

SYNTHESIS, SPECTRAL CHARACTERISATION AND BIOLOGICAL EVALUATION OF SCHIFF BASE COPPER(II) COMPLEXES**D. Shakila¹ A. Dinesh Karthik² and Kannappan Geetha^{3*}**

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Article Received on
05 March 2018,

Revised on 25 March 2018,
Accepted on 15 April 2018

DOI: 10.20959/wjpr20188-11020

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ABSTRACT

A potentially pentadentate Schiff base ligand H₂L and their binuclear copper complexes have been prepared by the condensation of 2,6-diformyl-4-methyl phenol, 2-aminophenol and o-phenylene diamine in the molar ratio 1:1:1. The Schiff base, H₂L, ligand with N₃O₂ pentadentate sites and can coordinate with two copper ions to form binuclear complexes after the deprotonation of the hydrogen atoms of the phenolic groups in all complexes. The ligand and the complexes were characterized by elemental analysis, conductivity measurements, ¹H NMR, ¹³C NMR, IR, UV-Vis and ESR spectral studies. All the complexes are 1:1 electrolyte in nature. Redox behaviours of the complexes have been investigated by cyclic voltammetry. The

copper(II) complexes were screened for antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* and antifungal activity against *Candida albicans*, *Aspergillus niger* and *Mucor indicus*. The results revealed that the synthesised compounds were more potent against all the microbes under investigation. DNA interaction of Schiff base complexes was monitored by electronic absorption spectra. It was found that the prepared complexes could bind to DNA in an intercalating mode.

KEYWORDS: Antimicrobial activity, Copper(II) complexes, DNA binding, Pentadentate Schiff base, Redox property.

1. INTRODUCTION

Schiff base and its metal complexes play a vital role in the field of medicinal chemistry. The compounds containing carbon nitrogen double bonds are known as Schiff bases and represent a novel class of medicinally and pharmacologically important compounds.^[1-3] In organic chemistry Schiff base transition metal complexes are used as catalysts to accelerate many reactions like polymerization and oxidation etc.^[4-6] Thus the biological activity of complexes chiefly depend upon their molecular structure and types of metal ions with which they co-ordinate. Presently, there is a growing interest in the design and synthesis of coordination compounds of Schiff base ligands with pentadentate substituents which are increasing due to their potential applications in the areas such as MRI, imaging with isotopes and radiotherapy, luminescent probes and DNA cleaver. Pentadentate Schiff base complexes are well known to form stable complexes, where the coordination takes place through the N₃O₂ type donor set. Especially dinucleating metal complexes with pentadentate substituents with N and O donor atoms have been a fascinating area of research, in view of their significance as biomimetic catalysts in the process of oxygenation.^[7-10]

In this paper, we report a synthetic approach and structural characterization of a Schiff base derived from the condensation of 2,6-diformyl-4-methylphenol, 2-aminophenol, o-Phenylene diamine and their complexes with Cu(II). The synthesised binuclear Schiff base complexes have been characterized by elemental analysis, molar conductance, infrared, electronic spectra, cyclic voltammetry, NMR and EPR studies. The Schiff base ligand and its complexes were investigated for their DNA binding and *in-vitro* antimicrobial activities.

2. EXPERIMENTAL

2.1. Materials and Reagents

All chemicals were of analytical grade and purchased from Merck and Sigma Aldrich. Commercial solvents were distilled and then used for the preparation of ligand and its complexes. DNA was purchased from Bangalore Genei (India). tris(hydroxymethyl) aminoethane-HCl (Tris-HCl) was purchased from sigma-aldrich and (tris-HCl) buffer solution was prepared using deionized, sonicated triply distilled water.

2.2. Instruments

Elemental analysis was performed using a Perkin-Elmer elemental analyzer. ¹H and ¹³C NMR of the ligand in DMSO were recorded in BRUKER model 400MHz. Molar conductivity of the metal complexes were determined by using DMF as a solvent in

Equiptronics digital conductivity meter at room temperature. FT-IR spectra of ligand and complexes were obtained on a Shimadzu IR-Affinity-I spectrometer with samples prepared using KBr pellets. UV-Visible spectra were recorded using Systronics spectrophotometer operating in the range of 200–800 nm with quartz cell. Electrochemical analyzer using a three-electrode cell in which a glassy carbon electrode was the working electrode, platinum wire was used as an auxiliary electrode and SCE was the reference electrode under inert condition. The concentration of the complexes was 10^{-3} M. Tetrabutylammonium perchlorate (TBAP) was used as the supporting electrolyte which was prepared and recrystallised from hot methanol (Caution! TBAP is potentially explosive; hence care should be taken in handling the compound). EPR spectra were recorded on powdered samples of complex-I, II and III using Bruker EPR spectrometer.

