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Preparation, Characterization and Biological Activity Screening on Some Metal Complexes Based of Schiff Base Ligand

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Abstract

A novel Schiff base ligand named (E)-2-(((3-hydroxyphenyl)imino)methyl)phenol (H_2L) was prepared through condensation of 2-hydroxybenzaldehyde with 3-aminophenol in1:1 ratio. The ligand was characterized using spectroscopic techniques. La(III), Er(III) and Yb(III) complexes derived from H_2L ligand have been prepared and characterized by conventional techniques including elemental analyses, infrared, electronic spectra, mass spectra, molar conductivity and thermal analysis. IR spectral data showed that H_2L ligand is coordinated to the metal ions in a bi-negative tridentate manner through the azomethine nitrogen and two deprotonated phenolic oxygen atoms. The thermogravimetric analysis data of the complexes displays the existence of hydrated and coordinated water molecules in the complexes. The ligand and its complexes were evaluated for their antibacterial and antifungal activities against different gram positive bacteria (*Staphylococcus Aureus* and *Bacillis subtilis*), gram negative bacteria (*Salmonella SP.*, *Escherichia Coli* and *Pseudomonas aeruginosa*) and fungi (*Aspergillus Fumigates* and *Candida albicans*). The complexes were found to have higher biological activity against bacteria and fungi more than the ligand. The calculated binding energy values of the receptors of the colon cancer (PDB code: 2hq6) and the lung cancer (PDB code: 1x2j) for Schiff base ligand (H_2L) were discussed.

*Keywords***:** Schiff base complexes; Characterization; Molecular docking; Thermal analysis; Biological activity.

Introduction

Schiff bases have received a great deal of attention in a wide variety of fields due to their simple synthesis and various applications. They can be readily synthesized by simple condensation of aldehydes or ketones with primary amines in an alcoholic solvent under anhydrous conditions [1,2]. Schiff bases and their metal complexes are used as catalysts for many reactions (e.g. oxidation, epoxidation, reduction, polymerization, ring-opening polymerization and Diels–Alder reactions. Their antibacterial, antifungal, antiviral and antitumor activities have been revealed [3-6]. Moreover, in recent research a number of Schiff bases have been used as highly selective fluorescent chemosensors and colorimetric sensors for cations.

Schiff base ligands and their complexes are used in pharmacology as antibacterial, anticancer, and antifungal agents [2,5,6]. Also, they are of significant interest for biochemistry, biomedicine, and environmental protection owing to their ability for chemical recognition of anions and metals.

Molecular docking aims to achieve an optimized conformation for both the protein and drug with relative orientation between them such that the free energy of the overall system is minimized, also, affinity of molecules to anticancer receptors is very important in drug design [7]. Improvement breast cancer control will be markedly supported by early detection [8].

The goal of the present work is to synthesize new Schiff base ligand formed from the condensation reaction of 2-hydroxybenzaldehyde with 3-aminophenol.

The reactions of the ligand with a series of metal ions were characterized by the means of IR, UV-Vis,

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elemental and thermal analyses and evaluation for their antibacterial and antifungal activities against different organisms are discussed. The calculated binding energy values of the receptors of the colon cancer (PDB code: 2hq6) and the human lung cancer for Schiff base ligand (H_2L) (PDB code: 1x2j) are discussed.

Experimental

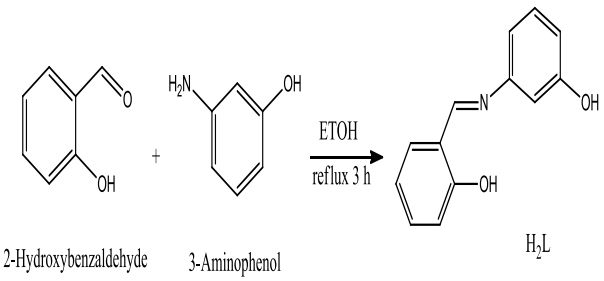
Materials and reagents

All chemicals used were of the analytical reagent grade (AR), and of highest purity available. They included 2-hydroxybenzaldehyde (Merck), 3-aminophenol (Merck), $LaCl_3 \cdot 7H_2O$, $ErCl_3 \cdot 6H_2O$) and $YbCl_3 \cdot 6H_2O$ (Sigma- Aldrich).

The organic solvents as absolute ethyl alcohol and dimethylformamide (DMF) were either spectroscopic pure from BDH or purified by the recommended methods [9] and tested for their spectral purity.

Synthesis of the Schiff base ligand (H_2L)

Schiff base ligand (H_2L) was synthesized by condensation of 3-aminophenol with 2-hydroxybenzaldehyde (Scheme 1). A solution of 2-hydroxybenzaldehyde (36.65 mmol, 4.48 g, 3.84 ml) dissolved in ethanol was added dropwise to 3-aminophenol (36.65 mmol, 4 g) dissolved in ethanol. The resulting mixture was stirred under reflux for about 3 h during which an orange solid compound was separated. It was filtered, recrystallized and washed with diethylether and dried in vacuum.



Scheme 1. Preparation of Schiff base ligand (**H_2L)**

H_2L

Yield 48.68 %; m.p. 115 °C; orange solid. Anal. Calcd. for $C_{13}H_{11}NO_2$ (%): C, 73.24; H, 5.16; N, 6.57. Found (%): C, 73.22; H, 5.15; N, 6.55. FT-IR (cm^{-1}): phenolic ν (OH) 3435, azomethine ν(C=N) 1616, ν(C-N) 1389, ν(C-O) phenolic 1271. ^{1}HNMR (300 MHz, DMSO-d*6*, δ, ppm): 5.35 (s, 2H, OH phenolic), 8.87 (s, H, CH=N), 6.01-6.97 (m, 8H, Ar H). λmax (nm): 220 π–π*, 340 n–π*.

