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Research Article

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Synthesis, Characterization, DNA Binding studies and Biological activities of Copper (II) Complexes containing 1,10- Phenanthroline / 2,2' - bipyridyl and L-Ornithine & Ethylamine

S. Kumaran, D. Ezhilarasan and M. N. Arumugham*
Department of Chemistry, Thiruvalluvar University, Vellore – 632 115, Tamilnadu, India.
E-mail: *aru_mugham@yahoo.com*

Abstract

Ternary copper(II) complexes [Cu(phen)(L-Orn) EA] ClO_4 **1** & [Cu(bipy)(L-Orn) EA] ClO_4 **2** (bipy = 2,2' - bipyridyl, L-Ornithine, EA= Ethylamine), have been synthesized and characterized by CHN analysis, molar conductance, electronic absorption, IR and EPR spectral studies. They have been tested for their in vitro DNA binding activities by the spectroscopic methods such as UV-Visible, Cyclic volumetric and viscosity measurement. Further complexes 1 & 2 were tested for their antimicrobial activities and it was found to have good antimicrobial activities.

Keywords: Copper (II) Complexes, 1,10- Phenanthroline , 2,2' - bipyridyl and L-Ornithine & Ethylamine, DNA Binding & antimicrobial activity.

Introduction

Transition metal complexes with their efficient DNA binding and cleavage properties under physiological conditions have found wide applications in nucleic acids chemistry. The use of such complexes in foot printing studies, as sequence specific DNA binding agents, as diagnostic agents in medicinal applications and for genomic research has generated current interests to develop this chemistry further[1-8]. The DNA cleavage reactions are generally targeted towards different constituents of DNA, viz. the heterocyclic bases, deoxyribose sugar moiety and phosphodiester linkage[9, 10]. The oxidative DNA cleavage involves in the nucleobase oxidation and/or degradation of the sugar moiety by abstraction of sugar hydrogen atom(s), while the hydrolytic cleavage of DNA takes place due to hydrolysis of the phosphodiester bond. Among different modes of DNA cleavage, oxidative cleavage of DNA on irradiation with visible light is of our interest for potential applications of such compounds in the chemistry of photodynamic therapy (PDT) of cancer[11-15].

In this chapter, we synthesized and characterization of copper (II) complexes by elemental analysis and IR, EPR spectra. The binding properties of the title complexes of CT-DNA were carried out using UV–Visible absorption, fluorescence spectroscopic, cyclic voltametric and viscosity techniques and the binding mode of the copper complexes to DNA is accessed to be intercalation from the experimental results, which implicated that the copper (II) complexes can be a candidate for DNA-binding reagents, as well as laying the foundation for the rational design of new useful DNA probes. We have also reported the antimicrobial activities of a sample of copper (II) complexes against Gram +ve and Gram -ve bacteria and fungus.

1.2 Experimental

1.2.1 Materials

All the reagents were of analytical grade (Sigma-Aldrich and Merck). Calf thymus DNA obtained from Sigma-Aldrich, Germany, was used as such. The spectroscopic titration was carried out in the buffer (50 mM NaCl–5 mM Tris–HCl, pH 7.1) at room temperature. A solution of calf thymus DNA in the buffer gave a ratio of UV absorbance 1.8–1.9:1 at 260 and 280 nm, indicating that the DNA was sufficiently free of protein[16]. Milli-Q water was used to prepare the solutions. Absorption spectra were recorded on a UV–VIS–NIR Cary 5E Spectrophotometer using cuvettes of 1 cm path length, and emission spectra were recorded on a flurolog.

1.2.2 Synthesis of [Cu(Phen)(L-Orn)(H_2O)]ClO_4 [17]

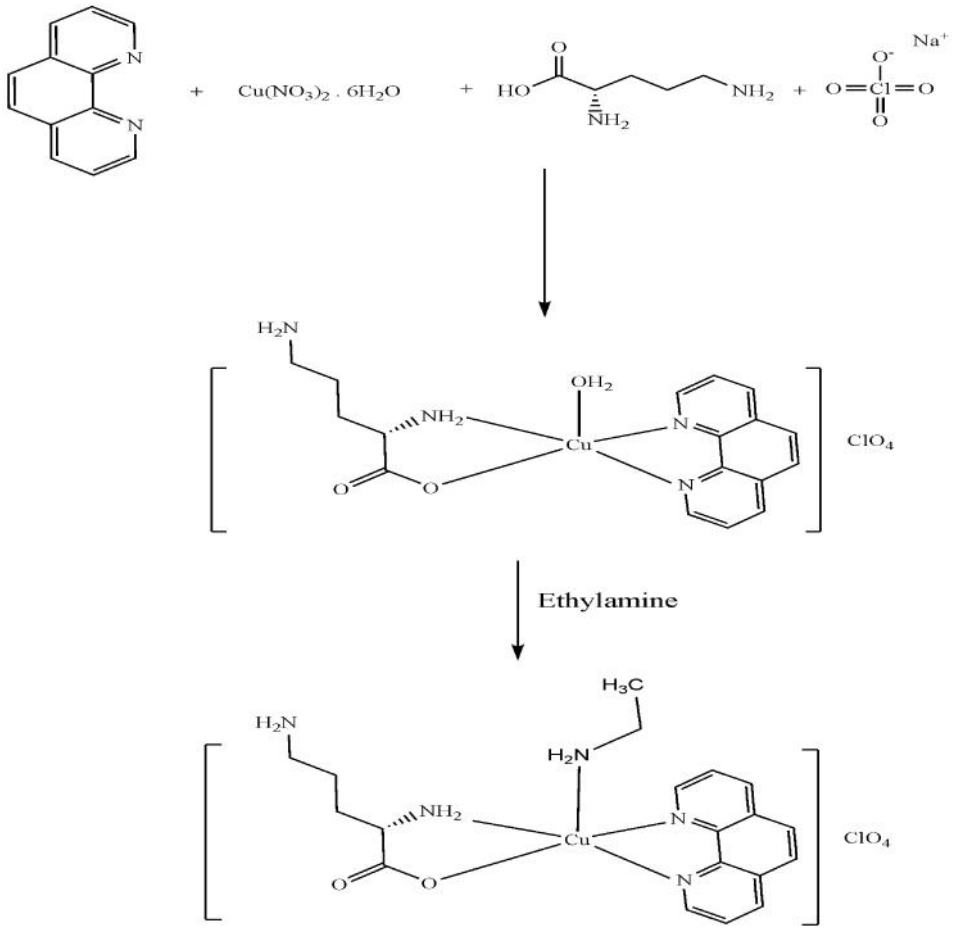
To the mixture of L-Ornithine (1 mmol) and NaOH (40 mg, 1mmol) in water, an aqueous solution of $Cu(NO_3)_2.3H_2O$ (170mg, 1mmol) was added with stirring. Several minutes later, the ethanolic solution of phen/bipy (1 mmol) was added and the solution was stirred for about 3h at 60^0C. To this 0.24488 g of $NaClO_4$ (2 mmol) was added 15 minutes before the completion of heating. Then the cooled solution was filtered and the filtrate was placed at room temperature on slow evaporation. After two weeks some blue crystals were obtained. Yield: 58%.

