



Synthesis, Spectral, Thermal and Biological Studies of Some Transition and Inner Transition Schiff base Metal Complexes



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Abstract

The new bidentate Schiff base ligand (L) named N¹-(diphenylmethylene)naphthalene-1,8-diamine was prepared by the condensation reaction of benzophenone and 1,8-naphthylenediamine. The complexes with Mn(II), Ni(II), Zn(II), La(III), Er(III), and Yb(III) metal ions were prepared and characterized by using elemental analyses (C, H, N and M), FT-IR, ¹H NMR, molar conductivity, magnetic moment, UV-Vis, mass and scanning electron microscope (SEM). The temperatures of decomposition of the Schiff base ligand and metal complexes were investigated using thermal analyses. The metal complexes were found to have the formulae [M(L)(H₂O)₃Cl]Cl.nH₂O (M = Mn(II) (n = 4); Ni(II) (n = 2)), [Zn(L)(H₂O)₂Cl₂] and [M(L)(H₂O)₂Cl₂]Cl (M = La(III), Er(III) and Yb(III)) according to the elemental analyses data. The geometrical structure of all complexes was found to be octahedral. The molar conductivity of the complexes in DMF indicated the electrolytic nature of all complexes except Zn(II) complex was non-electrolyte. From the spectroscopic data, the Schiff base ligand acts as NN-bidentate ligand. The biological and anticancer activities of the Schiff base ligand and its complexes were investigated against two bacterial strains, two fungal strains and breast cancer cell line (MCF-7). Docking studies were performed to study the possible interaction between the Schiff base ligand with the active sites of the 3HB5 and 5JPE receptors.

Keywords: Metal complexes; Schiff base; Spectroscopy; Thermal analyses; Biological and anticancer activity; Molecular docking

1. Introduction

Schiff bases were efficiently synthesized by the condensation reaction between aldehydes and amines so they were considered as “privileged ligands” [1]. Schiff bases were distinguished by an imine group HC=N which helped to elucidate the mechanism of Schiff transamination and racemization reaction in biological systems [1, 2]. Among the most extensively used organic compounds, the Schiff bases were exhibiting a broad range of applications, such as

intermediates in organic synthesis [3-6], polymer stabilizers [7-9], catalysis [10, 11], chemosensors [12-14], in food industry [15, 16], and others [17-19]. Also, Schiff bases represented a broad range of biological activities [20–23], for which the azomethine or imine group being in their structures seems to act a critical role [24–26]. The coordination capability of Schiff bases to the metal ions made the chemists perform research in preparation and characterization of metal(II) complexes of Schiff

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bases [27-29]. This capability was due to their stereo-electronic and flexible structures leading to highly versatile coordination compounds with a broad scope of applications ranging from subterranean fluid flow tracking [30, 31], to bioinorganic and medicinal chemistry [32, 33]. Also, the Schiff base complexes of inner transition metals had biological activities, such as antibacterial, antifungal and anticancer activities [34-36]. Furthermore, La(III), Er(III) and Yb(III) complexes had investigated due to their more apoptotic and antioxidant activities after coordination with ligands [33, 36-39].

Herein, the synthesis of Schiff base ligand (L) derived from the condensation of benzophenone with 1,8-naphthylenediamine and its Mn(II), Ni(II), Zn(II), La(III), Er(III) and Yb(III) complexes were reported. Several physicochemical techniques and thermal analyses have been used for compounds characterization. Their antimicrobial, anticancer activities and half-maximal inhibitory concentration (IC_{50}) have been also investigated. Molecular docking studies were used to identify the binding orientation of synthesized Schiff base ligand in the active site of different proteins receptors by using MOE 2008 software.

2. Experimental

2.1. Materials

All chemicals were acquired commercially of analytical grade (AR) and of highest purity available. They included benzophenone (Sigma-Aldrich), 1,8-naphthylenediamine (Merck), $MnCl_2 \cdot 2H_2O$ (Sigma-Aldrich), $NiCl_2 \cdot 6H_2O$ and $ZnCl_2$ (BDH), $LaCl_3 \cdot 7H_2O$ (Alpha Chemika), $ErCl_3 \cdot 6H_2O$ and $YbCl_3 \cdot 6H_2O$ (Strem Chemicals Inc.). Organic solvents were spectroscopic pure from BDH included absolute ethanol and dimethylformamide (DMF). Bidistilled

water collected from all glass equipment was usually used in all preparations. Human tumour cell line breast cell (MCF-7) was obtained frozen in liquid nitrogen ($-180\text{ }^\circ\text{C}$) from American Type Culture Collection. The tumour cell line (MCF-7) was maintained in the National Cancer Institute, Cairo, Egypt, by serial sub-culturing.

2.2 Solutions

Fresh stock solution of 1×10^{-3} M Schiff base ligand and its metal chelates were prepared by dissolving the accurately weighed amount (L, 0.322 g/L; Mn(II), 0.574 g/L; Ni(II), 0.524 g/L; Zn(II), 0.494 g/L; La(III), 0.603 g/L; Er(III), 0.631 g/L; Yb(III), 0.637 g/L) in 5 ml of N,N-dimethylformamide (DMF) for measuring the conductivity for all metal chelates [40]. Solutions of 1×10^{-4} M of Schiff base ligand and metal chelates were also prepared by dilution from the previous stock solutions in order to measure their UV-vis. spectra.