Synthesis of metal complexes of H_2L ligand

The metal complexes were prepared by the addition of the appropriate metal chloride (1.878 mmol) in ethanol to the hot solution (60 °C) of the ligand (0.4g, 1.878 mmol) in ethanol. The resulting mixture was stirred under reflux for two hours whereupon the complexes precipitated. They were removed by filtration, washed with hot ethanol and purified by washing several times with diethyl ether. The analytical data for C, H and N were repeated twice.

$[La(H_2L)(H_2O)_3].H_2O.Cl$

Yield 99.12 %; brick red solid, m.p. 123 °C. Anal. Calcd for $La(C_{13}H_{17}ClNO_6)$ (%): C, 34.11; H, 3.72; N, 3.06; La, 30.37. Found (%): C, 34.09; H, 3.70; N, 3.08; La, 30.39. FT-IR (cm^{-1}): phenolic ν (OH) 3401, azomethine ν(C=N) 1624, ν(C-N) 1373, phenolic ν(C-O) 1276, ν(H_2O) stretching bands of coordinated water 973 and 857, ν(M-O) stretching bands of coordinated water 524, metal-oxygen bond ν(M-O) 536, metal-nitrogen bond ν(M-N) 445. λmax (nm): 232 π–π*.

$[Er(H_2L)(H_2O)_2Cl].H_2O$

Yield 57.02 %; dark brown solid, m.p. 215 °C. Anal. Calcd for $Er(C_{13}H_{15}ClNO_5)$ (%): C, 33.35; H, 3.21; N, 2.99; Er, 35.76. Found (%): C, 33.36; H, 3.20; N, 2.98; Er, 35.77. FT-IR (cm^{-1}): phenolic ν(OH) 3372, azomethine ν(C=N) 1628, ν(C-N) 1355, phenolic ν(C-O) 1221, ν(H_2O) stretching bands of coordinated water 967 and 855, ν(M-O) stretching bands of coordinated water 517, metal-oxygen bond ν(M-O) 530, metal-nitrogen bond ν(M-N) 465. λmax (nm): 215 and 260 π–π*, 403 conjugation.

$[Yb(H_2L)(H_2O)_3].H_2O.Cl$

Yield 93.32 %; dark brown solid, m.p. 167 °C. Anal. Calcd for $Yb(C_{13}H_{17}ClNO_6)$ (%): C, 31.74; H, 3.46; N, 2.85; Yb, 35.21. Found (%): C, 31.75; H, 3.45; N, 2.86; Yb, 35.20. FT-IR (cm^{-1}): phenolic ν(OH) 3387, azomethine ν(C=N) 1605, ν(C-N) 1358, phenolic ν(C-O) 1244, ν(H_2O) stretching bands of coordinated water 949 and 828, ν(M-O) stretching bands of coordinated water 504, metal-oxygen bond ν(M-O) 567, metal-nitrogen bond ν(M-N) 466. λmax (nm): 213 and 251 π–π*, 330 n–π*.

Instruments

Microanalyses of carbon, hydrogen and nitrogen were carried out at the Microanalytical Center, Cairo University, Egypt, using CHNS-932 (LECO) Vario

Elemental Analyzer. FT-IR spectra were recorded on a Perkin-Elmer 1650 spectrometer (4000–400 cm^{-1}) in KBr pellets. Electronic spectra were recorded at room temperature on a Shimadzu 3101pc spectrophotometer as solutions in DMF.

Mass spectra were recorded by the EI technique at 70 eV using MS-5988 GS-MS Hewlett-Packard instrument at the Microanalytical Unit, National Center for Research, Egypt. The magnetic susceptibility was measured on powdered samples using the Faraday method. The diamagnetic corrections were made by Pascal's constant and $Hg[Co(SCN)_4]$ was used as a calibrant. Molar conductivities of 10^{-3} M solutions of the solid complexes in DMF were measured using Jenway 4010 conductometer. The thermogravimetric analyses (TG) of the solid complexes were carried out from room temperature to 1000 °C in a dynamic atmosphere of nitrogen (70 ml/min) using a Shimadzu TG-50H thermal analyzer. The antimicrobial activities were carried out at the Microanalytical Center, Cairo University, Egypt. Docking calculations were carried out on receptors of the structure of the Cyclophilin_CeCYP16-Like Domain of the serologically defined colon cancer Antigen 10 from Homo Sapiens (PDB code: 2hq6) and the structural basis for the defects of human lung cancer somatic mutations in the repression activity of Keap1 on Nrf2 (PDB code: 1x2j). The MMFF94 Force field was used for energy minimization of molecules using Docking Server [10-13].

Biological activity

Antimicrobial activity of the tested samples was determined using a modified Kirby-Bauer disc diffusion method [14]. 100 µl of the tested bacteria or fungi were grown in 10 ml of fresh media until they reached a count of approximately 108 cells/ml for bacteria and 105 cells/ml for fungi [15]. 100 µl of microbial suspension was spread onto agar plates corresponding to the broth in which they were maintained. Isolated colonies of each organism that might be playing a pathogenic role should be selected from primary agar plates and tested for susceptibility by disc diffusion method. Of the many media available, NCCLS recommends Mueller-Hinton agar due to: it results in good batch-to-batch reproducibility. Disc diffusion method for filamentous fungi tested by using approved standard method (M38-A) developed [16]. For evaluating the susceptibilities of filamentous fungi to antifungal agent, Disc diffusion method for yeast developed by using approved standard method (M44-P) [17].