2.3. Synthesis of Pentadentate Schiff base Ligand (L)

2,6-diformyl-4-methylphenol (2 mmol) was dissolved in 15 ml ethanol and then mixed with o-aminophenol (2 mmol) and o-Phenylene diamine (2 mmol) in 30 ml of ethanol and the mixture was refluxed for one hour at 60°C and the reaction was monitored by TLC primarily using hexane as eluent. Then the reaction mixture was left to cool and the ligand was obtained was washed with ethanol, filtered and dried.

2.4. Synthesis of copper(II) precursors

The copper(II) precursors were synthesized using organic compounds like p-amino, p-chloro and p-hydroxy benzoic acids with NaOH and stirred well for 15 minutes using magnetic stirrer, then $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ was added with the above mixture and stirred well for half an hour. The organic acid, base and metal was taken in the ratio of 2:2:1 for the synthesis of copper(II) precursors. The crude blue copper(II) precursors obtained was washed thoroughly with water and ethanol and dried well. The copper(II) precursors obtained was used for the synthesis of Copper(II) complexes as such.

2.5. Synthesis of copper(II) complexes

A general method was adopted for the preparation of copper(II) complexes. A solution containing the mixture of Schiff base ligand, KOH, various copper(II) precursors and sodium perchlorate in 25ml of ethanol was placed in a round bottomed flask. The mixture was stirred for five hours. The precipitate obtained was filtered and washed with ethanol and dried. The complexes were highly stable under laboratory conditions and can be stored for a long time. The ratio of the ligand, KOH, Copper(II) precursors and sodium perchlorate were taken as

1:2:1:1 for the synthesis of copper(II) complexes. The complexes formed were characterised by UV-Vis, FT-IR, ESR and Conductivity Measurement. The electrochemical behaviour was analysed using Cyclic Voltammetry. The complexes were subjected to *in-vitro* antimicrobial activity as well as DNA binding studies.

2.6. DNA binding

2.6.1. Electronic Absorption Spectra

All the experiments involving the interaction of complexes with CT-DNA were conducted in Tris buffer (10 mM Tris-HCl-50 mM NaCl buffer, pH 7.4). The concentration of the DNA used for binding experiments was determined by measuring the absorption intensity at 260 nm with molar extinction coefficient value $6600\text{M}^{-1}\text{cm}^{-1}$. The absorbance measurements were performed by keeping the concentration of the complex constant (1×10^{-5} M) while varying the DNA concentrations (1×10^{-5} M, 5, 10, 15, 20 and 25 μL).^[11] The intrinsic binding constant K_b for the interaction of these metal complexes with DNA has been calculated from the absorption spectral changes during the addition of increasing concentration of DNA by the following equation (1)

$$[\text{DNA}] / (\epsilon_a - \epsilon_f) = [\text{DNA}] / (\epsilon_b - \epsilon_f) + 1 / K_b(\epsilon_b - \epsilon_f) \text{ ----- (1)}$$

Where [DNA] is the concentration of DNA in base pairs, the apparent absorption coefficient ϵ_a , ϵ_f and ϵ_b correspond to $A_{\text{obs}} / [M]$, the extinction coefficient of the free and the extinction coefficient of the compound when fully bound to DNA, respectively.

2.7. Biological Studies

2.7.1. *In-Vitro* Antimicrobial activity of ligand and its complexes

The synthesized ligand and its complexes were tested for their *in-vitro* antimicrobial activity against the bacteria *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* as well as against the fungi *Candida albicans*, *Aspergillus niger* and *Mucor indicus* using agar well diffusion method. The stock solutions (10^{-2} mol L^{-1}) of the compounds were prepared in DMSO and the zone of inhibition values of the compound were determined by serial dilution method. For determination of zone of inhibition, the respective medium was poured into the petriplates and allowed to solidify at room temperature. Wells were made on the solidified medium and the serially diluted solutions were added on to the wells and allowed to diffuse into the wells. The indicator organisms were overlaid on to the agar medium and the plates were incubated for 37°C for 48 h. After incubation the zone of inhibition by the compound were measured and zone of inhibition was determined.