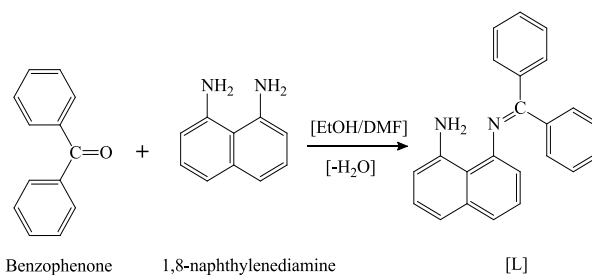
2.3 Instruments

Microanalyses of carbon, hydrogen and nitrogen were carried out at the Microanalytical Center, Cairo University, Egypt, using a CHNS-932 (LECO) Vario elemental analyzer. The metal content was measured at the Egyptian Petroleum Research Institute's using inductively coupled plasma atomic absorption spectrometry (ICP). Melting point measured by triforme XMTD-3000. Fourier-transform infrared spectroscopy (FT-IR) spectra were recorded on a Perkin-Elmer 1650 spectrometer ($4000\text{--}400\text{ cm}^{-1}$) using KBr disks. Molar conductivities of 10^{-3} M solutions of the solid complexes in DMF were measured using a Jenway 4010 conductivity meter. The magnetic susceptibilities were measured on powdered samples using the Faraday method. As

solutions in DMSO- d_6 , ^1H NMR spectra were reported using tetramethylsilane as an internal standard with a 300 MHz Varian-Oxford Mercury at room temperature. Mass spectra were recorded using the electron ionization technique at 70 eV with an MS-5988 GS-MS Hewlett-Packard instrument at the Microanalytical Center, Egypt. The spectrophotometric measurements in solution were carried out using automated spectrophotometer UV-vis Perkin-Elmer Model Lambda 20 ranged from 200 to 700 nm. Scanning electron microscopy (SEM) images of the ligand and complexes were recorded on a Quanta FEG250 instrument at the National Research Center, Egypt. Thermogravimetric (TG) and differential thermogravimetric (DTG) measurements of the Schiff base ligand and metal complexes were done using a Shimadzu TG-50H thermal analyzer from room temperature to 1000 °C. Anticancer activity experiments were performed at the National Cancer Institute, Cancer Biology Department, Pharmacology Department, Cairo University, Egypt. The optical density (OD) of each well was calculated spectrophotometrically at 564 nm with an ELIZA microplate reader (Meter tech. R960, USA). Antimicrobial measurements were carried out at the Microanalytical Center, Cairo University, Egypt.

2.4 Synthesis of Schiff base ligand

The new Schiff base ligand (L) was synthesized from the condensation of benzophenone (5.49 mmol, 1 g) dissolved in hot absolute ethanol (60 °C) and 1,8-naphthylenediamine (5.49 mmol, 0.87 g) dissolved in hot DMF (70 °C) in 1:1 molar ratio and the reaction mixture was left under reflux for 3 h. The reaction was shown in (Scheme 1). The reddish-brown product obtained was separated after evaporation then filtered off and recrystallized from DMF-ethanol mixture to give pure Schiff base with 82% yield [41].



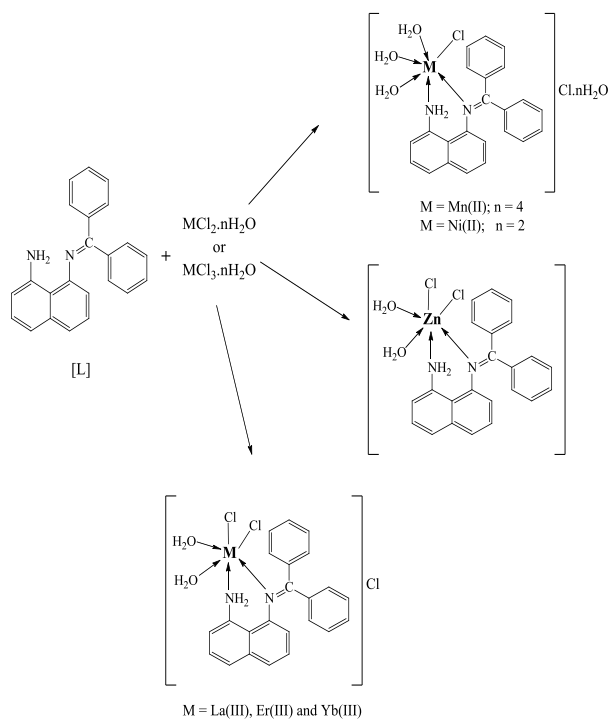
Scheme 1. General formation of Schiff base ligand (L).

2.5 Synthesis of metal complexes

The metal chelates were prepared by mixing hot solution of DMF (20 ml) (70 °C) of the Schiff base ligand (1.55 mmol, 0.5 g) with metal chloride salts (1.55 mmol, 0.25 g $\text{MnCl}_2 \cdot 2\text{H}_2\text{O}$, 0.37 g $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, 0.21 g ZnCl_2 , 0.57 g $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, 0.59 g $\text{ErCl}_3 \cdot 6\text{H}_2\text{O}$, 0.60 g $\text{YbCl}_3 \cdot 6\text{H}_2\text{O}$) dissolved in hot absolute ethanol (30 mL) (60 °C), as shown in (Scheme 2). The resulting mixture was stirred under reflux for 1 h whereupon the complexes precipitated. It was collected by filtration and purified by washing with ethanol several times and dried under vacuum over anhydrous CaCl_2 .