1.2.3 Synthesis of [Cu(Phen)(L-Orn)EA]ClO_4 (1)

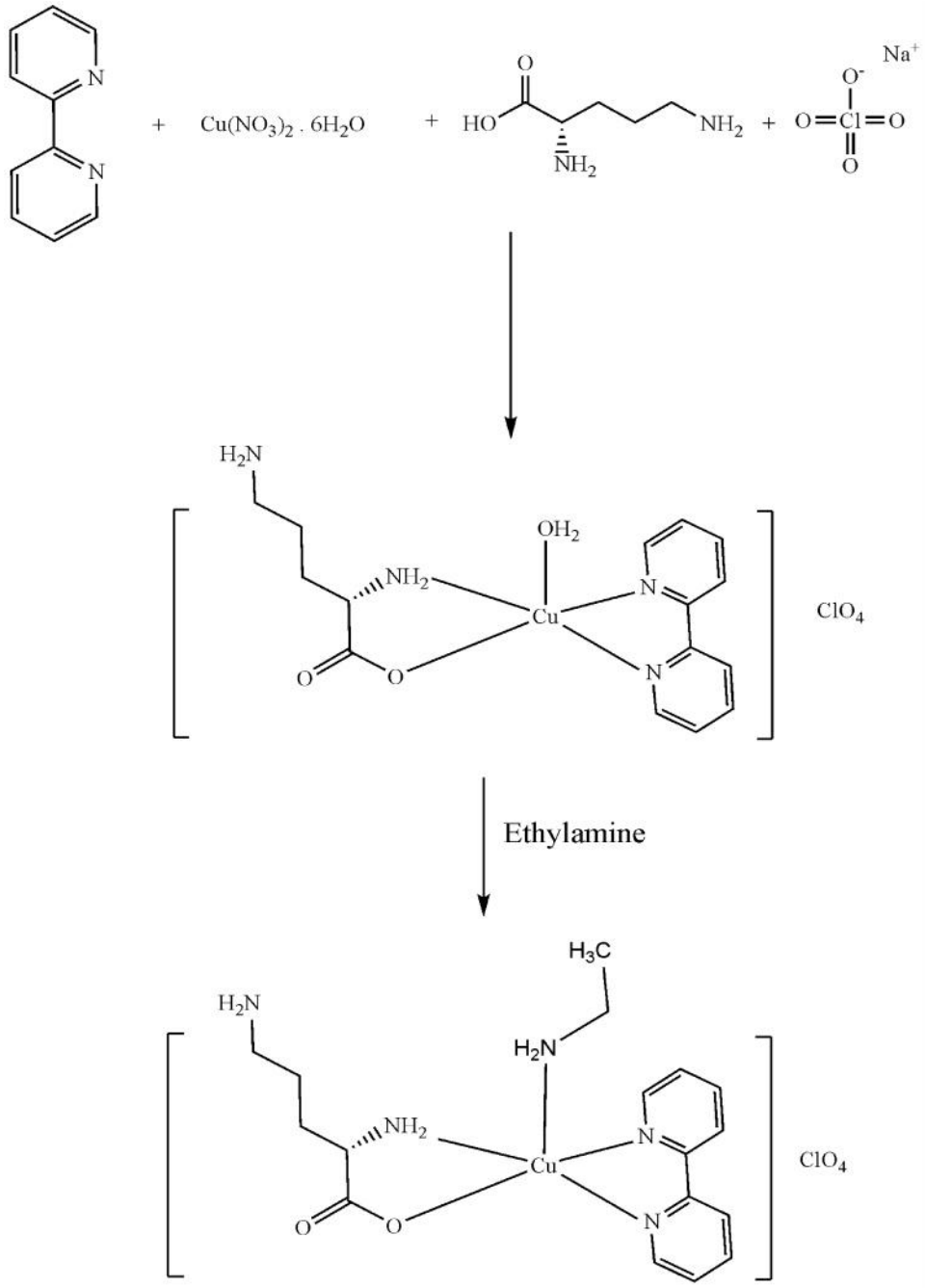
3 mmol of [Cu(phen)(L-Orn)(H_2O)ClO_4] complex dissolved in 50 ml of water. To this 3 mmol of ethylamine in 15 ml of distilled water was added slowly with constant stirring for 40 min. A dark brown **complex (1)** was separated out, which was filtered and dried. Yield: 52%.

1.2.4 Synthesis of [Cu(Bipy)(L-Orn)EA]ClO_4 (2)

3 mmol of [Cu(bipy)(L-Orn)(H_2O)]ClO_4 complex dissolved in 50 ml of water. To this 3 mmol of ethylamine in was added slowly with constant stirring for 40 min. 0.24488 g of $NaClO_4$ (2 mmol) was added 15 minutes before the completion of heating. A dark brown **complex (2)** was separated out, which was filtered and dried. Yield: 53%



Scheme 1: Synthesis of complex **1**



Scheme 2: Synthesis of complex 2

1.3 Results and discussion

1.3.1 Elemental Analysis

The elemental analysis data were found to be in good agreement, with those of the calculated values, the molar conductance value of the complexes indicated that the complexes is 1:1 electrolytes[18], the values given in the table 1.1. Synthetic route of the complexes is given scheme 1 and 2.

1.3.2 Electronic Spectra

The complexes are one electron paramagnetic at room temperature, corresponding to d^9 electronic configuration for the copper(II) center. The complexes display a copper(II) centered d-d bands 605 nm and 637 nm in addition to the ligands centered bands in the UV region of the electromagnetic spectra (Fig 1.1 and 1.2). The electronic spectra of the complexes are in good agreement with the previously reported square pyramidal geometry of the complexes[19-21].