Plates inoculated with Gram (+) bacteria as *Staphylococcus aureus* and *Bacillus subtilis*; Gram (-) bacteria as *Pseudomonas aeruginosa, Salmonella SP.* and *Escherichia coli*, they were incubated at 35-37ºC for 24-28 hours and yeast fungus as *Aspergillus fumigatus* and *Candida albicans* incubated at 30ºC for 24-28 hours and, then the diameters of the inhibition zones were measured in millimeters [17]. Standard discs of Ampicillin and Gentamycin (antibacterial agents), and Amphotericin B (antifungal agent) served as positive controls for antimicrobial activity but filter discs impregnated with 10 µl of solvent (distilled water, chloroform, DMSO) were used as a negative control. The agar used is Meuller-Hinton agar that is rigorously tested for composition and pH. Further the depth of the agar in the plate is a factor to be considered in the disc diffusion method. This method is well documented and standard zones of inhibition have been determined for susceptible and resistant values. Blank paper discs (Schleicher and Schuell, spain) with a diameter of 8.0 mm were impregnated with 10 µl of tested concentration of the stock solutions. When a filter paper disc impregnated with a tested chemical is placed on agar, the chemical will diffuse from the disc into the agar. This diffusion will place the chemical in the agar only around the disc. The solubility of the chemical and its molecular size will determine the size of the area of chemical infiltration around the disc. If an organism is placed on the agar, it will not grow in the area around the disc if it is susceptible to the chemical. This area of no growth around the disc is known as zone of inhibition or clear zone. For the disc diffusion, the zone diameters were measured with slipping calipers of the national committee for clinical laboratory standards [18]. Agar based methods such E-test and disc diffusion can be good alternatives because they are simpler and faster than broth-based methods [19].

Results and discussion

Characterization of Schiff base ligand

The symmetric Schiff base ligand was prepared by stirring an appropriate amount of 2-hydroxybenzaldehyde with the corresponding 3-aminophenol in ethanol. The new Schiff base ligand formed was characterized with respect to its composition using elemental and spectral analyses.

The results of elemental analysis (C, H, and N) with molecular formula and the melting point are

presented in Table 1. The results obtained are in good agreement with those calculated for the suggested formula, and the melting point is sharp indicating the purity of the prepared ligand. The ligand is soluble in ethanol, DMF and DMSO.

The electron impact spectrum of the newly prepared Schiff base ligand is recorded and investigated at 70 eV of electron energy. The mass spectrum of the newly synthesized Schiff base is characterized by moderate to high relative intensity molecular ion peaks. It is obvious that, the molecular ion peaks are in good agreement with its suggested empirical formula as indicated from elemental analyses. The mass spectrum shows a peak at m/z = 213 (M^+) which refers to the main molecular ion of the Schiff base (molar mass = 213 g mol^{-1}).

Fundamental IR spectral bands for the ligand are given in Table 2. The IR spectrum of the free ligand is characterized by the strong bands at 3435, 1389 and 1271 cm^{-1}, attributed to the stretching frequencies of ν(OH) phenolic, ν(C-N) stretching and ν(C-O) phenolic, respectively. Also a band for the azomethine ν(C=N) stretching vibration was recorded at 1616 cm^{-1} confirming the formation of the Schiff base ligand due to the condensation reaction between 3- aminophenol and 2-hydroxybenzaldehyde [20, 21]. The ^1H NMR data of the newly synthesized Schiff base ligand is featured by the peaks appeared at 6.01-6.97 ppm which may be assigned to the aromatic ring protons. Sharp band at 8.87 ppm may be assigned to the proton of azomethine (-CH=N-) group which confirms the formation of Schiff base ligand [21, 22]. A singlet peak at 5.35 ppm can be assigned to the protons of OH phenolic groups [23-26]. The decrease in chemical shift for phenolic protons may be due to intermolecular hydrogen bonding which is confirmed by the disappearance of this peak in addition of D_2O.

Molecular docking study of Schiff base ligand (H_2L)

Exploration of molecular docking interaction of the Schiff base ligand (H_2L) was performed through molecular docking studies using Docking Server [27-32]. The Schiff base ligand (H_2L) was evaluated for their inhibitory effect on receptors of the colon cancer (PDB code: 2hq6) and the lung cancer (PDB code: 1x2j) [33-37]. The data showed a favorable arrangement between the Schiff base ligand (H_2L) and the receptors of the colon cancer (PDB code: 2hq6) and the lung cancer (PDB code: 1x2j) and the interaction curves are shown in Figure 1 and the calculated energy as well as some parameters with the selected anticancer receptors are listed in Table 3. The estimated free energy of binding (kcal/mol) is -4.66 and -5.43 for the receptors of the colon cancer (PDB code: 2hq6) and the lung cancer (PDB code: 1x2j), respectively. The 2D plot curves of binding for Schiff base ligand (H_2L) with the receptors of colon cancer (PDB code: 2hq6) and lung cancer (PDB code: 1x2j) are shown in Figure 2. The HB plot curves explain the interactions between Schiff base ligand (H_2L) and receptors of the colon cancer (PDB code: 2hq6) and the lung cancer (PDB code: 1x2j) as shown in Figure 3.