2.6 Biological activity

The examinations for *in-vitro* antibacterial and antifungal activities were performed through the disc diffusion technique using gentamycin as a positive control for Gram-negative bacteria, ampicillin for Gram-positive bacteria and amphotericin B for fungi, respectively [42]. The bacterial organisms used were Gram-positive bacteria (*Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli*) and fungi (*Aspergillus flavus* and *Candida albicans*). Stock solution (1 mmol) was prepared by dissolving the Schiff base ligand and its complexes in DMSO. The nutrient agar medium for antibacterial was prepared, cooled to 47 °C and seeded with examined microorganisms. After solidification, 5 mm diameter holes were bored by a sterile corkborer.



Scheme 2. Preparation of the Schiff base metal complexes.

These culture plates were then incubated at 37 °C for 20 h for bacteria. The diameter of the inhibition zones was measured in millimeters. Antimicrobial activities were performed in triplicate and the average was taken as the final reading [43].

2.7 Anticancer activity

The potential cytotoxicity of the synthesized compounds was examined using the method of Skehan and Storeng [44]. Cells were plated in a 96-multiwell plate (104 cells/well) for 24 h before treatment with the compounds to allow attachment of the cell to the wall of the plate. Various concentrations of the compounds under examination (0, 5, 12.5, 25, 50 and 100 µg/mL) were added to the cell monolayer and triplicate wells were prepared for each individual dose. The monolayer cells were incubated with the compounds for 48 h at 37 °C and in 5% CO₂ atmosphere. After 48 h, cells were fixed, washed and stained with SRB stain. Excess stain was washed with acetic acid, and the attached stain was

recovered with tris-EDTA buffer. The optical density (O.D.) of each well was measured spectrophotometrically at 564 nm with an ELIZA microplate reader, the mean background absorbance was automatically subtracted and mean values of each drug concentration were calculated. The relation between surviving fraction and drug concentration was plotted to get the survival curve of breast tumour cell line for each compound. Calculation: The percentage of cell survival was calculated as follows:

$$\text{Survival fraction} = \frac{\text{O.D. (treated cells)}}{\text{O.D. (control cells)}}$$

The IC₅₀ values (the concentrations of Schiff base ligand or its metal complexes required to produce 50% inhibition of cell growth). The test was repeated 3 times.

2.8 Molecular docking

Molecular docking studies were very significant for prophesying the possible binding modes of the most active compounds with the receptors of breast cancer mutant oxidoreductase (PDB ID: 3HB5) and yeast-specific serine/threonine protein phosphatase (PPZ1) of *Candida albicans* (PDB ID: 5JPE). Also, these studies were done to assess the binding free energy of the inhibitor inside the macromolecule [45]. They were performed utilizing MOE 2008 (MOE source: Chemical Computing Group Inc., Quebec, Canada, 2008) software, an interactive molecular graphics program for calculating and presenting possible docking modes of a receptor and ligand [46]. It necessitated the ligand and the receptor as input in PDB format. The amino acid chain was kept and the water molecules, co-crystallized ligands and other unsupported elements (e.g., Na, K, Hg, etc.) were eliminated. The structure of the ligand in PDB file format was created by Gaussian03 software.

The crystal structures were downloaded from the Protein Data Bank (<https://www.rcsb.org/>).

3. Results and discussion

3.1. Elemental analyses and molar conductivity measurements

The new Schiff base ligand and metal complexes were prepared in 1:1 molar ratio. The elemental analysis results obtained for Schiff base ligand and its complexes were in good agreement with those calculated for the proposed formula. All compounds were stable at room temperature.

The molar conductivity values (Λ_m) of 10^{-3} M solutions of the metal complexes in DMF were measured at 25 ± 2 °C to be found in the range of 19–86 $\Omega^{-1} \text{ mol}^{-1} \text{ cm}^2$, which indicated that the Mn(II), Ni(II), La(III), Er(III) and Yb(III) complexes were electrolytes while Zn(II) complex was nonelectrolyte.

Table 1

Physical and analytical data of Schiff base ligand L and its metal complexes

The results were tabulated in (Table 1).