In the UV–Vis region, the intense absorption bands appeared from 240 to 300 nm is attributed to intraligand transitions. Another band which appeared around 270 nm is assigned to ligand field transitions[22].

The electronic absorption spectral data for Cu(II) complexes are given in the table 1.2.

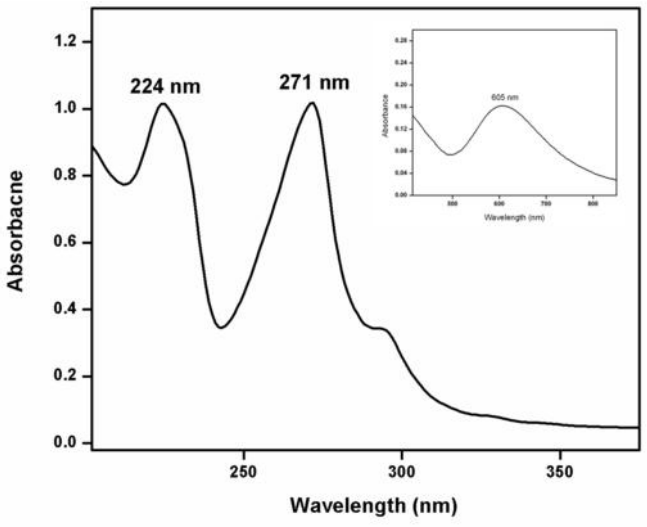


Fig 1.1: UV-Visible spectrum of complex **1**

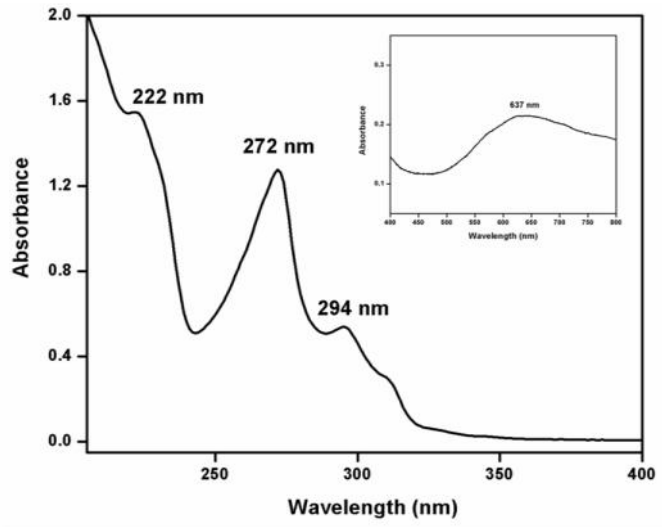


Fig 1.2: UV-Visible spectrum of complex 2

Table 1.1: Elemental analysis and molar conductance values of the complexes

Complexes	Calcd (Found)			Molar Conductance (Sm^2mol^{-1})
	Carbon	Hydrogen	Nitrogen	
Complex 1	41.63(41.52)	15.51 (15.32)	5.10 (5.22)	96
Complex 2	38.61 (38.26)	15.71 (15.52)	5.21 (5.34)	94

Table 1.2: UV-Visible spectral data of the complexes

Complexes	λ_{max}(nm)	ε_{max}(mol^{-1} cm^{-1})
complex **1**	271 224 605	122780 125290 170
complex **2**	272 294 637	127825 54080 210

1.3.3 Infrared spectra

In the IR spectra, the N-H stretching vibrations were observed at 3428 cm^{-1} for complex **1**, and 3412 cm^{-1} for complex 2. In complex **1**, the peaks obtained corresponding to the ring stretching frequencies (ν (C=C) and ν (C=N)) at 1632 & 1516 cm^{-1}, in bpy at 1614 & 1513 cm^{-1}. The strong bands at 1087 cm^{-1} for complex **1** and 1111 cm^{-1} for complex 2 were assigned to ν (Cl-O) of ClO_4. The non ligand peaks at 557 and 460 cm^{-1} were assigned to ν (Cu-O) and ν (Cu-N) for complex **1** (for complex 2, 575 and 468 cm^{-1}) (Fig 1.3 and 8.4)[23].

