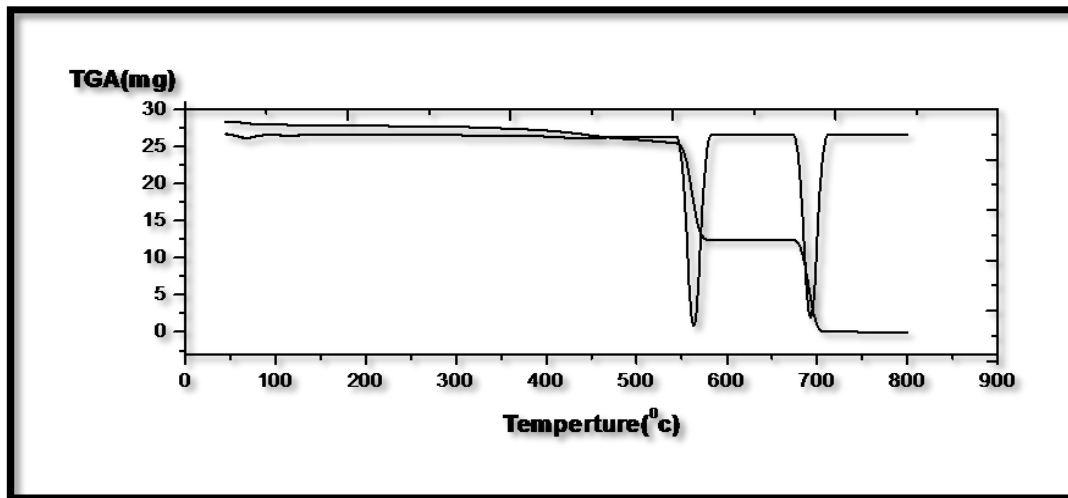
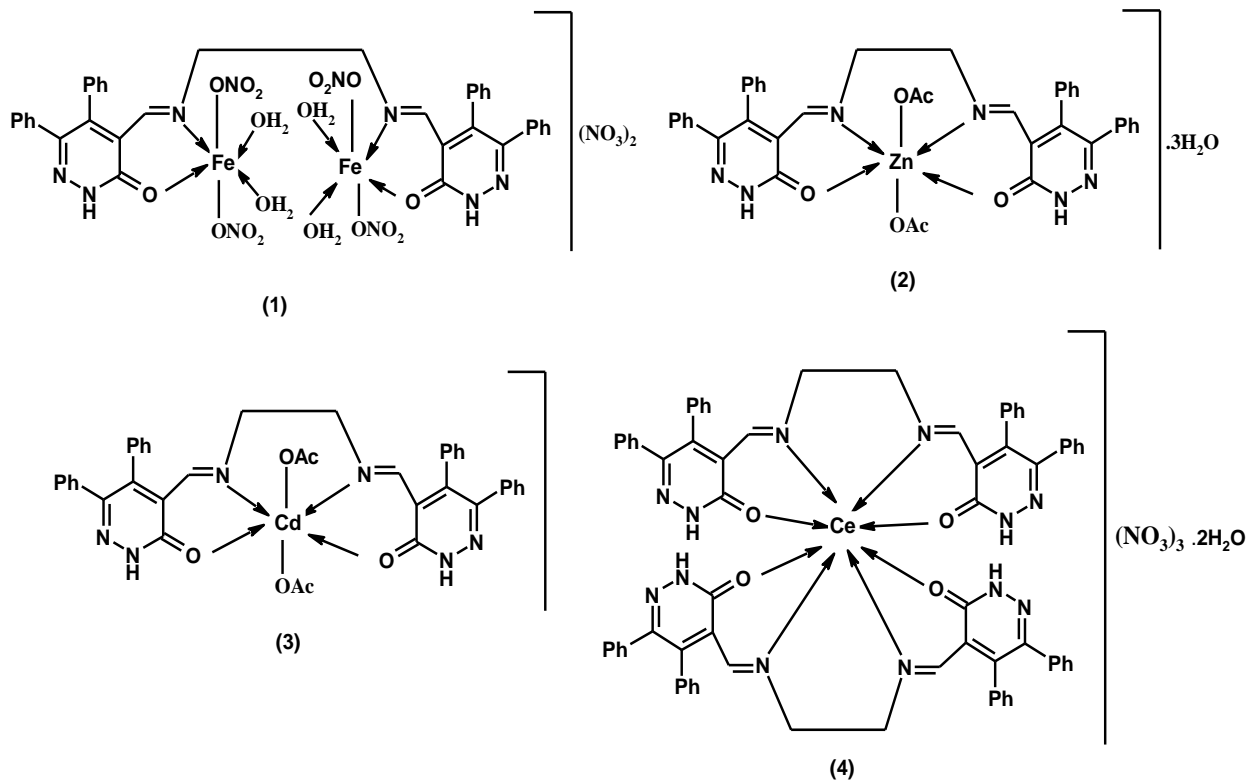


Figure 5. The TGA-DrTGA curves of $[(L)Cd(OAc)_2]$ (3).



Scheme 2. Representative structures of metal complexes.

Table 5. Antimicrobial activity of the ligand and its complexes

Organisms	Mean* of zone diameter, nearest whole mm.										Aspergillus fumigatus
	Gram - positive bacteria				Gram - negative bacteria				Yeasts and Fungi ^b		
	<i>Staphylococcus aureus</i> (ATCC 25923)		<i>Bacillus subtilis</i> (ATCC 6635)		<i>Salmonella typhimurium</i> (ATCC 14028)		<i>Escherichia coli</i> (ATCC 25922)		<i>Candida albicans</i> (ATCC 10231)		
	1000 µg/ml	500 µg/ml	1000 µg/ml	500 µg/ml	1000 µg/ml	500 µg/ml	1000 µg/ml	500 µg/ml	1000 µg/ml	500 µg/ml	1000, 500 µg/ml
L	-	-	9L	7L	-	-	-	-	-	-	-
1	-	-	-	-	-	-	-	-	9L	7L	-
2	-	-	17 I	13 I	-	-	-	-	19 I	17 I	-
3	15 I	12 I	16 I	14 I	11 L	8 L	11 L	8 L	33 H	28 H	-
4	-	-	-	-	-	-	-	-	-	-	-
(S)	35	26	35	25	36	28	38	27	35	28	

* = Calculated from 3 values.

^b = identified on the basis of routine cultural, morphological and microscopical characteristics.

- = No effect.

L: Low activity = Mean of zone diameter $\leq 1/3$ of mean zone diameter of control.

I: Intermediate activity = Mean of zone diameter $\leq 2/3$ of mean zone diameter of control.

H: High activity = Mean of zone diameter $> 2/3$ of mean zone diameter of control.

c: Chloramphenicol in the case of Gram-positive bacteria, cephalothin in the case of Gram-negative bacteria and cycloheximide in the case of fungi

4 Conclusions

The condensation reaction of 4-acetyl-5,6-diphenyl-3(2H)-pyridazinone with ethylenediamine in molar ratio 2:1 (pyridazinone: ethylenediamine) gave pyridazinone Schiff base ligand. Fe(III), Zn(II), Cd(II) and Ce(III) complexes have been synthesized. Schiff base and its complexes were characterized by various analytical and spectroscopic techniques. Fe(III) complex is binuclear complex, while Zn(II), Cd(II) and Ce(III) complexes are mononuclear complexes. The metal complexes exhibited octahedral and octa-coordinated geometrical arrangements. The biological activity of the Schiff base and its complexes was screened against selected kinds of bacteria and fungi.

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