3.2 IR spectral studies

The infrared spectrum of Schiff base ligand gave important peaks that predicting the successful synthesis of the Schiff base ligand. The spectrum evidenced disappearance of a sharp band at 1649 cm^{-1} of the $\nu(\text{C}=\text{O})$ of benzophenone and a new band was appeared at 1623 cm^{-1} , which characteristic to the $\nu(\text{C}=\text{N})$ of the azomethine moiety, indicating the formation of the Schiff base ligand [47, 48]. In the spectra of the metal complexes, this band shifted to higher frequencies at $1652\text{--}1660 \text{ cm}^{-1}$ [49]. This shift in band position intimated the participation of the azomethine nitrogen in coordination to the metal ions. Also, the spectrum of Schiff base ligand revealed bands at 3417 and 3364 cm^{-1} which assigned to $\nu(\text{NH}_2)$ group [50]. Since upon the stretching bands of $\nu(\text{NH}_2)$ in the IR spectra of metal complexes weren't been able to characterize because of its overlapping with the stretching band of water molecules [51], therefore, the $\rho(\text{NH}_2)_{\text{bending}}$ band of

all compounds must be detected. The $\rho(\text{NH}_2)_{\text{bending}}$

Compound (Chemical formula)	Color	Yield (%)	M.P (C°)	% Found (calcd.)				μ_{eff} (B.M)	Λ_m (Ω^{-1} $\text{mol}^{-1} \text{ cm}^2$)
				C	H	N	M		
L	Reddish brown	(82)	133	85.29 (85.71)	5.32 (5.59)	8.51 (8.69)	—	—	—
[Mn(L)(H ₂ O) ₃ Cl]Cl.4H ₂ O	Brown	(72)	>300	48.00 (48.08)	5.49 (5.57)	4.76 (4.88)	9.42 (9.58)	5.37	67
[Ni(L)(H ₂ O) ₃ Cl]Cl.2H ₂ O	Dark Brown	(75)	> 300	50.78 (50.92)	5.10 (5.17)	4.93 (5.17)	10.67 (10.88)	3.17	67
[Zn(L)(H ₂ O) ₂ Cl ₂]	Dark brown	(77)	173	55.79 (55.87)	4.32 (4.45)	5.48 (5.67)	12.93 (13.16)	Dia.	19
[La(L)(H ₂ O) ₂ Cl ₂]Cl	Brown	(74)	>300	45.49 (45.73)	3.57 (3.64)	4.48 (4.64)	22.89 (23.03)	Dia.	77
[Er(L)(H ₂ O) ₂ Cl ₂]Cl	Dark brown	(76)	>300	43.59 (43.70)	3.40 (3.48)	4.34 (4.43)	26.26 (26.44)	Dia.	80
[Yb(L)(H ₂ O) ₂ Cl ₂]Cl	Dark brown	(78)	180	43.11 (43.29)	3.34 (3.45)	4.29 (4.39)	27.08 (27.14)	Dia.	86

band was observed at 633 cm^{-1} for free Schiff base ligand, while in the metal complexes, it was shifted to higher frequencies at $635\text{--}637\text{ cm}^{-1}$ [48, 52]. This pointed out the participation of the NH_2 group in coordination to the metal ions.

New two bands observed in the spectra of the metal complexes at $872\text{--}918$ and $816\text{--}821\text{ cm}^{-1}$ which could be assigned to asymmetric and symmetric vibrations of coordinated water molecules, respectively [48]. Besides, new bands of low frequency had appeared in the spectra of all complexes at regions of $513\text{--}571$ and $419\text{--}456\text{ cm}^{-1}$ which assigned to the formation of M-O of coordinated water and M-N bonds, respectively [53, 54]. Therefore, from the results of IR spectra of the Schiff base ligand and its metal complexes, it was indicated that the synthesized Schiff base ligand was neutral bidentate ligand and form coordination bonds with metal ions through the nitrogen of azomethine group and the amino group. All stretching frequencies of the compounds were listed in (Table 2).

Table 2

Important IR frequencies ($4000\text{--}400\text{ cm}^{-1}$) of L and its metal complexes

Compound	$\nu(\text{C}=\text{N})_{\text{azomethine}}$	$\rho(\text{NH}_2)_{\text{bending}}$	$\nu(\text{H}_2\text{O})_{\text{coordinated}}$	$\nu(\text{M}-\text{O})$	$\nu(\text{M}-\text{N})$
L	1623s	633m	—	—	—
$[\text{Mn}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl}\cdot 4\text{H}_2\text{O}$	1653m	635m	890s, 821sh	513s	456s
$[\text{Ni}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl}\cdot 2\text{H}_2\text{O}$	1655m	637m	918s, 821sh	568s	443s
$[\text{Zn}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]$	1652m	637s	880s, 819sh	557s	454s
$[\text{La}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$	1655m	637w	887w, 816s	571s	419s
$[\text{Er}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$	1658m	635sh	873s, 816sh	516s	421w
$[\text{Yb}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$	1660m	635m	872m, 817sh	516m	453s

sh = sharp, m = medium, s = small, w = weak and br = broad.

3.3. Magnetic susceptibility and electronic absorption spectra

The magnetic moment values for Mn(II) and Ni(II) complexes were found to be 5.37 and 3.17 BM, respectively, which proposed an octahedral geometry [55, 56]. The Zn(II), La(III), Er(III) and Yb(III) complexes were determined to be diamagnetic.

The electronic spectral data for the free Schiff base ligand and its complexes were recorded in DMF solvent in the range of $200\text{--}700\text{ nm}$ at room temperature using the same solvent as blank. Three bands at 275, 340 and 470 nm were appeared in the spectrum of the Schiff base ligand. The first band might be congruent to $\pi\text{--}\pi^*$ transition of the naphthalene ring. The second and third higher absorption bands that were attributed to the $n\text{--}\pi^*$ transition of the azomethine group ($\text{C}=\text{N}$) and charge transfer, respectively [49, 57-59]. The shift of these transitions in the spectra of complexes indicated the coordination of the ligand with metal ions. The new

bands recorded in Zn(II), La(III), Er(III) and Yb(III) complexes at $484\text{--}490\text{ nm}$ might be attributed to the ligand to metal charge transfer [60]. In addition, in

the Mn(II) and Ni(II) complexes, a weak band appeared at 533 and 532 nm, which could be assigned to d-d transition [52, 57].

