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## Synthesis and Characterization of Complexes with Nd(III), Er(III) and Gd(III) with hexadentate Schiff base ligand and Study Bioactivity Application.

Baraa H Rashid\*.

Ministry of Education, Baghdad, Iraq

### ABSTRACT

New hexadentate ligand ( $N_2O_4$ ) type Schiff base 2-[(4-Bromo-2-hydroxy-benzylidene)-amino]-4-(3-{3-[(4-bromo-2-hydroxy-benzylidene)-amino]-3-carboxy-propylcarbamoyl}-propionylamino)-butyric acid ( $LH_4$ ) was synthesized from the reaction of succinic anhydride and glutamine and 4-Bromo-2-hydroxy-benzaldehyde. Monomeric complexes of this ligand, of general formula  $K[M(L)]$  with  $M(III)=Gd, Er$  and  $Nd$  are reported. The mode of bonding and over all geometry of complexes were determined through microanalysis (C.H.N),  $^1H$ -NMR, Mass, FT-IR and UV-Vis spectra, conductivity molar quantifications. These studies revealed octahedral geometries for all complexes. The compounds were also screened for their bioactive property such as antifungal and antibacterial.

**Keywords:** Hexadentate ligand, succinic anhydride, glutamine, Bio activity, Gd(III), Er(III) and Nd(III) complexes.

*\*Corresponding author*

## INTRODUCTION

Amino acids or amido acids can be prepared by the reaction of aliphatic amines with different cyclic anhydrides such as maleic, phthalic, succinic and citraconic anhydrides [1]. Schiff bases compounds containing azomethine group (-C=N-) formed by condensation of primary amine and carbonyl compounds under acid or base catalysis or with heat [2], Reaction of an equimolar mixture of amines with anhydrides below 100°C yield the acid amide quantitatively. Two factors generally determine the trend of the reaction: temperature and relative amount of the components whereas the reaction time is of minor important [3]. No information are available about amic acid derived from tertiary amines. In the metal complexes of Schiff base, the presence of azomethine group with a lone pair of electrons on the nitrogen atoms provides a binding site for coordination with a metal ion [4], which can stabilize the double bond of the Schiff base [5]. Information on metal complexes with Schiff base as monodentate ligands are limited [6] interest seems concentrated on more coordinatate sites, Bidentate [7], tridentate [8] and tetradentate [9]. On that work, a ligand of Schiff base functional group obtained of Succinic anhydride and Glutamine and Salicylaldehyde were produced. The complexes from Nd(III), Er(III) and Gd(III) with these ligand have been produced and identified physico-chemically.

## MATERIALS AND METHODS

All chemicals were purchased from commercial sources and were used without further purifications Succinic anhydride, Glutamine, Sodium hydroxide, CH<sub>3</sub>OH, C<sub>2</sub>H<sub>5</sub>OH, and HCL from B.D.H, acetic acid, 4-Bromo-2-hydroxy-benzaldehyde, DMSO from Fluka, Nd(NO)<sub>3</sub>.6H<sub>2</sub>O, Gd(NO)<sub>3</sub>.6H<sub>2</sub>O and Er(NO)<sub>3</sub>.5H<sub>2</sub>O from sigma Aldrich.

The <sup>1</sup>H-NMR spectrum were noted at Bruker-300 MHz Ultra Shield spectrometer in DMSO as solvent and TMS as reference. (C. H. N) analyses were well-done employing Euro vector EA 3000A Elemental Analyzer. Mass spectra were obtained by using LC-Mass 100P Shimadzu. Melting points obtained on a Buchi SMP - 20 capillary melting point apparatus and are uncorrected. Conductivity of the complexes dissolved in ethanol (10<sup>-3</sup> M) was recorded at 25°C using Philips PW- Digital Conductometer. UV- Vis spectrum was recorded by a Shimadzu UV- 160A Ultra Violet-Visible Spectrophotometer. IR- spectra were possessed at Shimadzu, FT-IR- 8400S Fourier Transform Infrared Spectrophotometer within 4000- 400 cm<sup>-1</sup> spectral areas for samples produced like KBr discs.