Compositions and structures of metal complexes

The synthesized Schiff base ligand and its complexes are very stable at room temperature in the solid state. The ligand is insoluble in common organic solvents on cold. The ligand and its metal complexes are generally soluble in DMF and ethanol. The yields, melting points, elemental analyses of H_2L and its metals complexes are presented in Table 1. Metal complexes were obtained upon reaction between metal ions and H_2L ligand at 1:1 M:L ratio. The analytical data are in a good agreement with the proposed stoichiometry of the complexes.

Molar conductivities were determined for solutions of the metal complexes at a concentration of 10^{-3} M in ethanol at room temperature (Table 1). Generally, higher molar conductance values are indicative of the electrolytic nature of the metal complexes and lower values show their non-electrolytic nature. The measured molar conductance value of the Er(III) metal complex was 49.9 Ω^{-1} $mol^{-1}cm^2$ indicating its non-electrolytic behavior [38]. In addition La(III) and Yb(III) complexes have molar conductance values of 88.4 and 64.1 $\Omega^{-1}mol^{-1}cm^2$, respectively, indicating their ionic nature and they are considered as 1:1 electrolytes.

The mass spectrum of La(III) complex showed a molecular ion peak at m/z = 457 amu, which is equivalent to its molecular weight of 457.35 amu corresponding to the molecular formula of $[La(H_2L)(H_2O)_3].H_2O.Cl$. The molecular formula of the complex was confirmed by observing a peak at 213 corresponding to the ligand moiety ($C_{13}H_{11}NO_2$) [atomic mass 213 amu]. The molecular ion peak of the complex is in good agreement with the suggested molecular formulae indicated from elemental and TG analyses.

In order to study the binding mode of the Schiff base to the metal in the complexes, the IR spectrum of the free ligand was compared with the spectra of metal complexes which exhibited characteristic frequencies of the expected functional groups and are tabulated in Table 2.

Table 1. Analytical and physical data of H_2L complexes.

Compound (Molecular Formula)	Colour (%yield)	M.p. (°C)	% Found (Calcd.) C	H	N	M	Λ_m $\Omega^{-1}mol^{-1}cm^2$
H_2L	Orange (78.68)	115	73.22 (73.24)	5.15 (5.16)	6.55 (6.57)	-----	-----
[La(H_2L)(H_2O)$_3$] .H_2O.Cl (1)	Brick red (99.12)	123	34.09 (34.11)	3.70 (3.72)	3.08 (3.06)	30.39 (30.37)	88.40
[Er(H_2L)(H_2O)$_2$ Cl].H_2O (2)	Dark brown (57.02)	215	33.36 (33.35)	3.20 (3.21)	2.98 (2.99)	35.77 (35.76)	49.90
[Yb(H_2L)(H_2O)$_3$].H_2O.Cl (3)	Dark brown (93.32)	167	31.75 (31.74)	3.45 (3.46)	2.86 (2.85)	35.20 (35.21)	64.10

Table 2. Important bands of the IR spectra (4000-400 cm^{-1}) of H_2L ligand and its metal complexes[a].

H_2L	(1)	(2)	(3)	Assignment
3435br	3401br	3372br	3387br	OH stretching
1616sh	1624sh	1628sh	1605sh	CH=N stretching
1389sh	1373sh	1355sh	1358sh	C-N stretching
1271sh	1276sh	1221sh	1244sh	C-O phenolic
-----	973w, 857m	967s, 855m	949sh, 828sh	H_2O stretching of coordinated water
-----	536s	530w	567sh	M-O
-----	524w	517sh	504sh	M-O stretching of coordinated water
-----	445w	465w	466s	M-N

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

[a]Numbers as given in Table 1.

Table 3. Energy values and parameters obtained in docking calculations for Schiff base ligand (H_2L) with receptors of the colon cancer (PDB code: 2hq6) and the lung cancer (PDB code: 1x2j)

Receptors	Estimated inhibition constant (K_i) (µM)	vdW+ bond+ desolv energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Total intercooled Energy (kcal/mol)	Interact surface (Å)
2hq6	385.20	-5.44	-0.07	-5.51	560.545
1x2j	104.40	-6.58	-0.06	-6.64	552.760

In the IR spectrum of the complexes, a strong band around 1605-1628 cm^{-1} is assigned to the ν(C=N) band [39], and the bands in the range 1221-1276 cm^{-1} can be related to the phenolic (C−O) group vibrations [40, 41]. The bands at 1355-1373 cm^{-1} in the spectra of metal complexes assigned to the (C−N) group vibrations. Broad bands which appeared at 3372-3401 cm^{-1} are indicative of the presence of water molecules outside the coordination sphere of the metal in the complex whereas medium bands which appeared at 949-973 and 828-857 cm^{-1} indicated the presence of H_2O coordinated with the metal in the lattice of complexes [42]. After coordination, the various vibrations of M−O are assigned to bands at 530-567 cm^{-1} and M−N are assigned to weak bands at 445-466 cm^{-1}, respectively, which confirms the involvement of the oxygen and nitrogen atoms in the coordination sphere of metal ions [43]. The metal chelates showed new bands in the region of 504-524 cm^{-1} which can be attributed to the formation of M−O of coordinated water [44, 45].

IR data showed that the ligand is a tridentate bi-negative ligand coordinating to the metal ions through azomethine nitrogen and two deprotonated phenolic oxygen atoms.