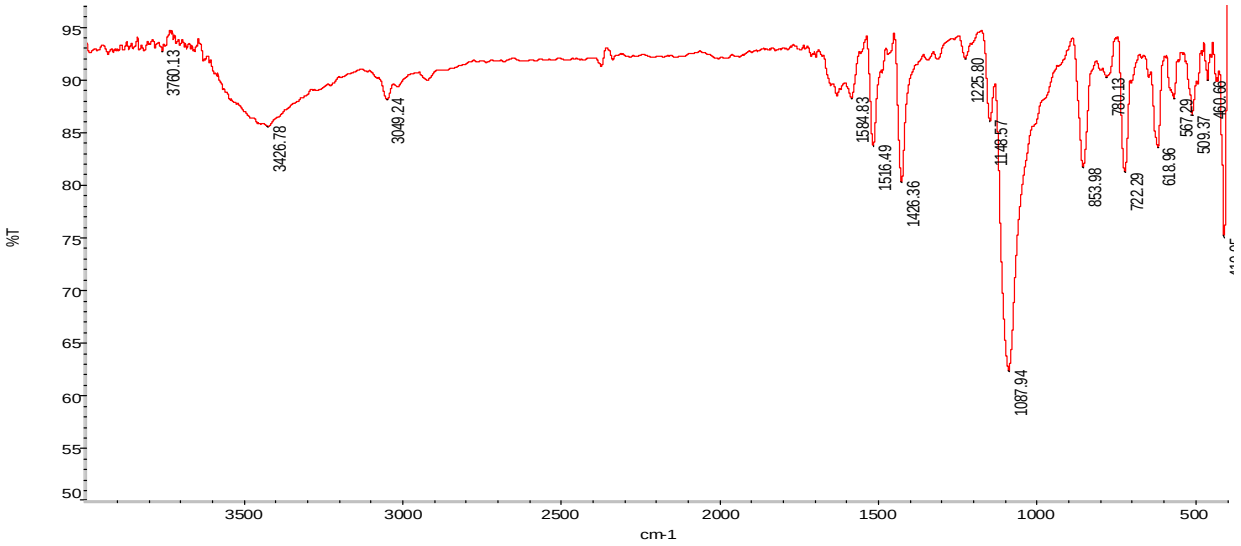


Fig 1.3: Infrared spectrum of complex **1**

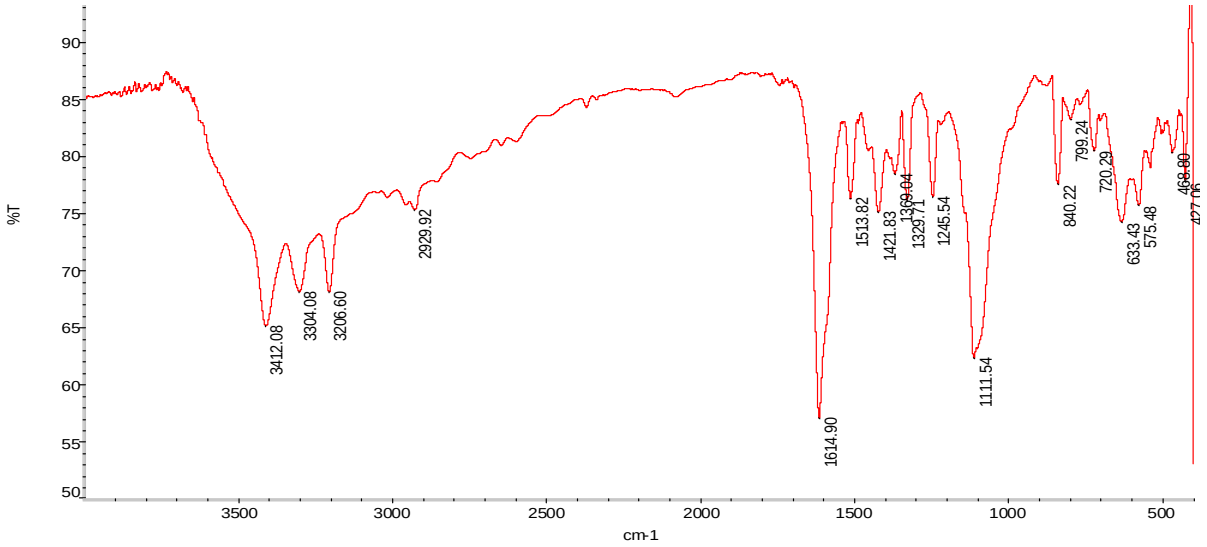


Fig 1.4: Infrared spectrum of complex 2

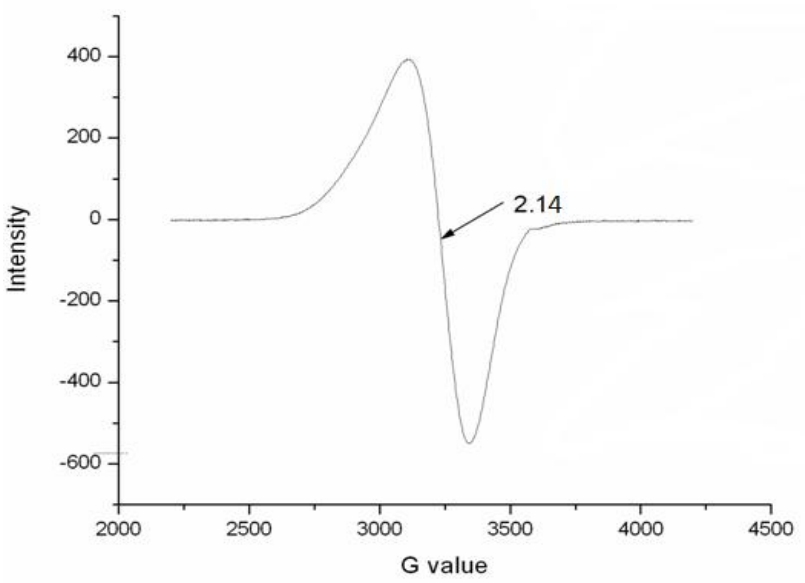


Fig 1.5: EPR spectrum of complex **1** in DMSO at liquid nitrogen temperature

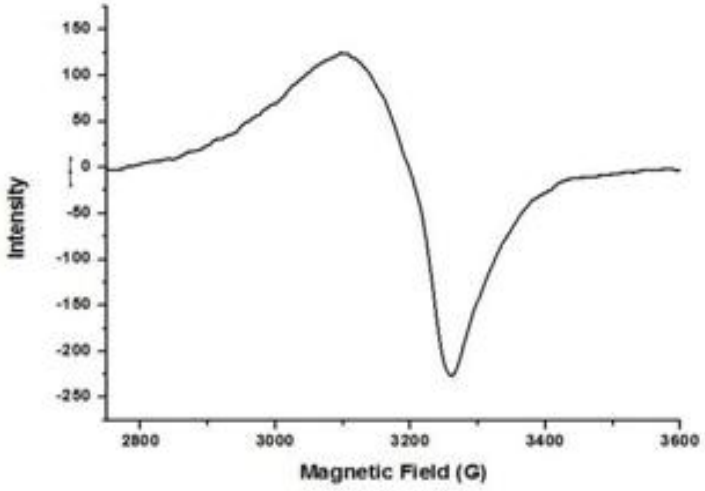


Fig 1.6: EPR spectrum of complex 2 in DMSO at liquid nitrogen temperature

1.3.4 Electron Paramagnetic Resonance

The solid state EPR spectra of the copper(II) complexes were recorded at X-band frequencies shows (Fig 1.5 and 1.6). At liquid nitrogen temperature, complexes **1** and 2 exhibit well defined single isotropic feature near g = 2.14 and 2.13 respectively. Such isotropic lines are usually the results of intermolecular spin exchange, which broaden the lines. This intermolecular type of spin exchange is caused by the strong spin coupling which occurs during a coupling of two paramagnetic species[24].

1.4 DNA binding studies

1.4.1 Electronic spectral studies

Electronic absorption spectroscopy was an effective method to examine the binding mode of DNA with metal complexes[25]. In general, hyperchromism and blue-shift associate with the binding of the complex to the helix by an intercalative mode, involving strong stacking interaction of the aromatic chromophore of the complex between the DNA base pairs. Fig 1.7 and 1.8 shows the UV absorption spectral study of complexes (**1** and 2) in the absence and presence of DNA. In the ultraviolet region from 240 to 300 nm, the complex **1** had strong absorption peaks at 271 nm, for the complex 2 the absorption peak at 272 nm.