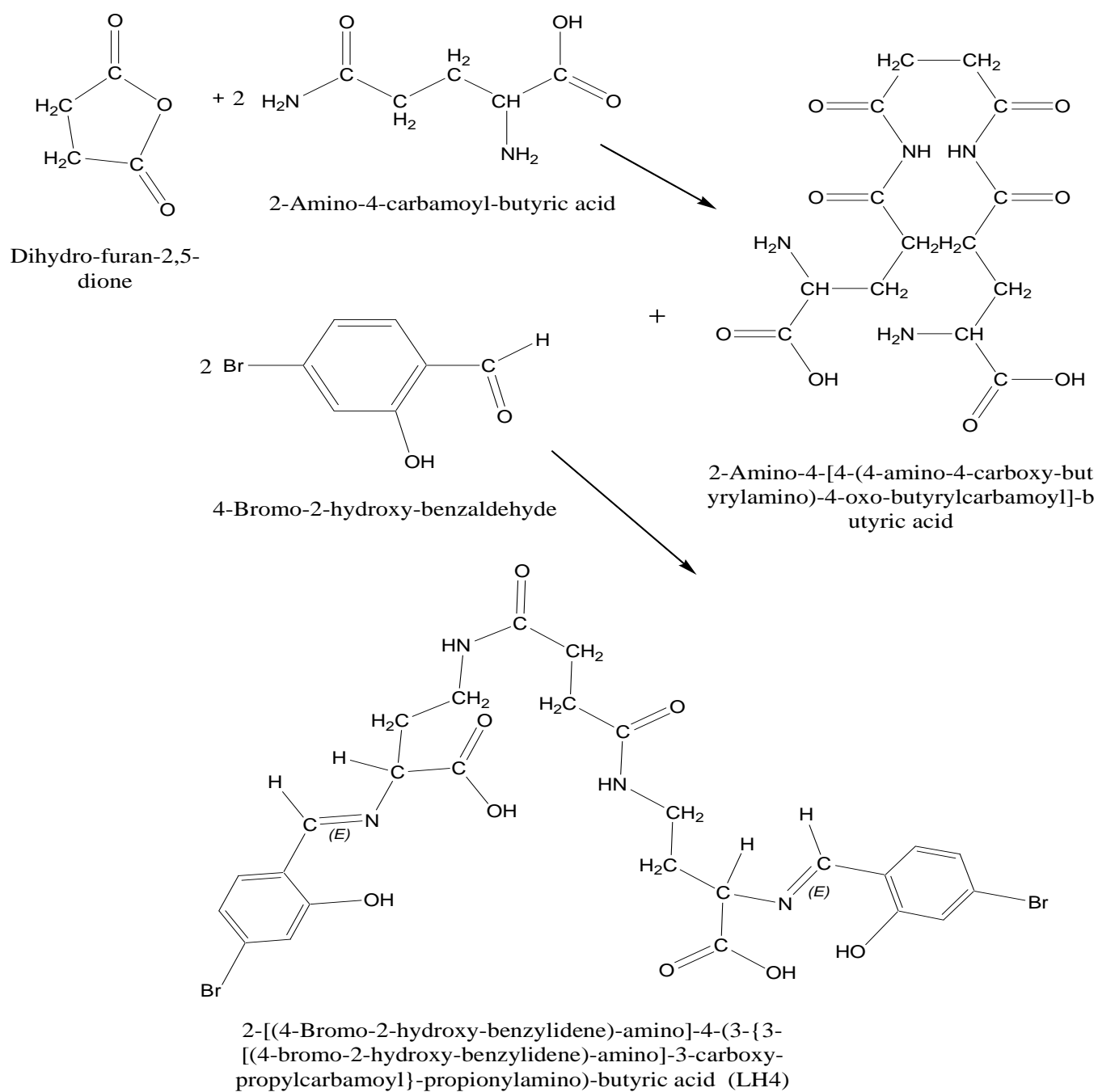
*Preparation 4-(3-{3-Carboxy-3-[(2-hydroxy-benzylidene)-amino]-propylcarbamoyl}-propionylamino)-2-[(2-hydroxy-benzylidene)-amino]-butyric acid (LH<sub>4</sub>)*