Thermal analysis

From TGA data presented in Table 4, the mass loss percentages were calculated for the different steps and compared with those theoretically calculated for the suggested formulae based on the results of elemental analyses as well as molar conductance measurements [21, 46]. TGA indicated the formation of metal oxide as the end product from which the metal content could be calculated and compared with that obtained from analytical determination.

The TGA curve of the Schiff base ligand with the molecular formula [$C_{13}H_{11}NO_2$] decomposed in four stages. The first step in the temperature range 40-400 °C, which can be attributed to weight loss of 31.92 % (calculated weight loss = 31.93 %) corresponding to the elimination of C_4H_4O molecule. The second step of the thermal decomposition, which occurred in the range 400-610 °C may be assigned to the loss of C_4H_2O molecule (found 30.97 %; calculated 30.98 %). The third and fourth steps of the thermal decomposition, which occurred within the range 610-1000 °C, may be assigned to the loss of C_5H_5N molecule (found mass loss = 37.08 %; calcd. = 37.09 %). The total weight loss amounts to 99.97 % (calcd. = 100 %).

The [$La(H_2L)(H_2O)_3$].H_2O.Cl complex was thermally decomposed in four successive decomposition steps. The first step with estimated mass loss of 13.72 % (calculated mass loss = 13.78 %) within the temperature range 35-150 °C may be attributed to the loss of $3.5H_2O$ molecules. The second step occurred within the temperature range 150-265 °C with the estimated mass loss 8.95 % (calculated mass loss = 8.97 %), which correspond to the loss of C_2NH_3 fragment. The third step with estimated mass loss of 11.01 % (calculated mass loss = 11.03 %) within the temperature range 265-450 °C may be attributed to the loss of CH_3Cl molecule. The last step occurred within the temperature range 450-1000 °C with the estimated mass loss 25.35 % (calculated mass loss = 25.36 %), which correspond to the loss of C_8H_4O organic moiety leaving metal oxide $½La_2O_3$ contaminated with carbon as residue. Total estimated mass loss was 59.03 % (calculated mass loss = 59.14 %).

The thermal degradation of [$Er(H_2L)(H_2O)_2$.Cl].H_2O complex takes place in four stages. The first decomposition stage in the temperature range of 15-110 °C, attributed to the loss of $3H_2O$ and $½N_2$ molecules with the observed mass loss of 14.53% (calculated mass loss = 14.54%). The second stage of decomposition occurs in the 110-220 °C temperature range, corresponding to the loss of C_2H_4 and $½Cl_2$ molecules, and is accompanied by a weight loss of 13.53% (calculated mass loss = 13.57%). The third decomposition stage is in the temperature range of 220-525 °C, which is attributed to the loss of C_4H_2 and $½C_2OH_2$ fragments, with the observed mass loss of 15.14% (calculated mass loss = 15.18%). The fourth decomposition step includes complete evaporation of the ligand and loss of C_6H_2 molecule with the observed mass loss of 15.79% (calculated mass loss = 15.82%) within the temperature range of 525-1000 °C as well as formation of metal oxide ($½Er_2O_3$) as final product from which the metal content was found to be in very good agreement with the data obtained from complexometric analysis. Total estimated mass loss was 58.99% (calculated mass loss = 59.11%).

The [$Yb(H_2L)(H_2O)_3$].H_2O.Cl complex is thermally decomposed in three stages. The first stage of decomposition corresponds to a mass loss of 25.34% (calcd. 24.91%) within the temperature range 35-170 °C and represents the loss of a molecule of hydrated water, three molecules of coordinated water and CH_3Cl organic moiety. The second stage corresponds to a mass loss of 13.22% (calcd. 13.22%) within the temperature range 170-385 °C and represents the loss of C_4H_3N organic part of the complex. The last stage occurring in the temperature range 385-1000 °C with a found mass loss of 11.16% (calcd. 12.00%), is reasonably accounted for the decomposition of the remaining organic part of the complex corresponding to $½C_4H_2O$ and C_2H_2 molecules leaving out $½Yb_2O_3$ contaminated with carbon as a residue. The overall weight loss percentage estimated a mass loss of 49.72% (calculated mass loss = 50.13%).

Structural interpretation

The structures of the complexes of H_2L with La(III), Er(III) and Yb(III) ions are confirmed by the elemental analyses, IR, ^1H NMR, molar conductance, mass, UV-vis and thermal analysis. In the present case, the Schiff base ligand has a number of potential donor atoms in various positions which can bind to the metal ions forming the chelates. From IR, The

ligand behaves as bi-negative tridentate ligand coordinated to the metal ions with ONO donor atoms. From conductance values of the complexes, La(III) and Yb(III) complexes are 1:1 electrolytes, while Er(III) complex is nonelectrolyte (Fig. 4). An octahedral geometry was suggested for the investigated complexes based on the above spectroscopic techniques.

Biological activity

The antimicrobial activity data of all synthesized compounds are summarized in Table 5 and show that the newly synthesized ligand and its metal complexes possess biological activities. These new derivatives were screened for their antibacterial activity against three Gram-negative (*Salmonella SP., E. coli* and *Pseudomonas aeruginosa*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) bacterial strains and two fungi (*Candida albicans* and *Aspergillus fumigatus*). The activity of the prepared compounds is quite comparable with the reference drugs Ampicillin and Gentamycin as antibacterial agents and Amphotericin B as antifungal agent as shown in Figure 5.

Table 4. Thermoanalytical TGA data of H_2L ligand and its metal complexes.