3. RESULTS AND DISCUSSION

The synthesized ligand and its Cu(II) complexes were found to be air-stable. The ligand was soluble only in common organic solvents. The synthesized complexes were soluble in DMF and DMSO. The ligand and its complexes were characterized by the analytical and spectral techniques. Physical characterization, microanalytical and molar conductance data are given in Table-1.

Table-1: Analytical and physical data of Schiff base ligand and its complexes.

Compound	Empirical Formula	melting point (°C)	Molar Conductance (mho cm ² mol ⁻¹)	Elemental Analysis Found (Cal.) (%)		
				C	H	N
Ligand	C ₂₁ H ₁₉ N ₃ O ₂	267	-	73.10 (73.04)	5.44 (5.50)	12.10 (12.17)
Complex-I	C ₂₈ H ₂₃ N ₄ O ₈ ClCu ₂	>360	89	47.65 (47.72)	3.20 (3.26)	7.91 (7.95)
Complex-II	C ₂₈ H ₂₁ N ₃ O ₈ Cl ₂ Cu ₂	>360	85	46.35 (46.41)	2.83 (2.90)	5.86 (5.80)
Complex-III	C ₂₈ H ₂₂ N ₃ O ₉ ClCu ₂	>360	77	47.61 (47.66)	3.18 (3.12)	5.91 (5.95)

3.1. Elemental analysis and Molar Conductance

The molar conductance values measured in DMF solution (1×10^{-3} mol dm⁻³) fall in the range 77-89 ohm⁻¹ cm² mol⁻¹. These observed values of the molar conductance are well within the expected range for 1:1 electrolyte.^[12] The elemental analysis data is in good agreement with the theoretical values.

3.2. Infrared spectra

In order to study the binding mode of ligand to metal in the complexes, IR spectrum of the free Schiff base ligand was compared with the IR spectra of the metal complexes. The structurally significant IR peaks for free Schiff base ligand and its complexes are given in the Table-2. The free ligand exhibits IR peaks at 3373 cm⁻¹ (O-H), 1616 cm⁻¹ (C=N) and 1240 cm⁻¹ (C-O). In the spectra of the complexes the peak due to (O-H) of the ligand disappeared indicating the coordination of phenolic oxygen to the metal ion via deprotonation. This was further supported by upward shift of the phenolic (C-O) mode. The peak at 1616 cm⁻¹ was due to azomethine group of the ligand and it was shifted to lower frequency (by 10-15 cm⁻¹) after complexation. This shows the coordination of the metal with the azomethine nitrogen.^[13]

The binding mode of the benzoate ion in all complexes has been determined from the IR spectra by considering the difference in energy (Δ) between the asymmetric and symmetric carboxylate stretching frequencies. According to Deacon and Philips^[14] for an unidentate coordination, the value of $\Delta\nu$ [$\nu_{as}(\text{COO}^-) - \nu_s(\text{COO}^-)$] is more than that of free carboxylate anion value, where as for bidentate bridging or chelating carboxylate group, the separation value is less than the free carboxylate. For the current series of binuclear complexes the lower value of $\Delta\nu$ which is in the range of 150-175 cm^{-1} suggests bridging coordination mode.

Table-2: The vibrational Spectral data of the ligand and its complexes.

Compound	$\nu(-\text{C}=\text{N})$ cm^{-1}	$\nu(-\text{C}-\text{O})$ cm^{-1}	$\nu(-\text{ClO}_4^-)$ cm^{-1}	$\nu(\text{Cu}-\text{N})$ cm^{-1}	$\nu(\text{Cu}-\text{O})$ cm^{-1}	$\nu(\text{Cu}-\text{OCO})$ cm^{-1}
Ligand	1616	1240	-	-	-	-
Complex-I	1606	1263	1026	561	443	1546, 1398
Complex-II	1604	1253	1028	545	460	1544, 1390
Complex-III	1602	1253	1072	553	480	1552, 1388

Further the peaks observed in the region 545-561 cm^{-1} can be attributed to $\nu(\text{Cu}-\text{N})$ linkage and around 443-480 cm^{-1} $\nu(\text{Cu}-\text{O})$ linkage respectively.