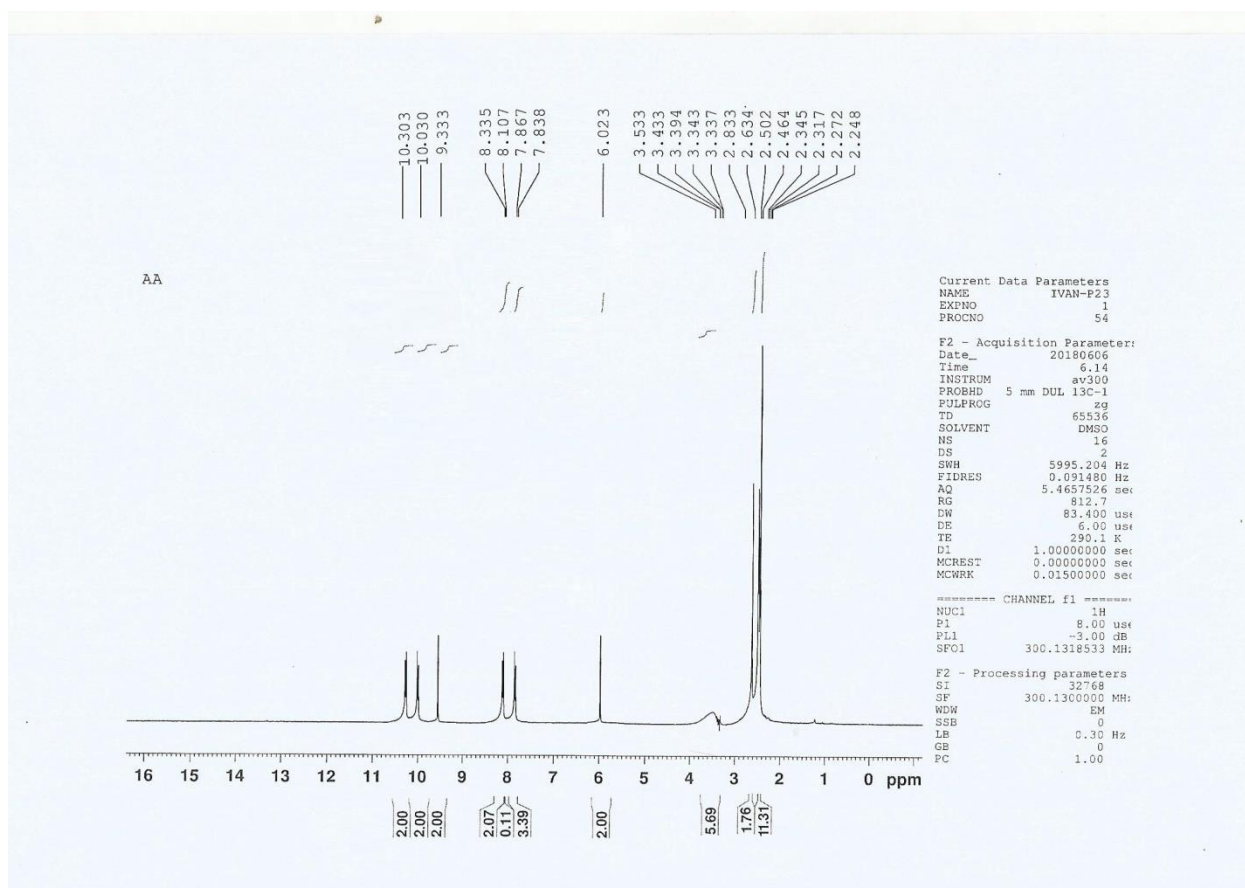
### *A-Preparation of Succinoyl diglutamide*

Succinic anhydride (1g, 10 mmole) was dissolved in absolut ethanol (10 cm<sup>3</sup>). Glutamine (2.923 g, 20mmole) was dissolved in deionized water (20 cm<sup>3</sup>) and then two drops of concentrated hydrochloric acid was added to the glutamine solution and this solution was added to the succinic anhydride solution. The mixture was heated under reflux at temperature (60°C) for (15min) and immediately the precipitation of the white solid was complete. Then, the solid collected by filtration, was washed with water (15 cm<sup>3</sup>×2) and dried at temperature (50°C) for three hours, yield=85%, m.p = 168°C.

### *B-Preparation of Dislicylaldene Succinoyldiglutamide*

Sodium hydroxide (0.4 g, 10mmole) was dissolved in methanol (30 cm<sup>3</sup>) and (2.076g, 6mmole) of succinoyldiglutamide was added to the solution. The mixture was stirred at room temperature until the mixture become homogenous. 4-Bromo-2-hydroxy-benzaldehyde (2.412 g, 12 mmole) was dissolved in (5 cm<sup>3</sup>) of absolute ethanol and then added to the mixture. After two minutes the mixture was evaporated to 20% of its original volume and (1cm<sup>3</sup>) of acetic acid was added immediately. After two hours, light yellow crystal was appeared. Then the solid collected by filtration, was washed with ethanol (15 cm<sup>3</sup>×2), and then recrystallized from (ethanol - water) (1 :1) mixture. The yellow powder was collected by filtration and then dried at temperature (50°C) for three hours. <sup>1</sup>H-NMR- (Figure -1) (DMSO, ppm): 10.03 (s,-CH=N, 2H), 7.838 to 8.335 (m, arom-6H), 6.023(s,-OH phenol, 2H), 10.303(s,-OH carboxylic acid, 2H), 2.272 (t, CH<sub>2</sub>, 12H), 9.333 (s, N-H,2H), 3.533 (s, CH-carboxylic, 2H), (2.502, DMSO) [10]. The preparation of ligand is shown in Scheme (1).