Compound[a]	TG range (°C)	DTG_{max} (°C)	n*	Mass loss Estim (Calcd) %	Total mass loss	Assignment	Residues
H_2L	40-400 400-610 610-1000	287 511 708, 789	1 1 2	31.92 (31.93) 30.97 (30.98) 37.08 (37.09) 99.97 (100)		- Loss of C_4H_4O - Loss of C_4H_2O - Loss of C_5H_5N	-------
(1)	35-150 150-265 265-450 450-1000	86 230 315 640	1 1 1 1	13.72 (13.78) 8.95 (8.97) 11.01 (11.03) 25.35 (25.36) 59.03 (59.14)		- Loss of $3.5H_2O$ - Loss of C_2NH_3 - Loss of CH_3Cl - Loss of C_8H_4O	½La_2O_3+ 2C
(2)	15-110 110-220 220-525 525-1000	82 160 353 650	1 1 1 1	14.53 (14.54) 13.53 (13.57) 15.14 (15.18) 15.79 (15.82) 58.99 (59.11)		- Loss of $3H_2O$ and ½ N_2 - Loss of C_2H_4 and ½ Cl_2 - Loss of C_4H_2 and ½ C_2H_2O - Loss of C_6H_2	½ Er_2O_3
(3)	35-170 170-385 385-1000	82 228 642	1 1 1	25.34 (24.91) 13.22 (13.22) 11.16 (12.00) 49.72 (50.13)		- Loss of $4H_2O$ and CH_3Cl. - Loss of C_4H_3N. - Loss of ½C_4H_2O and C_2H_2.	½Yb_2O_3+ 4C

[a]Numbers as given in Table 1.

Table 5. Biological activity of H_2L ligand and its metal complexes[a].

Sample	Inhibition zone diameter (mm / mg sample)						
	***Staphylococcus aureus* (G^+)**	***Bacillis subtilis* (G^+)**	***Salmonella SP.* (G^-)**	***Escheri-chia coli* (G^-)**	***Pseudomonas aeruginosa* (G^-)**	***Aspergillus fumigatus***	***Candida albicans***
Control: DMSO	0	0	0	0	0	0	0
H_2L	15	17	12	14	16	15	13
(1)	14	17	16	15	14	18	17
(2)	15	19	16	18	17	19	18
(3)	18	22	21	20	19	20	19
Ampicillin	23	32	-	-	-	-	-
Gentamycin	-	-	17	19	16	-	-
Amphotericin B	-	-	-	-	-	23	25

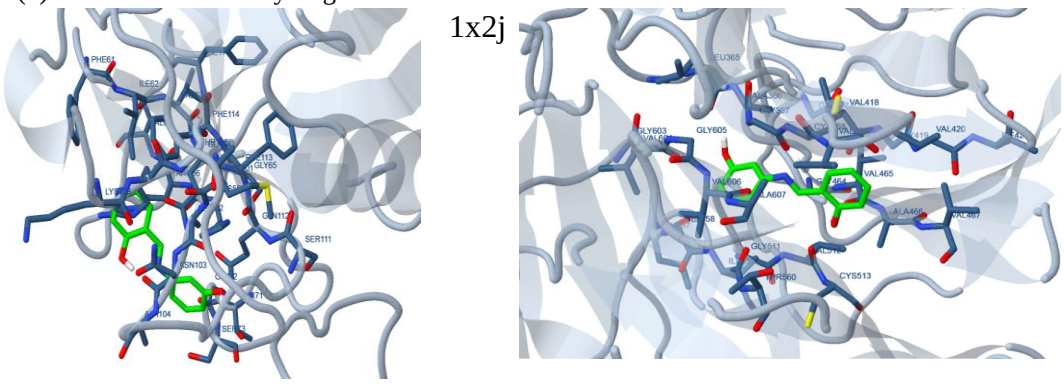
[a]Numbers as given in Table 1.

Antimicrobial agents act selectively on vital microbial functions with minimal effects or without affecting host functions. Different antimicrobial agents act in different ways. The understanding of these mechanisms as well as the chemical nature of the antimicrobial agents is crucial in the understanding of the ways how resistance against them develops [47-50].

Based on a study published on some Schiff base complexes, it was suggested that the mode of action may involve various targets in microorganisms. These mechanisms can be classified into four points: (1) the interference with the cell wall synthesis as a result the cell permeability may be altered or they may disorganize the lipoproteins leading to cell death, (2) Deactivate various cellular enzymes which are important in the microorganism's metabolic pathways, (3) Formation of a hydrogen bond through the azomethine group with the active centres of cell constituents resulting in interfering with the normal cell processes, (4) Denaturation of one or more proteins of the cell, as a result of which the normal cellular processes are impaired [51].

In this research, all complexes were found to have higher biological activity against *Salmonella SP.*, *E. coli*, *Candida albicans* and *Aspergillus fumigatus* than the free ligand. Of all complexes, Yb(III) complex has the highest biological activity against different microorganisms than the free ligand and other complexes. La(III) complex showed the lowest biological activity against different microorganisms than other complexes.