3.4. ^1H NMR spectra

The ^1H NMR spectrum of the Schiff base ligand was characterized by singlet signal at 5.42 ppm (s, 2H, NH_2) and multiple signals at 6.54–7.72 ppm (m, 16H, ArH) which could be assigned to protons of NH_2 group, aromatic and naphthalene ring, respectively [61, 62]. On chelation, the position of NH_2 signal was shifted to a higher value at 5.50 ppm, indicating the involvement of the NH_2 group in coordination [49, 63]. The multiple signals still appeared within the range of 6.54–7.74 ppm in Zn(II) complex [64]. The ^1H NMR spectra of Schiff base ligand and its Zn(II) complex were presented in (Fig. 1).

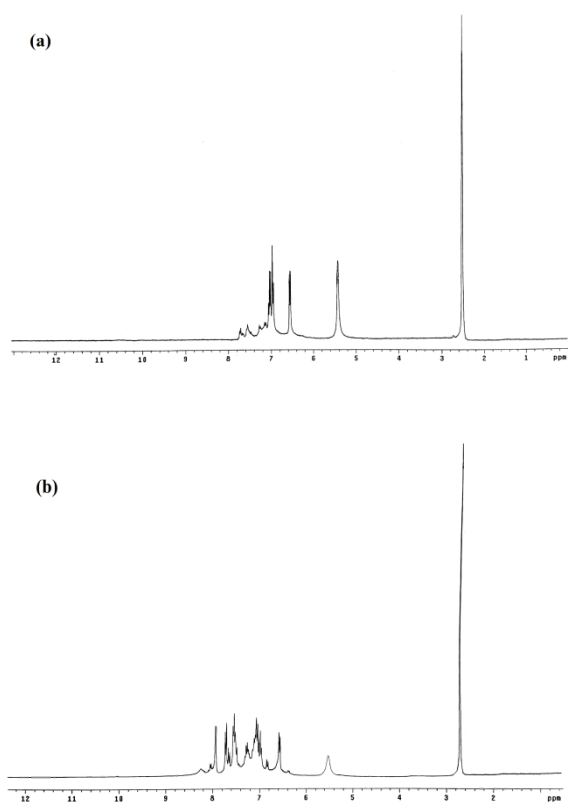


Fig. 1. ^1H NMR spectra of (a) Schiff base ligand and (b) its $[\text{Zn}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]$ complex.

3.5. Mass spectral studies

The mass spectra of the synthesized free Schiff base ligand and its Yb(III) complex were reported and the obtained molecular ion peaks confirmed their proposed formula and geometry. A well-defined parent peak in the spectrum of Schiff base ligand could be seen at $m/z = 322$ (calculated = 322) which was in agreement with the formula $\text{C}_{23}\text{H}_{18}\text{N}_2$. The molecular ion peak for $[\text{Yb}(\text{C}_{23}\text{H}_{18}\text{N}_2)(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$ complex was observed at $m/z = 638.3$ (calculated = 637.5; M^{+1}), consistent with the proposed molecular formulae of the complex. The parent Schiff base ligand peak appeared in the mass spectrum of the complex at 322 amu, confirming complex formation [65].

3.6. Scanning electron microscope

The SEM micrographs of Schiff base ligand and Mn(II) complex were studied and presented in (Fig. 2). The SEM image of the ligand gave rod-like shaped particles. On the other hand, Mn(II) complex exhibited non-uniform clusters structure. The average particle size of nanostructured Schiff base ligand was 77 nm, while the average particle size of the Mn(II) complex was 58 nm. The synthesized nanoparticles of Mn(II) complex were observed to develop from just a single molecule to numerous molecules in the nanoscale [58, 66, 67].

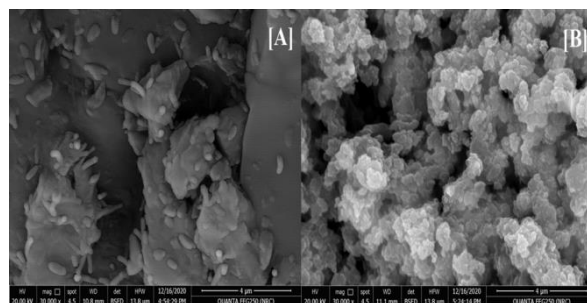


Fig. 2. SEM images of the synthesized nanoparticles a) L ligand and b) $[\text{Mn}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl}.4\text{H}_2\text{O}$.

3.7. Thermal analyses (TG and DTG)

Thermogravimetric measurements of the solid Schiff base ligand and metal complexes were characterized using TG and DTG analyses within the temperature range from room temperature to 1000 °C. The Schiff base ligand was thermally stable up to 130 °C and then successively decomposed in three steps as presented in (Table 3).