 Scheme (1): Preparation of the Ligand (LH<sub>4</sub>)



**Figure 1:**  $^1\text{H-NMR}$  spectrum of ligand HL4

### Synthesis of Schiff base complexes

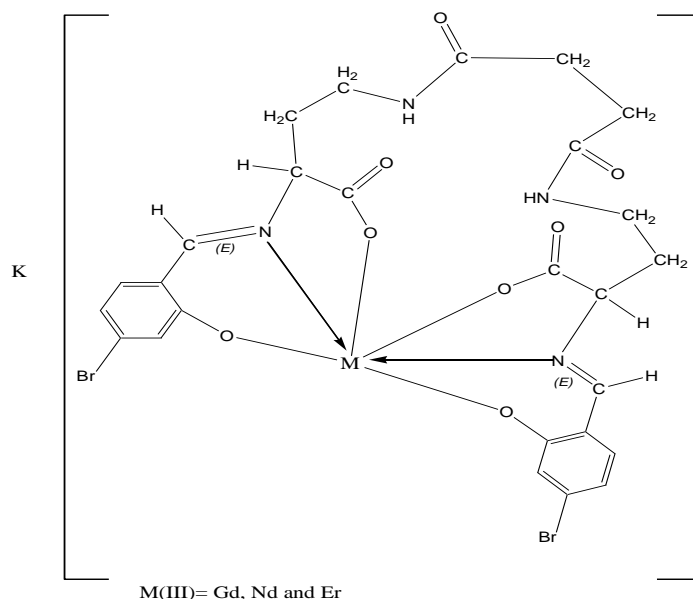
The preparation of all complexes is essentially the same and so a generic description will be presented. To a solution of (LH<sub>4</sub>) (0.006mole) in ethanol and (KOH solution 0.024mol) was added slowly to a solution of metal salt (Nd(NO<sub>3</sub>)<sub>3</sub>.6H<sub>2</sub>O, Gd(NO<sub>3</sub>)<sub>3</sub>.6H<sub>2</sub>O, and Er(NO<sub>3</sub>)<sub>3</sub>.5H<sub>2</sub>O) in (ethanol and water) ratio (1:1) with stirring the mixture was refluxed for (6 hrs). Elemental micro analysis data, color and yield for the complexes are given in Table (1).

### Study of Bioactivity

All the metal ion complexes and ligand were screened against *staphylococcus aureus* (gram positive) and *Pseudomonas aeruginosa* (gram negative) bacteria as well fungi like *Penicillium expansum*, *Fusarium graminearum*, *Macrophomina phaseolina*, and *Candida albicans*, by using the wall agar diffusion method. The concentration of the compounds in this exposure was ( $1 \times 10^{-3}$  M) in DMSO solvent by using disc sensitivity test. This method involves the exposure of the zone inhibition toward the diffusion of microorganism on agar plate. The plates were incubated for 24 and 48 hours of bacteria and fungi respectively at 37°C.

## RESULTS AND DISCUSSION

All the complexes are powder, insoluble in water, whereas soluble in solvents such as, DMF, and DMSO. The molar conductance data Table (1), indicate that all the complexes are electrolytes [1 :1 ], (Figure - 2). The ligand was characterized by elemental microanalysis and physical properties Table (1) and IR Table (2), respectively. Monomeric complexes of the ligand with [Nd(NO<sub>3</sub>)<sub>3</sub>.6H<sub>2</sub>O, Gd(NO<sub>3</sub>)<sub>3</sub>.6H<sub>2</sub>O and Er(NO<sub>3</sub>)<sub>3</sub>.5H<sub>2</sub>O ] were synthesized. However, deprotonation of the ligand occur facilitating the formation of the complexes. The complexes are air-stable solids, solution in DMF and DMSO, sparingly soluble in MeOH, Ethanol. The analytical data Table (1), agree well with the suggested formulae. The most important infrared bands of the ligand and its complexes together with their assignments are collected in Table (2).