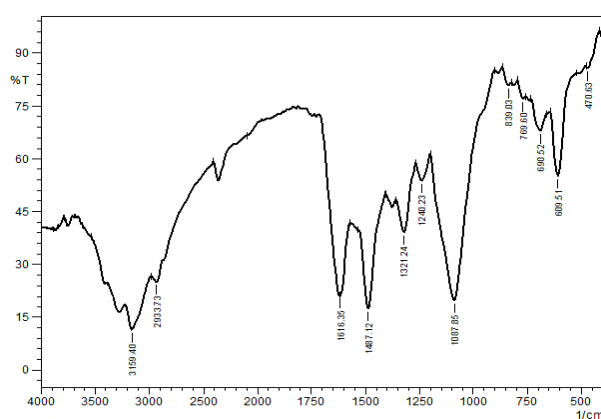


Fig 1a: FT-IR spectrum of Ligand.

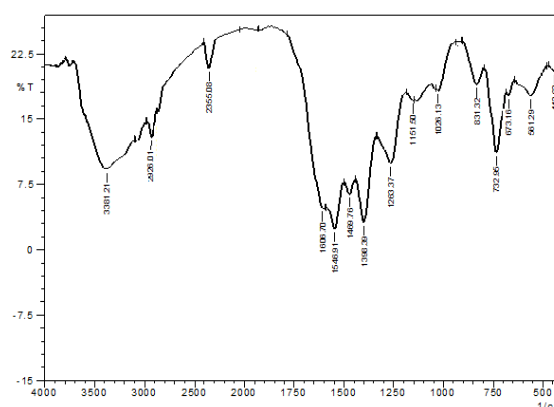


Fig 1b: FT-IR spectrum of complex-I.

3.3. Electronic Spectra

The UV-Visible spectra of the ligand and its complexes were recorded in the DMF solution is given in the Table-3. The electronic spectrum of the ligand exhibit a band at 37735 cm^{-1} which is due to $\pi-\pi^*$ transition of the benzene ring and it was shifted to higher wavelength (red shift) upon complexation. The band at 29586 cm^{-1} which is due to $n-\pi^*$ transition of the azomethine group present in the ligand, upon complexation it undergoes a red shift in the

complexes. This supports the coordination of metal with the azomethine nitrogen.^[15] In all the complexes, the charge transfer bands were observed in the range 24390-23923 cm^{-1} and its broadness can be explained as due to the combination of $\text{O} \rightarrow \text{Cu}$ and $\text{N} \rightarrow \text{Cu}$ LMCT transitions. All the complexes gave d-d bands in the range 15923-16340 cm^{-1} . The ligand field parameters such as Dq and LFSE have been calculated and the values are listed in the Table-3.

Table 3: Electronic Spectral data and ligand field parameters for ligand and its copper(II) complexes.

Compound	$\pi-\pi^*$ (cm^{-1}) (benzene)	$\pi-\pi^*$ (cm^{-1}) (-HC=N)	$n-\pi^*$ (cm^{-1})	d-d (cm^{-1})	Dq (cm^{-1})	LFSE K.Cal.mol ⁻¹
Ligand	37735	29586	24390	-	-	-
Complex-I	37175	29326	23923	16340	1634.0	46.72
Complex-II	35842	29155	24154	15923	1592.3	45.53
Complex-III	35970	29069	24038	16077	1607.7	45.97

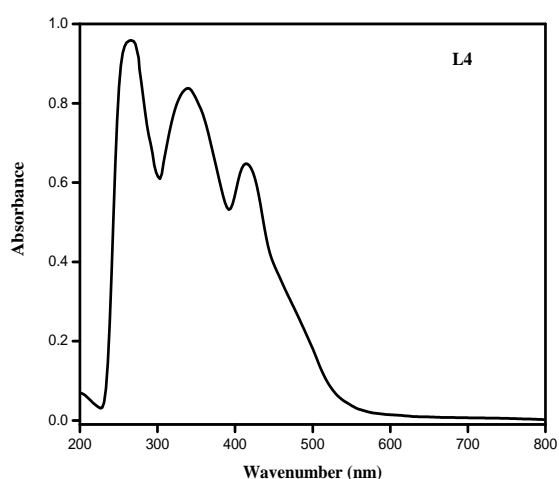


Fig 2a: UV-Visible spectrum of Ligand.