The thermogram of $[\text{Mn}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl}\cdot 4\text{H}_2\text{O}$ complex showed its decomposition in five successive steps. The first decomposition step corresponds to the loss of hydrated water molecules. The second and third steps represented the loss of coordinated water molecules, Cl_2 gas and C_3H_8 molecule. Accordingly, the fourth and fifth steps could be attributed to degradation of the remaining ligand molecule, leaving MnO as a residue.

The TG curve of $[\text{Ni}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl}\cdot 2\text{H}_2\text{O}$ complex showed three decomposition steps. The first step was associated with the loss of hydrated water molecules. The second could be attributed to the loss of coordinated water molecules, Cl_2 gas and C_3H_8 molecule. The last step corresponds to the elimination of remaining ligand molecule to give the NiO as a residue.

The thermogram of $[\text{Zn}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]$ complex showed four decomposition steps. The first two steps attributed to the loss of coordinated water molecules and HCl. The third and fourth steps correspond to the removal of remaining part of the ligand, leaving ZnO as a residue.

The $[\text{La}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$ and $[\text{Yb}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$ complexes were thermally decomposed in three steps. The first step corresponds to the loss of Cl_2 gas and

Table 3

Thermo gravimetric results of Schiff base ligand and its metal complexes

Compound	TG range (°C)	DTG (°C)	n*	Found (calcd.) %		Assignment	Metallic residue Found (calcd.) %
				Weight loss	Total weight loss		
L	130-425 425-986	262 480, 642	1 2	39.48(39.75) 59.96(60.25)	99.44 (100)	-Loss of C_{10}H_8 . -Loss of $\text{C}_{13}\text{H}_{10}\text{N}_2$.	—
$[\text{Mn}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl}\cdot 4\text{H}_2\text{O}$	33-143 143-304 304-751	96 170, 241 530, 688	1 2 2	12.24(12.54) 26.11(26.31) 49.25(48.78)	87.60 (87.63)	-Loss of $4\text{H}_2\text{O}$. -Loss of $2\text{H}_2\text{O}$, Cl_2 and C_3H_8 . -Loss of $\text{C}_{20}\text{H}_{12}\text{N}_2$.	MnO 12.40 (12.37)
$[\text{Ni}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl}\cdot 2\text{H}_2\text{O}$	30-178 178-347 347-852	93 239 584	1 1 1	6.34(6.64) 27.96(27.86) 52.10(51.66)	86.40 (86.16)	-Loss of $2\text{H}_2\text{O}$. -Loss of $2\text{H}_2\text{O}$, Cl_2 and C_3H_8 . -Loss of $\text{C}_{20}\text{H}_{12}\text{N}_2$.	NiO 13.60(13.84)
$[\text{Zn}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]$	146-422 422-912	195, 346 683, 860	2 2	19.03(18.42) 65.04(65.18)	84.07 (83.60)	-Loss of H_2O and 2HCl . -Loss of $\text{C}_{23}\text{H}_{18}\text{N}_2$.	ZnO 15.93(16.40)
$[\text{La}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$	38-202 202-637	123 275, 487	1 2	23.86(23.86) 48.32(49.13)	72.18 (72.99)	-Loss of Cl_2 and $\text{C}_4\text{H}_{11}\text{N}$. -Loss of $\text{C}_{19}\text{H}_{11}\text{NO}_{0.5}\text{Cl}$.	$\frac{1}{2}\text{La}_2\text{O}_3$ 27.82(27.01)
$[\text{Er}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$	45-224 224-550 550-987	141 354, 487 687	1 2 1	19.55(19.48) 17.33(17.02) 23.25(23.75)	60.13 (60.25)	-Loss of Cl_2 and C_4H_4 . -Loss of $\text{C}_4\text{H}_{10}\text{NCl}$. -Loss of $\text{C}_{10}\text{H}_8\text{NO}_{0.5}$.	$\frac{1}{2}\text{Er}_2\text{O}_3 + 5\text{C}$ 39.87(39.75)
$[\text{Yb}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$	30-239 239-984	130 348, 787	1 2	21.15(21.65) 48.65(47.45)	69.80 (69.10)	-Loss of Cl_2 and $\text{C}_4\text{H}_5\text{N}$. -Loss of HCl and $\text{C}_{19}\text{H}_{16}\text{NO}_{0.5}$.	$\frac{1}{2}\text{Yb}_2\text{O}_3$ 30.20(30.90)

* n = number of decomposition step.

organic moiety. The last two steps represented the elimination of remaining organic moiety to give $\frac{1}{2}\text{La}_2\text{O}_3$ and $\frac{1}{2}\text{Yb}_2\text{O}_3$ as metallic residues.

The thermal analysis curve of $[\text{Er}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$ complex reported that decomposition occurred in four steps. The first step of decomposition was attributed to the loss of Cl_2 and C_4H_4 . The second, third and fourth steps represented the loss of remaining ligand molecule, leaving $\frac{1}{2}\text{Er}_2\text{O}_3$ as a residue contaminated with carbon atoms.

3.8. Antimicrobial activity

The biological activity of the synthesized bidentate NN Schiff base ligand and its metal complexes were investigated by disc diffusion method [42]. The data of the *in-vitro* antibacterial examinations proposed that the Schiff base ligand was biologically active and also its complexes. They showed significantly improved antibacterial activity against Gram-positive bacteria: *Bacillus subtilis* and Gram-negative bacteria: *Escherichia coli*. Also, these data were summarized in (Table 4) and represented in (Fig. 3).