**Figure 2: Structure of complexes**
**Table 1: Elemental microanalysis results and some physical properties of the ligand and their metal complexes**

Compounds	Formula M.wt	Mp °C d=decom	Color	Elemental microanalysis experimental (theoretical) %			Molar Conductivity (cm <sup>2</sup> Ω <sup>-1</sup> mol <sup>-1</sup> )
				C	H	N	
LH <sub>4</sub>	C <sub>26</sub> H <sub>28</sub> N <sub>4</sub> O <sub>8</sub> Br <sub>2</sub> 684	194-196		44.36 (45.63)	4.01 (4.12)	10.14 (8.19)	-
K[ Gd (L) ]	C <sub>26</sub> H <sub>24</sub> N <sub>4</sub> O <sub>8</sub> Br <sub>2</sub> GdK 876.65	285d	Light yellow	36.11 (35.62)	2.00 (2.76)	7.45 (6.39)	45
K[ Nd (L) ]	C <sub>26</sub> H <sub>24</sub> N <sub>4</sub> O <sub>8</sub> Br <sub>2</sub> NdK 863.64	291d	Light yellow	36.91 (36.16)	3.12 (2.80)	8.06 (6.49)	51
K[ Er (L) ]	C <sub>26</sub> H <sub>24</sub> N <sub>4</sub> O <sub>8</sub> Br <sub>2</sub> ErK 886.66	280d	Light yellow	34.65 (35.22)	3.14 (2.73)	8.09 (6.32)	56

#### Mass spectrum

#### Synthesis of LH<sub>4</sub>

The electron impact spectrum of the ligand (LH<sub>4</sub>) (Figure- 3) confirms the probable formula by showing a peak at 684 m/z, corresponding to Schiff base moiety [(C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>8</sub> Br<sub>2</sub>), calculated atomic mass 684]. The series of peaks in the range of 430, 429, 205, 204, 79 and 36 m/z may be assigned to various fragments. Their intensity gives an idea of the stability of fragments [11-12].

#### Synthesis of Er(III) complex

The electron impact spectrum of K[Er (L)] (Figure- 4) confirms the probable formula by showing a peak at 886 m/z, corresponding to complex moiety [(C<sub>26</sub>H<sub>24</sub>N<sub>4</sub>O<sub>8</sub> Br<sub>2</sub>KEr), calculated atomic mass 886.66]. The series of peaks in the range of 684, 430, 429, 205, 204, 79 and 36 m/z may be assigned to various fragments [12].

Synthesis of Nd(III) complex

The electron impact spectrum of K[Nd (L)] (Figure- 5) confirms the probable formula by showing a peak at 863 m/z, corresponding to complex moiety [(C<sub>26</sub>H<sub>24</sub>N<sub>4</sub>O<sub>8</sub> Br<sub>2</sub>KNd), calculated atomic mass 863.64]. The series of peaks in the range 689, 429,300 and 204 m/z may be assigned to various fragments [12].

Synthesis of Gd(III) complex

The electron impact spectrum of K[Gd (L)] (Figure- 6) confirms the probable formula by showing a peak at 876.5 m/z, corresponding to complex moiety [(C<sub>26</sub>H<sub>24</sub>N<sub>4</sub>O<sub>8</sub> Br<sub>2</sub>KGd), calculated atomic mass 876.65]. The series of peaks in the range 689, 336.5, 326 and 204 m/z may be assigned to various fragments [12-13].