The absorption intensity of the complex **1** increased and 2 decreased evidently after the addition of DNA, which indicated the interactions between DNA and the complexes. We have observed a minor bathochromic shift for complexes. The intrinsic binding constant, Kb, was determined by using the following equation[26]

$$[DNA] / (\varepsilon_a-\varepsilon_f) = [DNA] / (\varepsilon_o-\varepsilon_f) +1/K_b(\varepsilon_o-\varepsilon_f)$$

Where [DNA] is the concentration of DNA in base pairs, ε_a, ε_f and ε_o correspond to A_{obsd} / [Cu], the extinction coefficient of the free copper complexes and the extinction coefficient **o**f the complexes in the fully bound form, respectively, and Kb is the intrinsic binding constant. The ratio of the slope to intercept in the plot of [DNA]/(ε_a-ε_f) versus [DNA] gives the value of K_b and for complex **1** it is 3.47 x 10^{-5} (for complex 2 K_b = 3.3 x 10^{-5} M). The binding propensity of the complex **1** is more than complex 2 due to the presence of the extended planar aromatic ring. Earlier studies on bis-phen copper complexes have shown that this complex binds to DNA either by partial intercalation or binding of one phen ligand to the minor groove while the other phen making favourable contacts within the groove[27-29]. The nature of binding of the phen complex is proposed to be similar as observed for the bis-phen species.

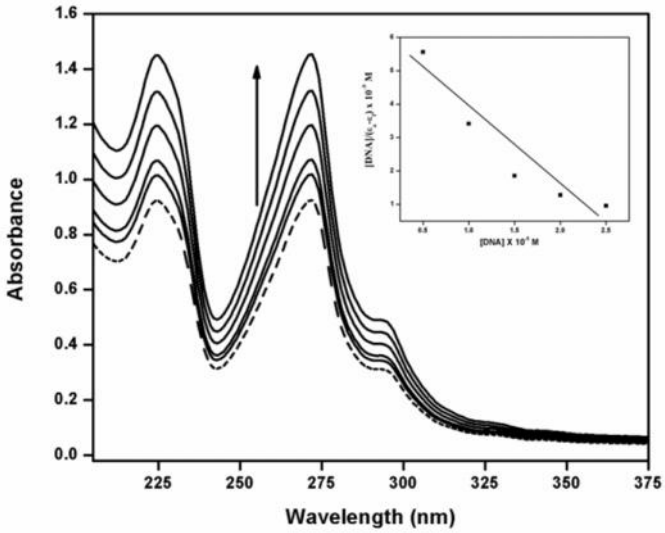


Fig 1.7: Absorption spectra of Complex **1**. In the absence and in the presence of increasing amounts of DNA. (Complex) = 15 µM. (DNA) = (5, 10, 15, 20, 25) µM. Inset: plot of (DNA) / (ε_a -ε_f) vs. (DNA). Spectra shows the absorbance changes upon increasing DNA concentrations.

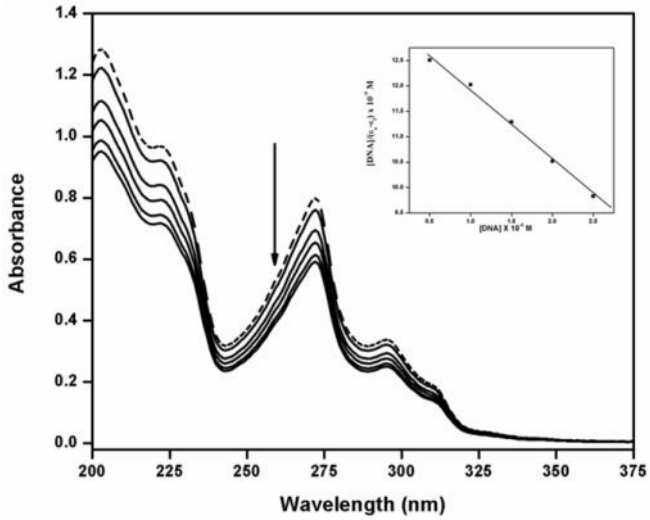


Fig 1.8: Absorption spectra of Complex 2. In the absence and in the presence of increasing amounts of DNA. (Complex) = 15 µM. (DNA) = (5, 10, 15, 20, 25) µM. Inset: plot of (DNA) / (*εa -εf*) vs. (DNA). Spectra show the absorbance changes upon increasing DNA concentrations.

1.4.2 Fluorescence spectral studies

As the copper (II) complexes are non-emissive, competitive binding studies with EthBr were carried out to gain support for the mode of binding of the complexes with DNA. The study involves addition of the complexes to DNA pretreated with EthBr ([DNA]/ [EthBr] = 1) and then measurement of intensity of emission.

The observed enhancement in the emission intensity of EthBr bound to DNA is due to intercalation of the fluorophore[30] in between the base pairs of DNA and stabilization of its excited state (Figure 1.9 and 1.10) the addition of the complexes to DNA pretreated with EB causes appreciable reduction in the emission intensity. This behaviour can be analyzed through the Stern–Volmer equation[31], $I_o/I = 1 + K_{sv}r$, where I_o and I are the fluorescence intensities in the absence and the presence of complexes, respectively. K_{sv} is a linear Stern–Volmer quenching constant, r is the ratio of the total concentration of complexes to that of DNA.

The quenching plot (Fig 1.9 and 1.10) illustrates that the quenching of EB bound to DNA by the copper (II) complexes is in good agreement with the linear Stern–Volmer equation, which also indicates that the complex binds to DNA. In the plot of I_o/I versus [Complex] / [DNA], K_{sv} is given by the ratio of the slope to intercept. The K_{sv} values for complexes (**1** and **2**) are 1.75 and 1.82, which is higher than that for ordinary transition metal copper complex[32]. This suggests that copper (II) complexes bind strongly with DNA, which is also consistent with our absorption spectral results.