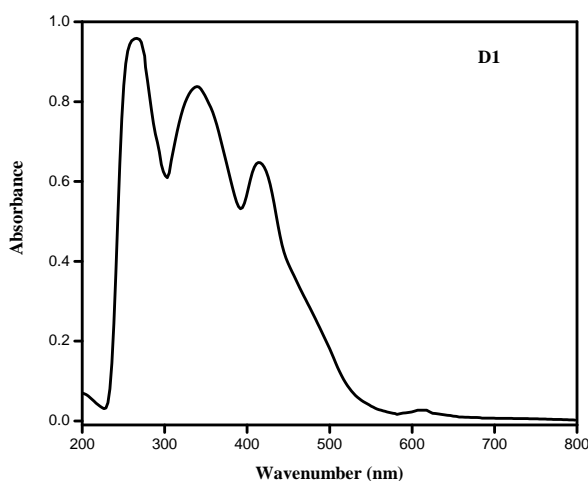


Fig 2b: UV-Visible spectrum of complex-I.

3.4. ¹H NMR Spectra

The Ligand was characterized by ¹H NMR and the values were obtained in ppm, 2.3 δ (3H, methyl protons); 6-8 δ (10H, Aromatic protons); 7.87 δ (2H, HC=N-) of azomethine group; 9.04 δ (2H, Ar-OH) deshielded due to one hetero atom; 15.01 δ (1H, Ar-OH) deshielded due to two hetero atoms.

3.5. ¹³C NMR Spectra

The ¹³C NMR spectrum of the Schiff base ligand showed an aliphatic CH₃ signals at 20.3 ppm, Ar.C-OH signals at 157.2 ppm and HC=N signals at 161.7 ppm.^[16]

3.6. ESR Spectra

The ESR spectra of complexes provide information of importance in studying the metal ion environment. The ESR spectra of the copper(II) complexes in the polycrystalline state at 298K were recorded in the X band using DPPH as an external standard. The ESR spectra could provide only value of g_{iso} and does not give g parallel and g perpendicular values. The g_{iso} value of the copper(II) complexes are tabulated in Table-4.

Table-4: g_{iso} values of complexes.

Compound	g_{iso}
Complex-I	2.0281
Complex-II	2.0846
Complex-III	2.0678

The ESR spectrum of the copper(II) complexes show a single unresolved signal with g_{iso} value around 2, which can be corroborated with a square planar environment.^[17] The ESR spectra of the complexes are given in the Fig 3a and 3b.

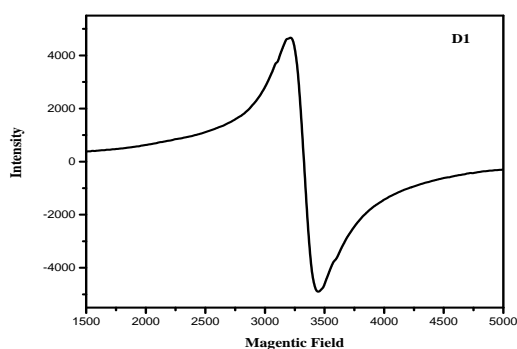


Fig 3a: ESR spectrum of complex-I

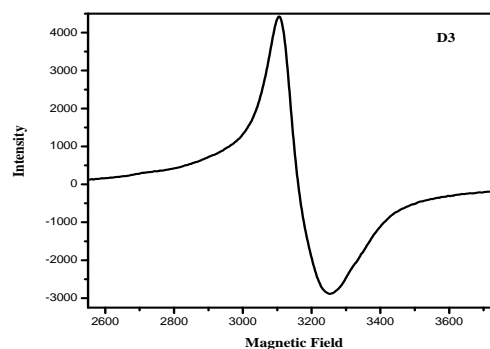


Fig 3b: ESR spectrum of complex-II

3.7. Electrochemical Studies

The electrochemical behaviour of binuclear copper(II) complexes have been studied by cyclic voltammetry (CV) in DMF containing TBAP as supporting electrolyte. The electrochemical data are summarized in Table-5 and the CV of the copper(II) complexes depicted in Fig 4. The binuclear copper(II) complexes were associated with two quasireversible reduction waves.^[18] -0.7179V and -1.0867V are the first reduction potential value for complex-I, II & III respectively. -1.0867V and -0.7625 V are the second reduction potential value for complex-I, II & III respectively. The first reduction wave consumed approximately one electron ($n \approx 0.86$). This indicates that each process corresponds to single electron-transfer process, and this can be assigned to the redox couple $Cu^{II}Cu^{II}/Cu^{II}Cu^I$. The

second quasi-reversible wave can be attributed to the formation of the mixed valent $\text{Cu}^{\text{II}}\text{Cu}^{\text{I}}/\text{Cu}^{\text{I}}\text{Cu}^{\text{I}}$ species.