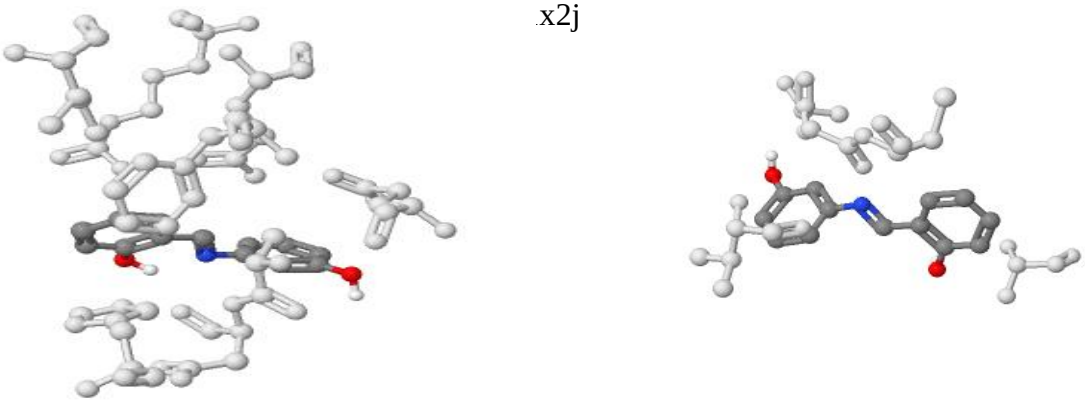
2hq6 1x2j



(a) **(a)**

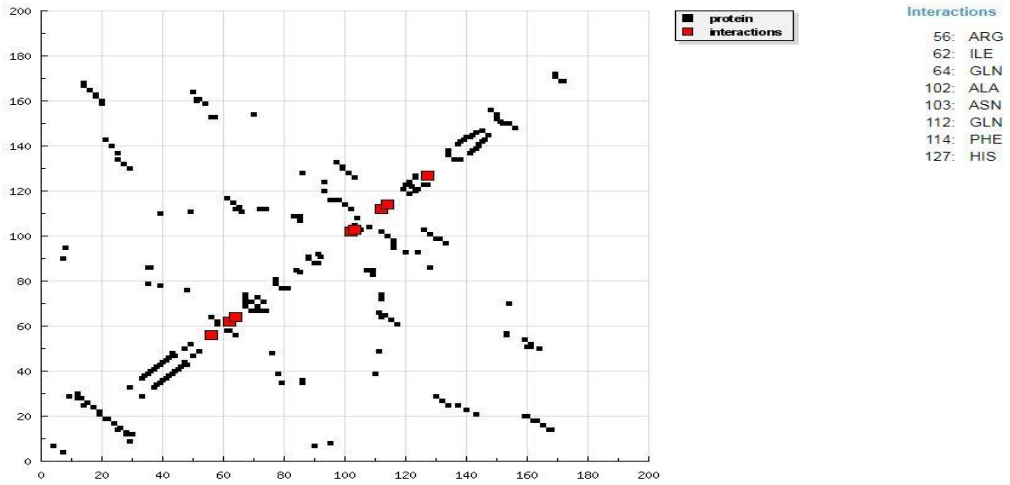
Figure 1. The Schiff base ligand (H_2L) (green in (a) and gray in (b)) in interaction with receptors of colon cancer (PDB code: 2hq6) and lung cancer (PDB code: 1x2j).

2hq6 x2j



(b) **(b)**

2hq6



1x2j

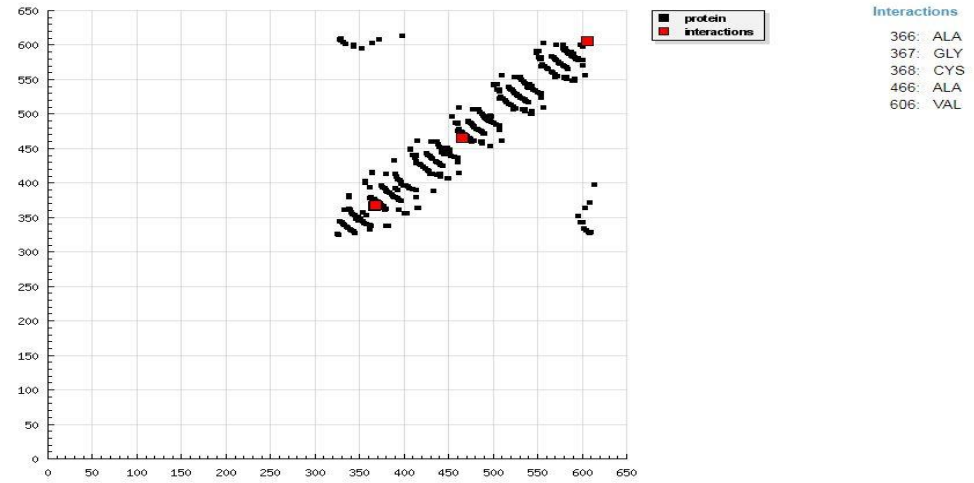
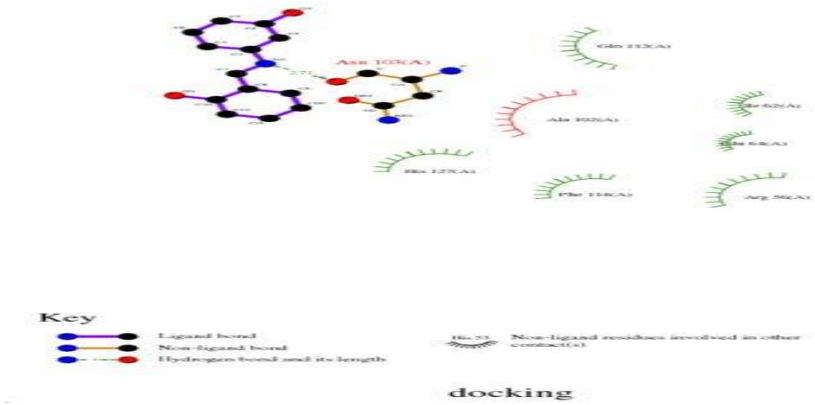


Figure 2. HB plot of interaction between Schiff base ligand (H_2L) and receptors of colon cancer (PDB code: 2hq6) and lung cancer (PDB code: 1x2j).