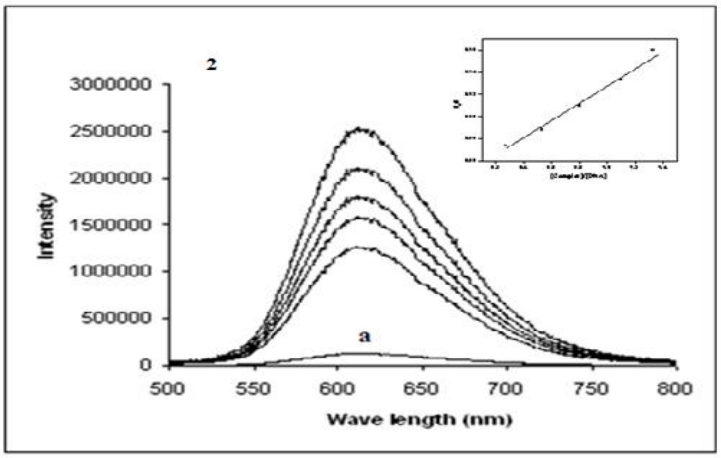
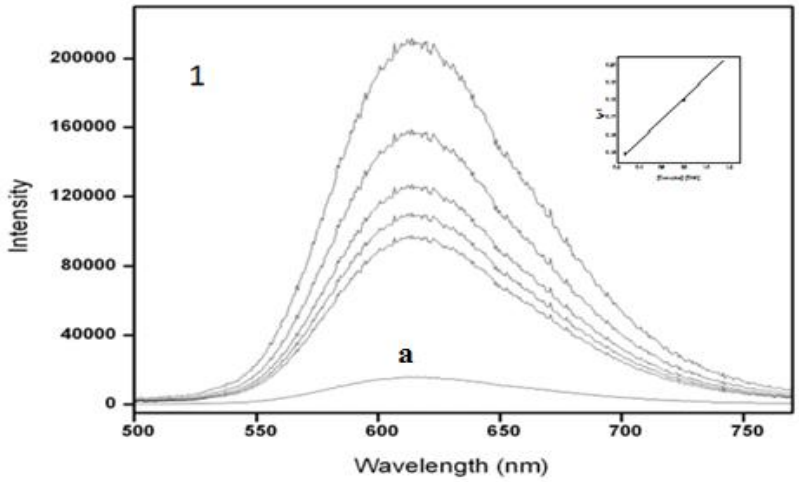


Fig 1.9: Emission spectra of EB bound to DNA in the absence (a) and in the presence of Complex **1** (Complex) = 8 - 32 x 10^{-6} M. (DNA) = 3 x 10^{-5} M, (EB) = 3 x 10^{-5} M. The arrow shows the intensity changing upon the increasing complex. Inset: plot of *Io/I* vs. (Complex) /(DNA). Emission spectrum of EB alone (a) concentrations.



1.10: Emission spectra of EB bound to DNA in the absence (a) and in the presence of Complex **2** (Complex) = 8 - 32 x 10-6 M. (DNA) = 3 x 10-5 M, (EB) = 3 x 10-5 M. The arrow shows the intensity changing upon the increasing complex. Inset: plot of *Io/I* vs. (Complex) /(DNA). Emission spectrum of EB alone (a) concentrations.

1.4.3 Viscosity studies

To explore further the interaction between the copper (II) complex and DNA, viscosity measurements were carried out on CT DNA by varying the concentration of the complex. Spectroscopic data are necessary, but insufficient to support an intercalative binding mode[33]. A classical intercalation mode causes a significant increase in the viscosity of DNA solution due to the increase in separation of the base pairs at intercalations sites and hence to an increase in overall DNA contours length. A partial and/or nonclassical intercalation of ligand would reduce the DNA viscosity[34]. The effects of the complexes (1 and 2) on the viscosity of the CT DNA solution are given in (Fig 1.11 and 1.12)

The plot shows that complexes had a reverse effect on the relative viscosity of the CT DNA. With the addition of the complex 10, the relative viscosity of DNA increased. Since the increase is far less than that observed for an intercalator such as EB. This observation leads us to support the above spectral studies which suggest that the complex 1 interaction with DNA via partial intercalation between DNA base pairs, which is similar to the interaction of $[Cu(phen)_2]^{2+}$ with DNA[35, 36]. Similarly, the same results were obtained from complex 2 (Fig 1.11 and 1.12).

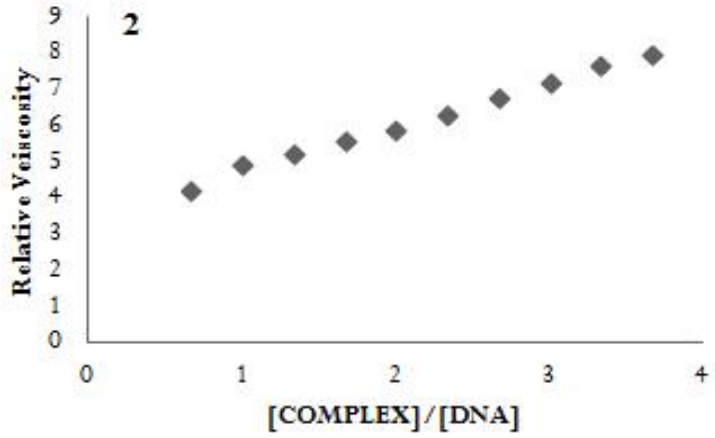


Fig 1.11: Effect of increasing amount of complex **1** (1,15,20,25,30,35,40,45,50 µM) on the relative viscosity of calf thymus DNA (15 µM) in 5mM Tris-HCl/50mM NaCl buffer.

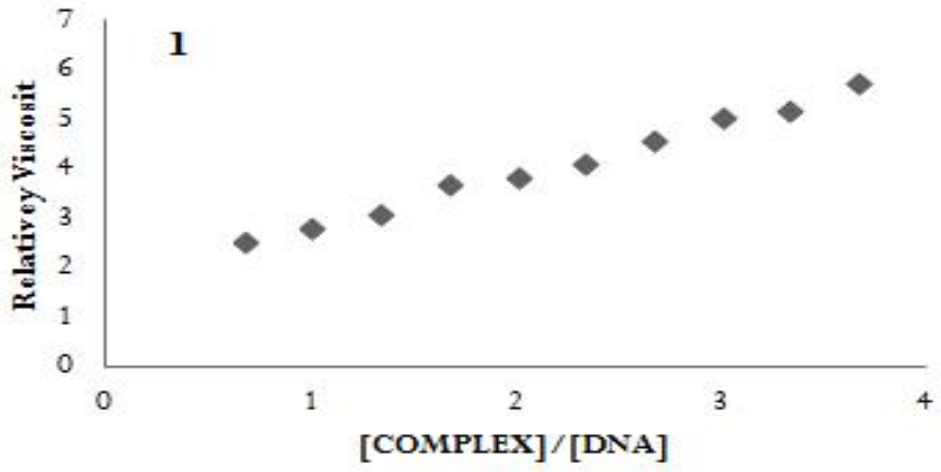


Fig 1.12: Effect of increasing amount of complex 2 (1,15,20,25,30,35,40,45,50 µM) on the relative viscosity of calf thymus DNA (15 µM) in 5mM Tris-HCl/50mM NaCl buffer.