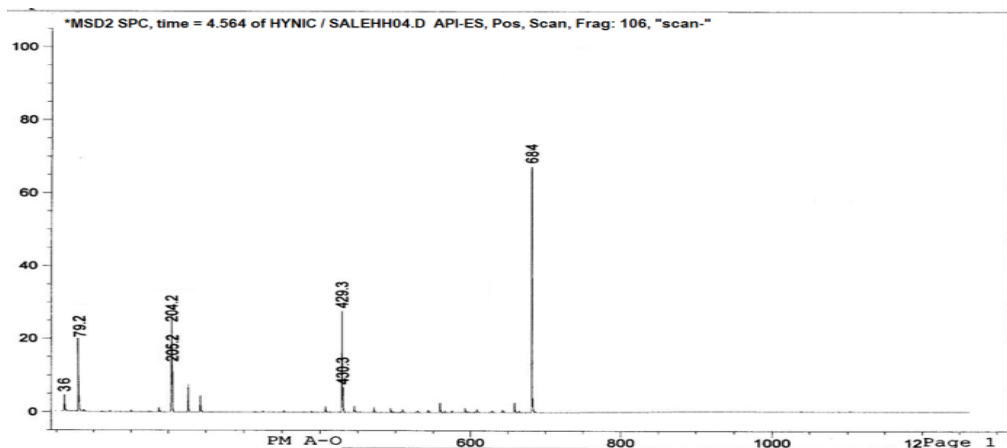


Figure 3: Mass spectrum of ligand HL<sub>4</sub>

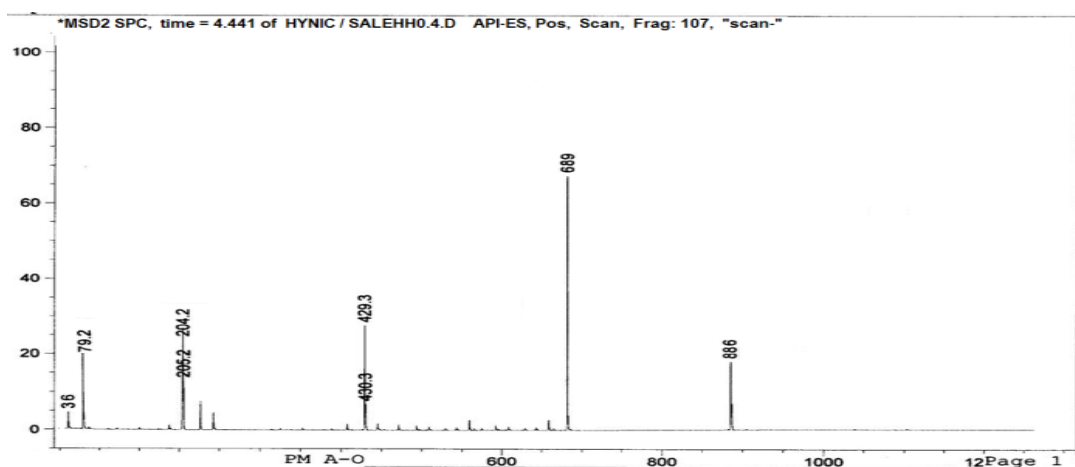


Figure 4: Mass spectrum of Er complex

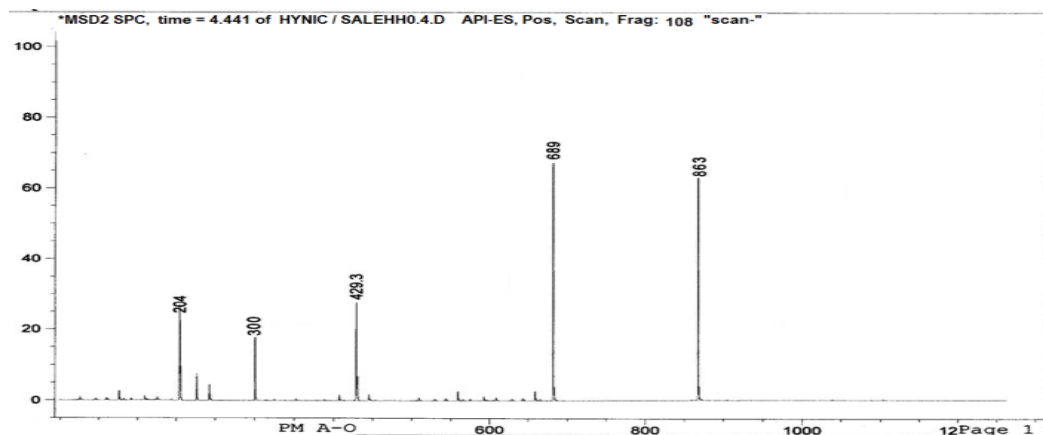


Figure 5: Mass spectrum of Nd complex

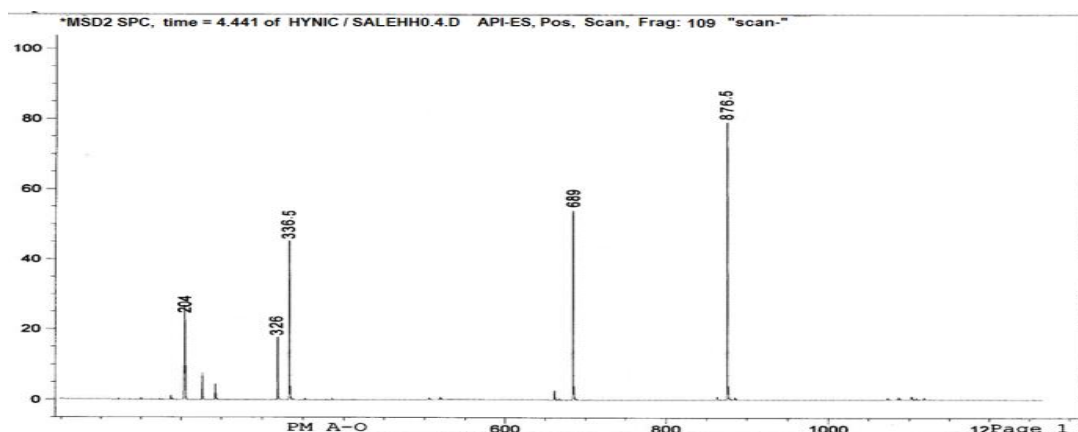


Figure 6: Mass spectrum of Gd complex

#### IR spectra

The characteristic stretching vibration modes concerning Schiff base (LH<sub>4</sub>) and its metal complexes are described in Table (2). The ligand (LH<sub>4</sub>) exhibited a strong high intensity bands appeared at (3059) cm<sup>-1</sup>, (2933) cm<sup>-1</sup>, (1585) cm<sup>-1</sup>, (3406) cm<sup>-1</sup>, (3530) cm<sup>-1</sup>, (3325-3115) cm<sup>-1</sup>, (1685) cm<sup>-1</sup> and (1635) cm<sup>-1</sup> which were ascribed to the stretching mode of  $\nu$ (C-H aromatic),  $\nu$ (C-H aliphatic),  $\nu$ (C=N azomethine),  $\nu$ (O-H phenol),  $\nu$ (O-H carboxylic),  $\nu$ (N-H),  $\nu$ (C=O carboxylic) group and  $\nu$ (C=O carbonyl) group, as show in Table (2), respectively [14, 15].

The spectra of the metal complexes showed bands at range (3325-3115) cm<sup>-1</sup> assigned to the stretching vibration of (N-H) due to the intermolecular hydrogen bonding [15], which indicated the non involvement of the (N-H) for coordination.

The (C=N) band at (1585) cm<sup>-1</sup> in the spectrum of the free Schiff base ligand, shifted to lower frequencies in the spectra of all metal complexes in the range between (1568-1571) cm<sup>-1</sup> which indicated the coordination of the ligand through nitrogen atom of the azomethine group [15,16]. The band (C=O) at (1685) cm<sup>-1</sup> in the spectrum of the free Schiff base ligand, shifted to lower frequencies in the spectrum of all complexes in the range (11678- 1666) cm<sup>-1</sup> [14, 17].