1x2j

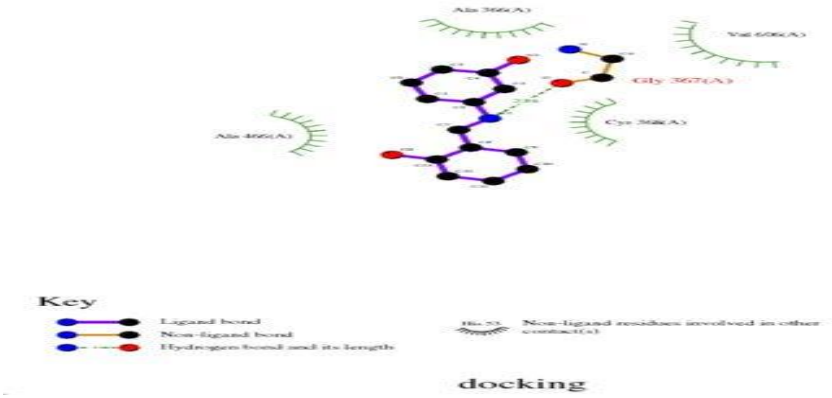
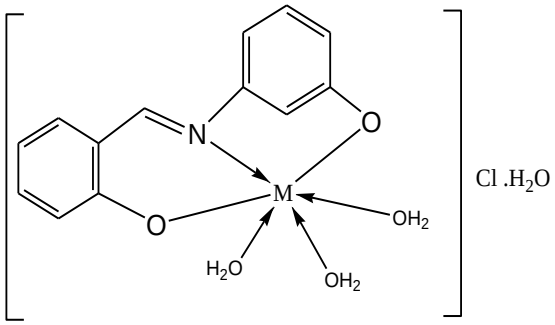


Figure 3. 2D plot of interaction between Schiff base ligand (H_2L) of HL and receptors of colon cancer (PDB code: 2hq6) and lung cancer (PDB code: 1x2j).



M = La(III), Yb(III)

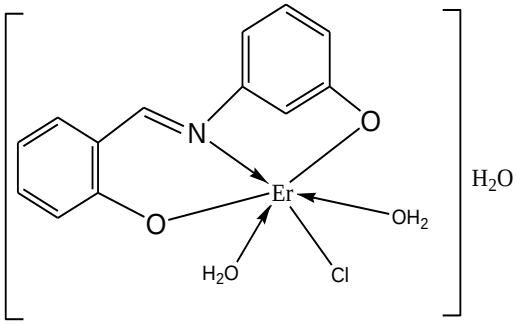


Figure 4. The proposed structures of metal complexes.

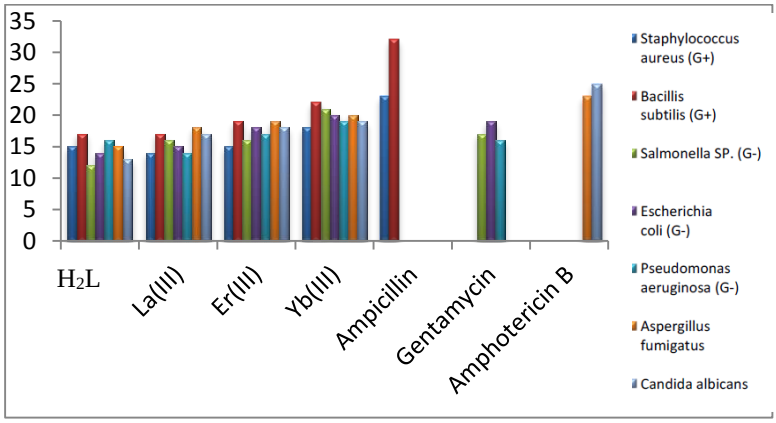


Figure 5. Biological activity of the Schiff base ligand (H_2L) and its metal complexes.

Conclusion

A novel Schiff base ligand named (E)-2-(((3-hydroxyphenyl)imino)methyl)phenol was synthesized and its La(III), Er(III) and Yb(III) complexes were prepared. According to the analytical analyses, UV–visible and IR data, the ligand was found to be bi-negative tridentate ligand and its coordination to metal ions occurs through the azomethine nitrogen atom and two deprotonated

phenolic oxygen atoms. On the basis of different techniques, it is tentatively proposed that, the metal complexes have octahedral geometries. The molar conductance values indicated that Er(III) complex is nonelectrolyte, while La(III) and Yb(III) complexes are 1:1 electrolytes. The presence of hydrated and coordinated water molecules in the complexes was confirmed by thermal analysis. The results demonstrated that the compounds have good antibacterial and antifungal activity against the bacterial and fungal strains tested. Apart of membrane permeability, antibacterial activity of the Schiff base ligand and its metal complexes depends mainly on the metal ion and the type of microorganism.proposed that, the metal complexes have octahedral geometries. The molar conductance values indicated that Er(III) complex is nonelectrolyte, while La(III) and Yb(III) complexes are 1:1 electrolytes. The results demonstrated that the compounds have good antibacterial and antifungal activity against the bacterial and fungal strains tested. Apart of membrane permeability, antibacterial activity of the Schiff base ligand and its metal complexes depends mainly on the metal ion and the type of microorganism

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