Table-5: Redox potentials of copper(II) complexes in DMF solution at 298 K.

Complex	E^1_{PC} (V)	E^1_{Pa} (V)	E^2_{PC} (V)	E^2_{Pa} (V)
I	-0.7179	-0.8352	-1.1296	0.8576
II	-0.8625	0.6167	-0.9651	0.8998
III	-1.0867	0.4036	-0.7625	0.9212

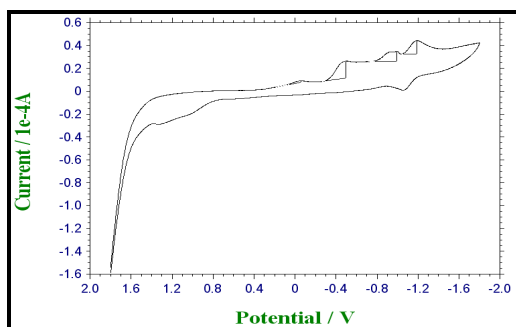


Fig 4a: CV of complex-I.

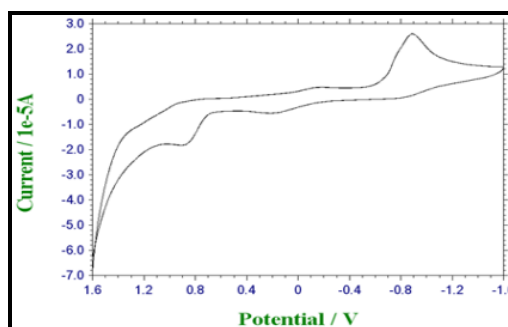


Fig 4b: CV of complex-II.

3.8. DNA Binding ability

3.8.1. Absorption Spectroscopy

A complex bound to DNA through intercalation is characterized by the change in absorbance (hypochromism) and red-shift in wavelength. This may be due to the π^* orbital of the intercalated ligand which can couple with the π orbital of the DNA base pairs (stacking interaction between the aromatic chromophore and the DNA base pairs) thus, decreasing the $\pi \rightarrow \pi^*$ transition energy and resulting in the bathochromism.^[19] The electronic spectra of the complexes in the presence and absence of DNA were monitored at a wavelength range of 250–600 nm, as shown in Fig 5. The electronic absorption spectra of all the complexes exhibited broad absorption bands in the region 420–430 nm. Upon increasing the concentration of CT DNA, a considerable shift in the wavelength (bathochromicity) was observed for all the complexes. This bathochromicity (red shift) exhibits due to intercalative binding nature of the complexes with the base pair of DNA.^[20] In order to compare the binding strength of the complexes with CT-DNA, the intrinsic binding constants, K_b were obtained by monitoring the changes in the absorbance of the complexes with increasing concentration of DNA. The K_b values obtained for complexes Complexes-I, II & III were $4.46 \times 10^4 \text{ M}^{-1}$, $3.63 \times 10^4 \text{ M}^{-1}$ and $3.01 \times 10^4 \text{ M}^{-1}$ respectively.

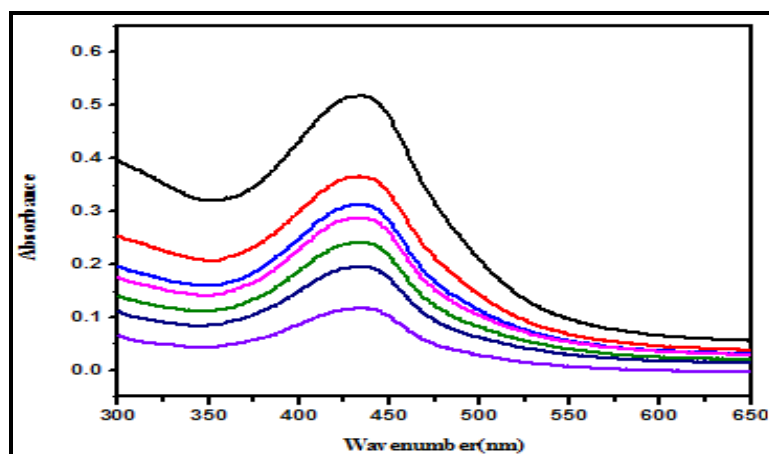


Fig 5: Absorption spectra of complex Cu(II) (1×10^{-5} M) in the absence and presence of increasing amounts of CT- DNA (0 - 2.5×10^{-5} M) at room temperature in 50 mM tris-HCl / NaCl buffer (pH = 7.4).