1.4.4 Cyclic voltammetric study

Cyclic voltammetric techniques were employed to study the interaction of the present redox active metal complex with DNA with a view to further explore the DNA binding modes assessed from the above spectral and viscometric studies. Typical cyclic Voltammetry (CV) behaviors of complexes 1 and 2 in the absence and presence of CT-DNA are shown in (Fig 1.13 and 1.14). The cyclic voltammogram of copper (II) in the absence of DNA featured reduction of Cu(II) to the Cu(I) form at a cathodic peak potential, E_{pc} of -0.7 V and anodic peak potential, E_{pa} of -0.65 V for complex 1 and cathodic potential E_{pc} of -0.65 V and anodic peak potential E_{pa} of -0.6 V for complex 2 respectively. The separation of the anodic and cathodic peak potentials, Ep = -0.05 V from Complex 1 and E_p = -0.05 V for complex 2 respectively. The formal potential $E_{1/2}$, was taken as the average of Epc and Epa, is -0.067 V in the absence of DNA for complex 1 and -0.14V in the absence of DNA for complex 2 respectively.

The presence of DNA in the solution at the same concentration of Copper (II) causes a considerable decrease in the voltammetric current coupled with a slight shift in the $E_{1/2}$ ($E_{1/2}$ = -0.065 V from complex 1 and $E_{1/2}$ = -0.112 V for complex 2). The drop of the voltammetric currents in the presence of CT-DNA can be attributed to diffusion of the metal complex bound to the large, slowly diffusing DNA molecule. Obviously, $E_{1/2}$ undergoes a positive shift (25 mV) after forming an aggregation with DNA, suggesting that the copper complex bind to DNA mainly by intercalation binding mode[37, 38] and this result also proves the results obtained from viscosity and absorption spectrum studies again.

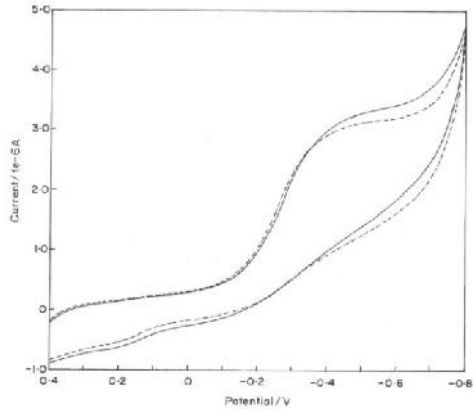


Fig 1.13: Cyclic voltammogram of complex **1** (1 mM) in the absence (—) and in the presence (---) of CT-DNA (1.5 x 10^{-5} M). 5 mM in buffer containing 50 mM NaCl–5 mM Tris–HCl, pH 7.2. Scan

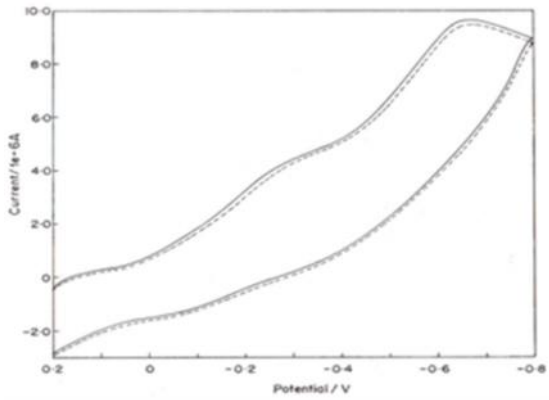


Fig 1.14: Cyclic voltammogram of complex 2 (1 mM) in the absence (—) and in the presence (---) of CT-DNA (1.5 x 10^{-5} M). 5 mM in buffer containing 50 mM NaCl–5 mM Tris–HCl, pH 7.2. Scan

1.5 Antibacterial and Antifungal screening

The copper (II) complex was screened *in vitro* for its microbial activity against certain pathogenic bacterial and fungal species using disc diffusion method (Fig 1.15 and 1.16). The complex was found to exhibit considerable activity against Gram positive and Gram negative bacteria and the fungus *C. albicans.* The test solutions were prepared in dimethyl sulphoxide and the results of the antimicrobial activities are summarized in Table 1.3. Zoroddu et al[39] have reported that copper complex show any significant activity against the Gram positive and Gram negative bacteria. Recently Patel et al. indicated that the copper (II) complex with L-phenylalanine has exhibited considerable activity against some human pathogens[40]. In our biological experiments, using copper(II) complexes (1 & 12), we have observed antibacterial activity against Gram positive bacteria *Staphylococcus aureus* and *B. subtilis* and Gram negative bacteria *E. coli* and *Pseudomonas aeruginosa*. The copper (II) complexes have shown high activity against Gram positive than Gram negative bacteria. The copper (II) complex is also very active against the fungus *C. albicans* than the standard antifungal drug, clotrimazole. It may be concluded that our copper (II) complexes inhibits the growth of bacteria and fungi to a greater extent.