In addition, ligand shows a broad band at ca. (3406) cm<sup>-1</sup> due to intra molecular H-bonded (O-H) phenol group. This band disappears in their corresponding metal complexes indicating the coordination of phenol oxygen to metal ion through deprotonation [2, 7, 14, 17 ]. This finding indicated that the ligand was coordinated with the metal ions through the OH phenol group, OH carboxylic group and C = N azomethine group atoms, respectively. At lower frequency, the complexes exhibited bands around (514-542) cm<sup>-1</sup> due to the  $\nu$ (M-N) and exhibited bands around (411-487) cm<sup>-1</sup> due to the  $\nu$ (M-O) for complexes [14,17].

**Table 2: Infrared Spectra Data of the Free Ligand (LH<sub>4</sub>) and its Complexes in (cm<sup>-1</sup>)**

Comp.	$\nu_{\text{C=O}}$ carboxylic	$\nu_{\text{C=N}}$	$\nu_{\text{C=O}}$ carbonyl	$\nu_{\text{(O-H)}}$ phenol	$\nu_{\text{(O-H)}}$ carboxylic	$\nu_{\text{M-N}}$	$\nu_{\text{M-O}}$	Other bands
LH <sub>4</sub>	1685	1585	1635	3406	3530			$\nu$ C-H aromatic= 3059 $\nu$ C-H aliphatic= 2933 $\nu$ N-H = 3325, 3115
K[ Gd (L) ]	1666	1568	1632	-	-	514	471 411	$\nu$ C-H aromatic= 3064 $\nu$ C-H aliphatic= 2943 $\nu$ N-H = 3333, 3219
K[ Nd (L) ]	1675	1559	1633	-	-	542	487 409	$\nu$ C-H aromatic= 3069 $\nu$ C-H aliphatic= 2933 $\nu$ N-H = 3329, 3275
K[ Er (L) ]	1678	1571	1631	-	-	519	479 426	$\nu$ C-H aromatic= 3055 $\nu$ C-H aliphatic= 2943 $\nu$ N-H = 3334, 3217