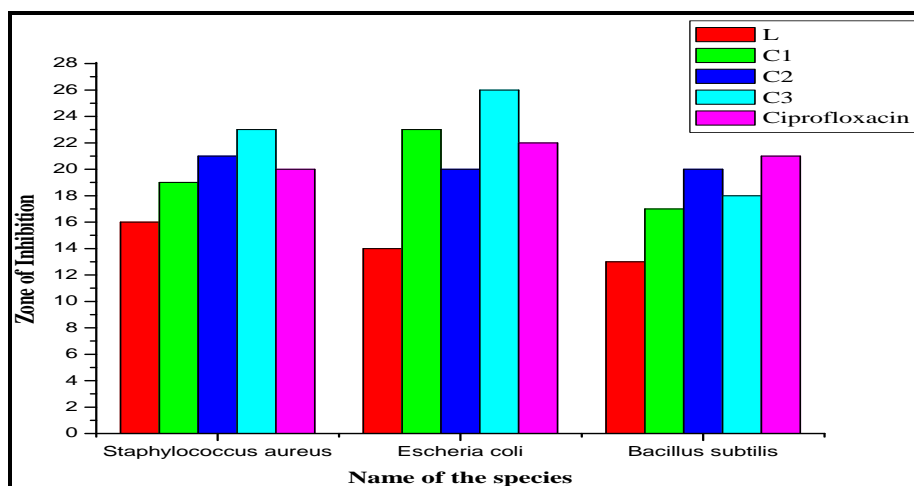
3.9. BIOLOGICAL RESULTS

3.9.1. Antimicrobial activity

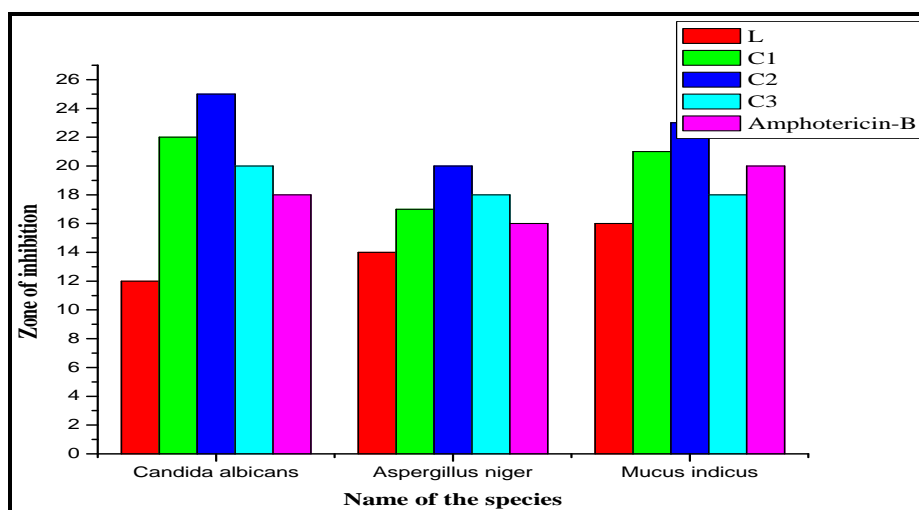
The Schiff base ligand and its copper(II) complexes have been monitored for their antibacterial activity against various pathogenic bacteria such as *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* and antifungal activity against *Candida albicans*, *Aspergillus niger* and *Mucor indicus*. Ciprofloxacin and Amphotericin-B were used as the standard for bacterial and fungal studies respectively. The antimicrobial activity of the Schiff base and its complexes were tested against human pathogenic bacteria as well as fungi and the zones of inhibition are given in Table-6&7. A comparative study of the growth inhibition zone values of Schiff base and its complexes show that metal complexes display higher antibacterial activity than the free ligand and this is probably due to the greater lipophilic nature of the complexes.^[21] Metal complexes activity can be explained on the basis of Overtone's concept and Tweedy's chelation theory. According to the overtone concept of cell permeability, the lipid membrane surrounding the cell favours the passage of only lipid-soluble materials, which means that liposolubility is an important factor controlling antimicrobial activity. On chelation, the polarity of metal ion is reduced to a greater extent due to overlap of the ligand orbital and partial sharing of its positive charge with the donor groups.^[22] In addition, it is also due to delocalization of the π -electrons over whole chelate ring, enhancing the penetration of the complexes into the lipid membranes and the blocking of the metal binding sites of the enzymes of the microorganisms.