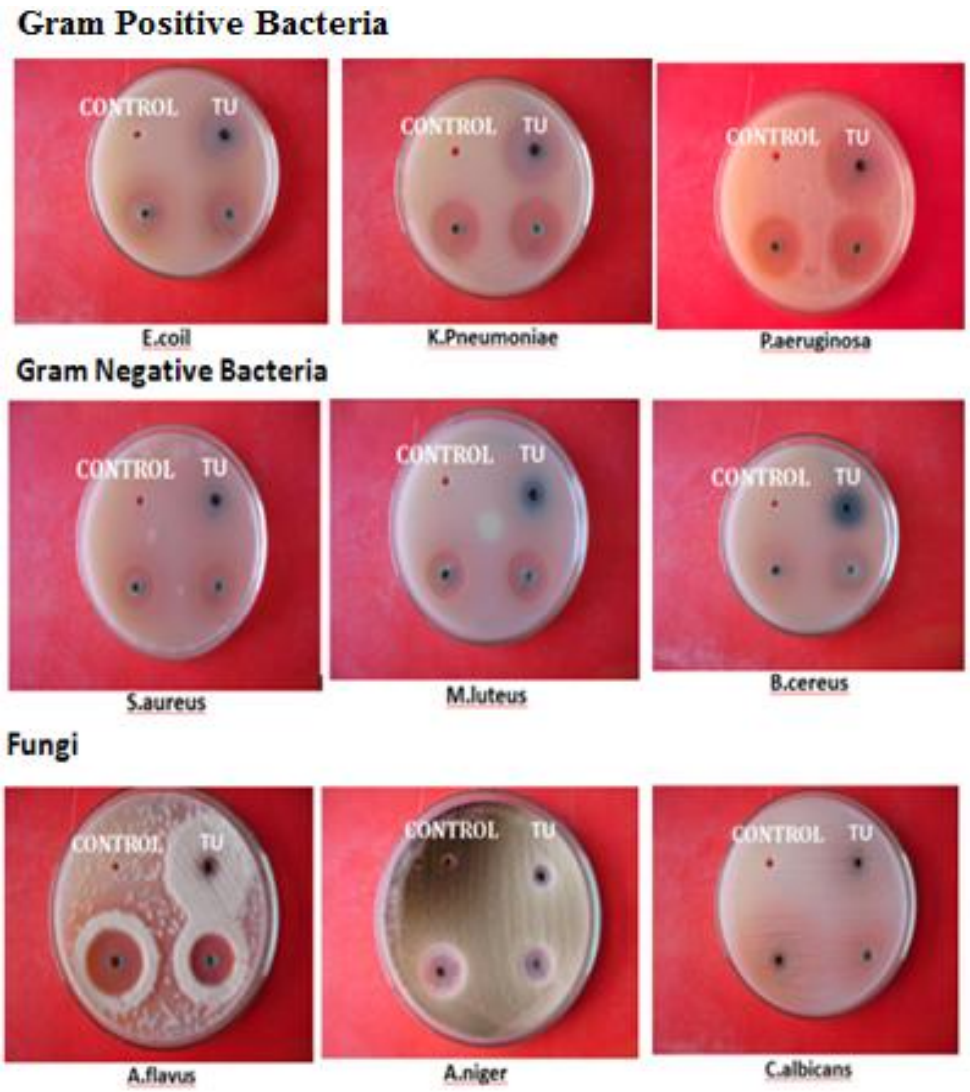


Fig. 1.15: Antimicrobial activity of Complex 1

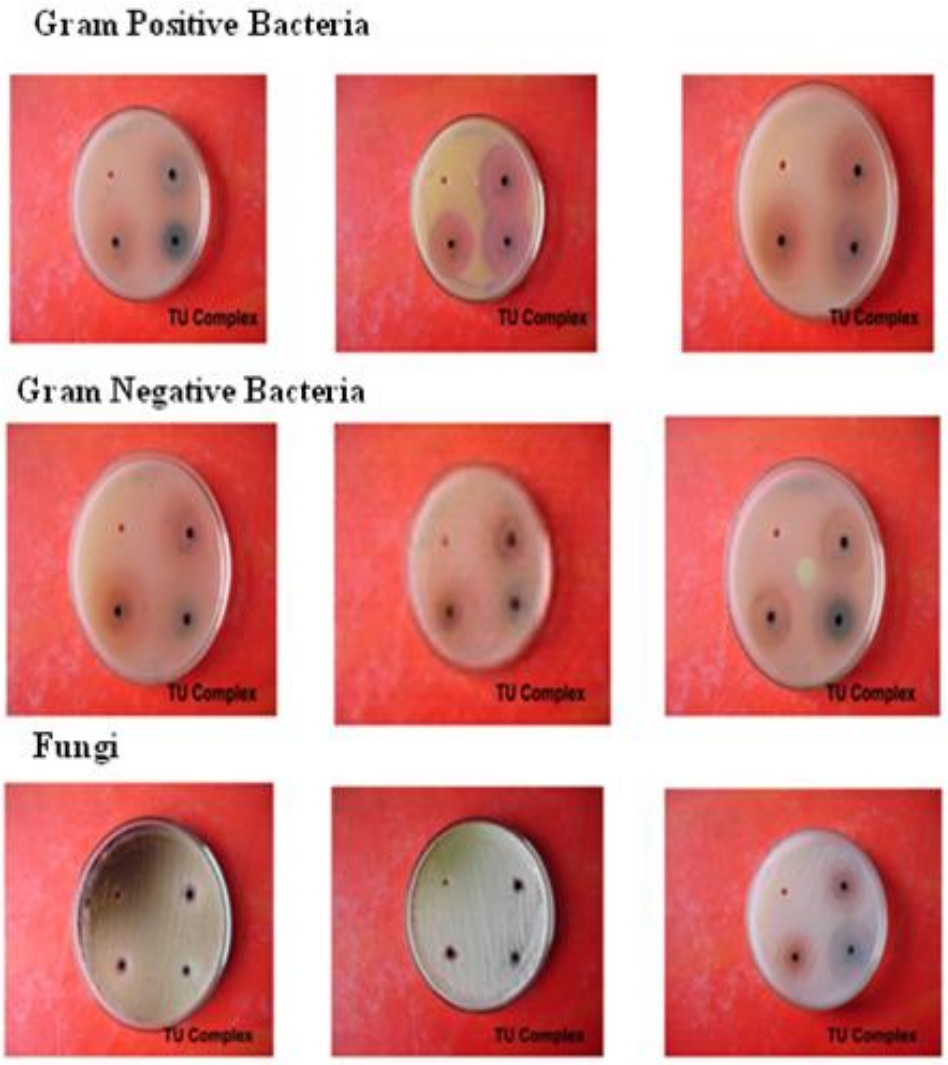


Fig. 1.16: Antimicrobial activity of Complex 2

Table 1.3: Biological activity of complexes 1 and 2

Name of the Organism	Diameter Zone of Inhibition (mm)	
	Complex 1	Complex 2
B. cereus	12	8
M. luteus	-	35
S. aureus	25	22
E. coli	21	17
K. pheumoniae	22	5
P. aeruginosa	5	7
A. flavus	15	12
A. niger	8	14
C. albicans	8	10

1.6 Conclusion

In this chapter, we have described new copper(II) complexes. Further characterization of the complexes was achieved through physio-chemical and spectroscopic methods. The effectiveness of the binding of the complexes is being confirmed by means of hypochromism in the electronic spectral studies and change in intensity of emission in the case of emission spectral studies. Besides, the effect of binding is also confirmed by the viscometric and cyclic voltammetric studies. This shows that the complexes interact with DNA base pairs effectively. The copper (II) complexes exhibit good antimicrobial activity.

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