Table 4

The antimicrobial activities of L and its metal complexes

Ligand / Complex	Inhibition zone diameter (mm/mg)			
	Fungi		G(+ve)	G(-ve)
	<i>Aspergillus flavus</i>	<i>Candida albicans</i>	<i>Bacillus subtilis</i>	<i>E-coli</i>
L	NA	NA	9	10
$[\text{Mn}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl} \cdot 4\text{H}_2\text{O}$	NA	NA	NA	NA
$[\text{Ni}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl} \cdot 2\text{H}_2\text{O}$	NA	17	14	14
$[\text{Zn}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]$	NA	NA	16	15
$[\text{La}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$	NA	NA	10	10
$[\text{Er}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$	NA	NA	11	11
$[\text{Yb}(\text{L})(\text{H}_2\text{O})_2\text{Cl}_2]\text{Cl}$	NA	NA	9	10
Amphotericin B	17	21	—	—
Ampicillin	—	—	26	—
Gentamicin	—	—	—	20

Note: NA: No activity

It was clear that the order of antibacterial activity was found to be: ampicillin > Zn(II) > Ni(II) > Er(III) > La(III) > Yb(III) = L > Mn(II) for *Bacillus subtilis* and gentamicin > Zn(II) > Ni(II) > Er(III) > La(III) = Yb(III) = L > Mn(II) for *Escherichia coli*. The results could be illustrated according to the basis of Overtone's concept and Chelation theory [68, 69]. This proposed the ability of such complexes to pass through the cell membrane of the tested organism.

For the antifungal activity, it was found that the Schiff base ligand and its complexes had no antifungal activity against *Aspergillus flavus*, while Ni(II) was found to have good antifungal activity against *Candida albicans* compared with the parent Schiff base ligand and other complexes.

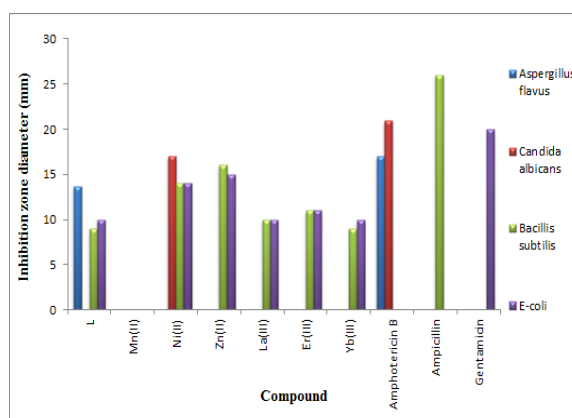


Fig. 3. Antimicrobial activity of Schiff base ligand and its metal complexes.

3.9. Evaluation of cytotoxic activity

The cytotoxic ability of Schiff base ligand and its complexes were screened against the MCF-7 cell line (breast carcinoma cells), which was one of the most common forms of cancer. Therefore, all the synthesized compounds were investigated against single-dose concentration (100 $\mu\text{g}/\text{ml}$) of MCF-7 cell line. The *in-vitro* screening of the compounds indicated that the Schiff base had good anticancer activity (65% inhibition), while Mn(II) complex exhibited inhibition higher than that of the parent

Schiff base ligand and other complexes of about 67%. Also, La(III) complex had good anticancer activity (63% inhibition) but less than that of the free Schiff base ligand.

The half-inhibitory concentration (IC_{50}) values and the mode of anticancer activity were estimated for more active complexes with inhibition ratio value $> 60\%$ as shown in (Fig. 4), by using various concentrations (5, 12.5, 25 and 50 $\mu\text{g/ml}$). The data obtained were illustrated in (Table 5) and (Fig. 5). Mn(II) complex exhibited the lowest IC_{50} value (20 $\mu\text{g/ml}$), which was more efficient against breast carcinoma cells than free ligand [50,70]. The Ni(II) and Yb(III) complexes had moderate activities of 58 and 50%, respectively, while Zn(II) and Er(III) complexes had weak inhibitions of less than 50% for MCF-7 cell line [71].

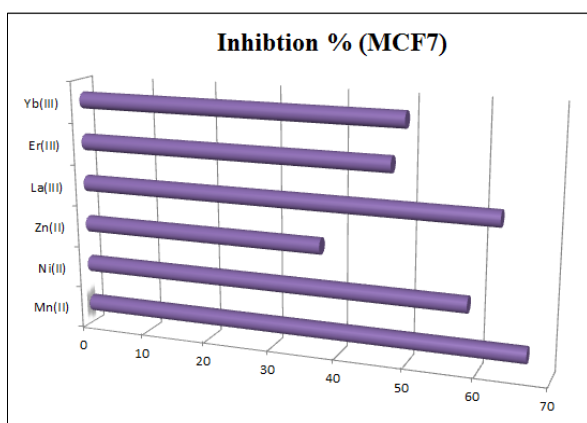


Fig. 4. Single-dose of (100 $\mu\text{g/ml}$) metal complexes on MCF-7 cell line.