Table-6: Antibacterial Activity of the Schiff base ligand and its complexes

S.NO.	MICRO ORGANISMS	L	C1	C2	C3	Ciprofloxacin
1.	<i>Staphylococcus aureus</i>	16	20	21	20	20
2.	<i>Escherichia coli</i>	14	22	20	26	23
3.	<i>Bacillus subtilis</i>	13	17	20	18	21

**Fig. 6: Graphical representation of Antibacterial activity.****Table-7: Antifungal Activity of the Schiff base ligand and its complexes.**

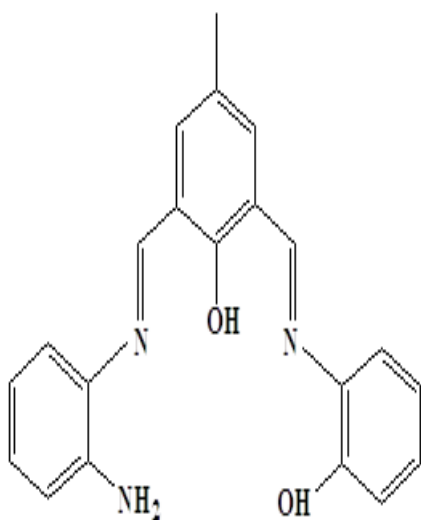
S.NO.	MICRO ORGANISMS	L	C1	C2	C3	Amphotericin-B
1.	<i>Candida albicans</i>	12	22	15	18	17
2.	<i>Aspergillus niger</i>	14	15	12	13	15
3.	<i>Mucus indicus</i>	16	21	22	18	19

**Fig 7: Graphical representation of Antifungal activity.**

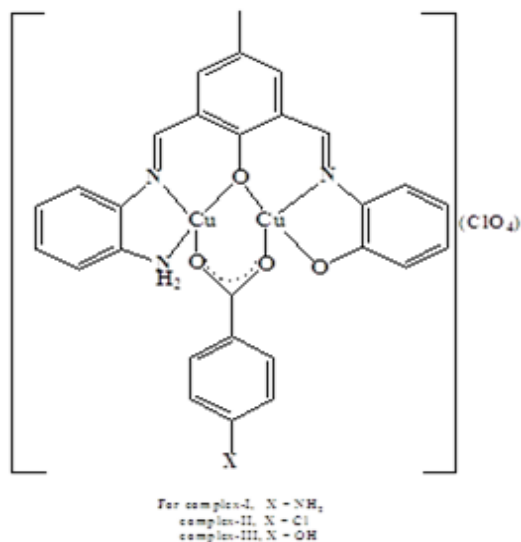
4. CONCLUSION

In the present study, the Schiff base, H_2L , ligand is dibasic N_3O_2 pentadentate sites. The Schiff base was allowed to react with metal ions in 1:1 molar ratio (ligand:metal ion) to form

the binuclear complexes. The binding sites are the azomethine nitrogen atoms and the phenolic oxygen atoms respectively. The bonding of ligand to metal ion is confirmed by elemental analyses, spectral studies like UV-Vis, FT-IR, NMR, ESR and conductance measurements. The molar conductance values reveal that the complexes were 1:1 electrolytic nature of the complexes. The cyclic voltammogram of the complexes confirmed the redox property. From the analytical and spectral data, all the copper(II) complexes were shown to exhibit a square planar geometry. The binding behaviour of metal complexes with DNA was studied by UV absorption spectra which indicate that all the three synthesized complexes can strongly bind to CT-DNA via an intercalation mode. Antibacterial and antifungal studies of the ligand and complexes have also been studied which indicate that activity increases on chelation. Based on the results obtained from the spectral data, the structure of the ligand and its complexes are proposed as follows.



Structure of Ligand



Structure of Cu(II) complex

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