#### Electronic spectra

The UV-Vis spectrum from the produced compounds melted at ethanol ( $1 \times 10^{-3}$  M) have been gauging. The UV- Vis spectra from ethanolic solution for the ligand ( $1 \times 10^{-3}$  M) displayed generally two peak, the first peak in the (325 nm) were attributed to the mild energy  $\pi$ -  $\pi^*$  transition. The second peak in the (375 nm) was gestured to the n-  $\pi^*$  transition [18].

The spectra of Gd(III), Nd(III) and Er(III) complexes appeared absorption peaks in the average (364, 369 and 370 nm) respectively, were concerning to ligand felid, after that another peaks in 477 and 490 nm were assigned to charge transfer. The spectra of these complexes show absorbance three peaks in [(490, 588 and 984) nm, (487, 677 and 974) nm and (475, 597 and 887) nm] respectively, due to (f-f) electronic transition [18]. This suggesting octahedral geometry around all complexes. The molar conductivity value of the complexes at the range (37-46)  $\Lambda_m(\text{S.cm}^2.\text{mol}^{-1})$  in absolute DMSO ( $1 \times 10^{-3}\text{M}$ ) is consistent with electrolytes for all complexes 1:1 electrolytes for complexes [19]. See structure for the complexes (Figure -2).

#### Antimicrobial activity of ligand and all complexes

Schiff base and their complexes were screened for antifungal and antibacterial activity. The entire tested compounds exhibited variable.

Schiff base activity exhibited antibacterial against *Staphylococcus aureus* and *Pseudomonas aeruginosa* in Concentration but activity was found to be lower than the metal ion complexes, Schiff base which did not exhibit has antifungal activity but exhibited activity was in some metal complexes.

Prepared antifungal activity strong against *Penicillium expansum*, *Candida albicans* *Fusarium graminearum* and *Macrophomina phaseolina* as compared with the ligand which did not exhibit antimicrobial activity. From the data shown in Table (3) a lot of compounds exhibited bio activity against two kinds of bacteria and four kinds of fungus [20].

**Table 3: Antibacterial and antifungal activities for ligand and complexes.**

Compound	<i>Staphylococcus aureus</i> G(+)		<i>Pseudomonas aeruginosa</i> G(-)		<i>Penicillium expansum</i>		<i>Fusarium graminearum</i>		<i>Macrophomina phaseolina</i>		<i>Candida albicans</i>	
	A	B	A	B	A	B	A	B	A	B	A	B
LH <sub>4</sub>	12	-	12	-	-	-	-	-	-	-	-	-
K[ Gd (L) ]	30	25	24	18	23	19	24	14	25	20	23	15
K[ Nd (L) ]	28	22	22	14	30	28	30	22	30	20	25	17



K[ Er (L) ]	<b>38</b>	<b>30</b>	<b>28</b>	<b>18</b>	<b>23</b>	<b>17</b>	<b>19</b>	<b>12</b>	-	-	<b>29</b>	<b>18</b>
Control	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

A=conc., B=dilu.

### CONCLUSION

In this paper (N<sub>2</sub>O<sub>4</sub>) type we prepared ligand. 2-[(4-Bromo-2-hydroxy-benzylidene)-amino]-4-(3-{3-[(4-bromo-2-hydroxy-benzylidene)-amino]-3-carboxy-propylcarbamoyl}-propionylamino)-butyric acid (LH<sub>4</sub>) which were used in the preparation of Gd(III), Nd(III) and Er(III) complexes characterization data by FT.IR, <sup>1</sup>H-NMR, Mass UV-Vis spectrometer, element microanalysis (C.H.N.), melting point for free Schiff base ligand and FT.IR, Mass, UV-Vis spectrometer, element microanalysis (C.H.N), molar conductivity, melting point for complexes. The compounds were also screened for their bioactive property such as antifungal and antibacterial *staphylococcus aureus* (gram positive) and *Pseudomonas aeruginosa* (gram negative) bacteria as well fungi like *Penicillium expansum*, *Fusarium graminearum*, *Macrophomina phaseolina*, and *Candida albicans*.

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