Table 5

Anti-breast cancer activity of L and its complexes

Compound	Surviving fraction (MCF7)					IC_{50} ($\mu\text{g/ml}$)
	Concentration ($\mu\text{g/ml}$)					
	0	5	12.5	25	50	
L	1	0.746	0.560	0.522	0.410	29
Mn(II)	1	0.784	0.597	0.410	0.373	20
La(III)	1	0.933	0.896	0.672	0.485	48

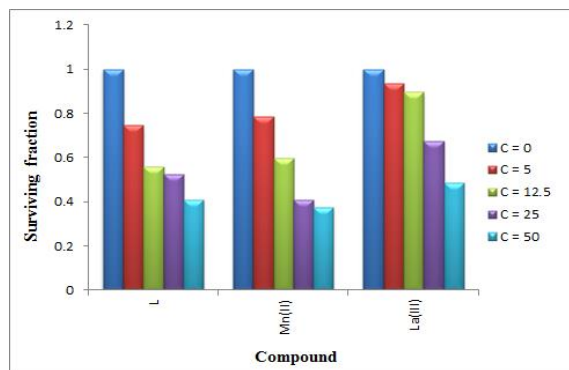


Fig. 5. Anti-breast cancer activity of L ligand and its Mn(II) and La(III) complexes.

3.10. Molecular modeling

Docking studies were performed to predict the binding modes of Schiff base ligand with two different receptors: breast cancer mutant oxidoreductase (PDB ID: 3HB5) and yeast-specific serine/threonine protein phosphatase (PPZ1) of *Candida albicans* (PDB ID: 5JPE) [72]. The results revealed that the main interaction forces of Schiff base ligand with the active sites were H-donor and H-acceptor. The lowest binding energies for Schiff base ligand were found to be -1.2 and -1.6 kcal/mol with 3HB5 and 5JPE receptors, respectively. From the previous data, it was found that the Schiff base ligand had possible interactions with 3HB5 and 5JPE receptors as illustrated in (Fig. 6). It was obvious that the Schiff base ligand had stronger interaction with 5JPE receptor than 3HB5 receptors with minimum binding energy (-1.6 kcal/mol) through H-bonding with the nitrogen atom of the arginine amino acid residue of the protein phosphatase of *Candida albicans* [50].

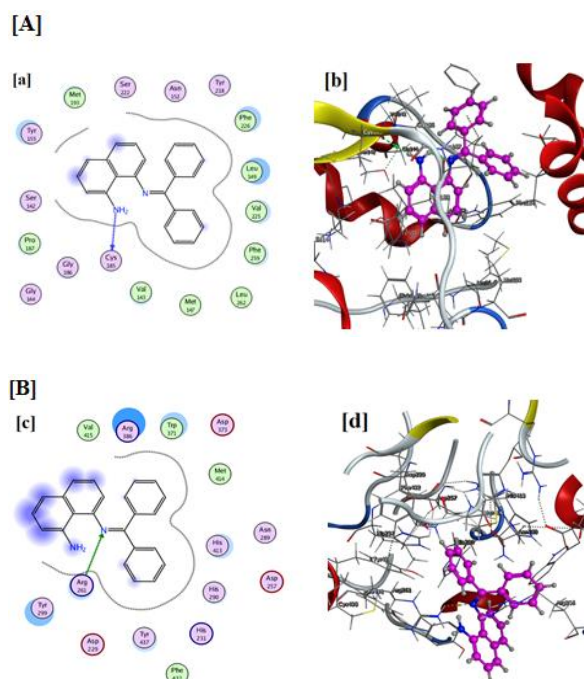


Fig. 6. [A] The interaction between Schiff base ligand (L) with receptor 3HB5 [a] 2D plot of L and [b] 3D plot of L. [B] The interaction between Schiff base ligand (L) with receptor 5JPE [c] 2D plot of L and [d] 3D plot of L.

4. Conclusions

The coordination behaviour of some metal ions: Mn(II), Ni(II), Zn(II), La(III), Er(III) and Yb(III) with bidentate Schiff base ligand was elucidated. The metal chelates were characterized by different physicochemical and spectroscopic techniques. The spectroscopic data showed that the Schiff base ligand acts as neutral bidentate ligand and it coordinated to metal ions through the nitrogen of azomethine and amino groups. The molar conductivity intimated that all complexes were monomeric and electrolytic in nature except Zn(II) complex was nonelectrolyte. The data confirmed the octahedral geometry of the complexes. SEM analysis for L ligand and its $[\text{Mn}(\text{L})(\text{H}_2\text{O})_3\text{Cl}]\text{Cl}\cdot 4\text{H}_2\text{O}$ complex, it exhibited that they were prepared in nano-scale with particle size 77 and 58 nm, respectively. The thermal analyses of the compounds were used to support the suggested molecular formulae and to determine the stability of

Schiff base ligand and its chelates. The synthesized Schiff base ligand and its metal chelates had been screened against various fungal and bacterial organisms. The results exhibited that Zn(II) complex had higher antibacterial activity than the Schiff base ligand and other chelates while, Mn(II) complex had no biological activity. The examined compounds also gave reasonable cytotoxicity against MCF-7 breast cancer cell line. The binding between Schiff base ligand with the receptors of breast cancer (PDB ID: 3HB5) and the crystal structures of *Candida albicans* (PDB ID: 5JPE) also examined using molecular docking.

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

No fund

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