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Synthesis, Characterization, DNA Binding, Antimicrobial Activity of Copper (II) Complexes Containing 1, 10-Phenanthroline, Bipyridine and L-Tryptophan.

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Abstract: A new two copper (II) complexes are namely **[Cu(Phen)(L-Try)(TU)]ClO_4 (1)** and **[Cu(Bipy)(L-Try)(TU)]ClO_4 (2)** [Phen=1,10-Phenanthroline, L-Try= L-Tryptophan, TU=Thiourea and Bipy=Bipyridine have been synthesised and characterised by elemental analysis, conductivity, UV-visible, infrared and electro paramagnetic spectra. The absorption intensity of the copper (II) complexes changed i.e., complex 1and 2 has shown hyperchromism with blue shift an evidently after the addition of Calf-Thymus (CT-DNA), which indicated the interactions between DNA and the complexes. The complexes to DNA pretreated with Ethidium Bromide (EB) cause appreciable change in the emission intensity. The linear binding behavior can be analyzed through the Stern–Volmer equation. In the viscosity method, the binding of the copper (II) complexes with CT-DNA solution are observed. The plot shows that the complexes had a reverse effect on the relative viscosity of the CT- DNA with the addition of the complexes, the relative viscosity of DNA changed. The cyclic voltammetry (CV) behaviours of our copper (II) in the absence and presence of CT-DNA can be studied. The change of the voltametric currents in the presence of CT-DNA can be attributed to diffusion of the metal complex bound to the large, slowly diffusing DNA molecule.

Keywords
Copper (II) complexes
L-Tryptophan
1, 10-Phenanthroline
Bipyridine
CT-DNA Binding

1. INTRODUCTION

Metal complexes constitute a growing field in drug design and have been considered as promising antitumor agents in recent decades by the virtue of their unique spectroscopic and electrochemical signatures. The interest in the role of metal complexes in cancer therapy was triggered by the discovery of the potent epithelial ovarian cancer drug *cis*platin[1]. Metal complexes with tunable coordination environments and versatile physicochemical properties offer scope for designing and developing highly sensitive diagnostic agents for medicinal applications[2–17]. Metal complexes with polypyridyl phenanthroline bases have attracted great attention by virtue of their binding propensity to nucleic acids under physiological conditions. In addition to the rich coordination chemistry of the metal ions, they have great potential in constructing metal complexes with diverse structures and redox potentials[18–22].

Amino acids are the basic structural units of proteins that recognize a specific base sequence of DNA. An amino acid with a side chain aromatic ring, eg. L-tryptophan, contributes mainly to the stabilization of proteins through hydrophobic interactions and the formation of hydrophilic environments. Copper complexes containing amino acids have been studied as models for the behaviour of copper enzymes and some copper complexes with amino acid ligands were reported to exhibit potent anti-tumor and artificial nuclease activities[23–25].

Synthesis and characterization of Copper (II) complexes are done by elemental analysis, conductivity measurement, IR and EPR spectral methods. The binding property of the complexes to calf thymus DNA has been studied using different physico-chemical methods and the binding modes are discussed. The experimental results show that the copper (II) complex samples bind effectively with DNA-binding agents and good activity against gram positive, gram negative bacteria as well as fungus.

2. EXPERIMENTAL

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[26]. 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.

2.2 Synthesis of [Cu(Phen)(L-Try)(H_2O)]ClO_4 and [Cu(Bipy)(L-Try)(H_2O)]ClO_4[27]

To the mixture of L-Tryptophan 0.20423 g (1mM) and NaOH 0.04 g (1mM) in water, an aqueous solution of $Cu(NO_3)_2.3H_2O$ 0.2416 g (1mM) was added with stirring. Several minutes later, the ethanolic solution of phen/bipy 0.1982 g / 0.156 g (1mM) was added and the solution was stirred for about 3 hrs at 60 ^{0}C. $NaClO_4$ 0.1224 g (1mM) 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.

2.2.1 Synthesis of [Cu(Phen)(L-Try)(TU)]ClO_4 (1)

About 1.686g (3 mM) of [Cu(phen)(L-Try)(H_2O)]ClO_4 complex dissolved in 50 mL of water. To this 0.2282 g (3 mM) of Thiourea in 15 ml of distilled water was added slowly with constant stirring for 45 min. A dark yellowish substance was separated out, which was filtered and dried.

2.2.2 Synthesis of [Cu(Bipy)(L-Try)(TU)]ClO_4 (2)

About 1.614g (3 mM) of [Cu(Bipy)(L-Try)(H_2O)]ClO_4 complex dissolved in 50 mL of water. To this 0.2282 g (3 mM) of Thiourea in 15 ml of distilled water was added slowly with constant stirring for 40 min. A dark yellowish substance was separated out, which was filtered, dried and yield: 65 %,

3 RESULTS AND DISCUSSION

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[28], the values given in the table 1.1. Synthetic route of the complexes is given scheme 1 and 2.

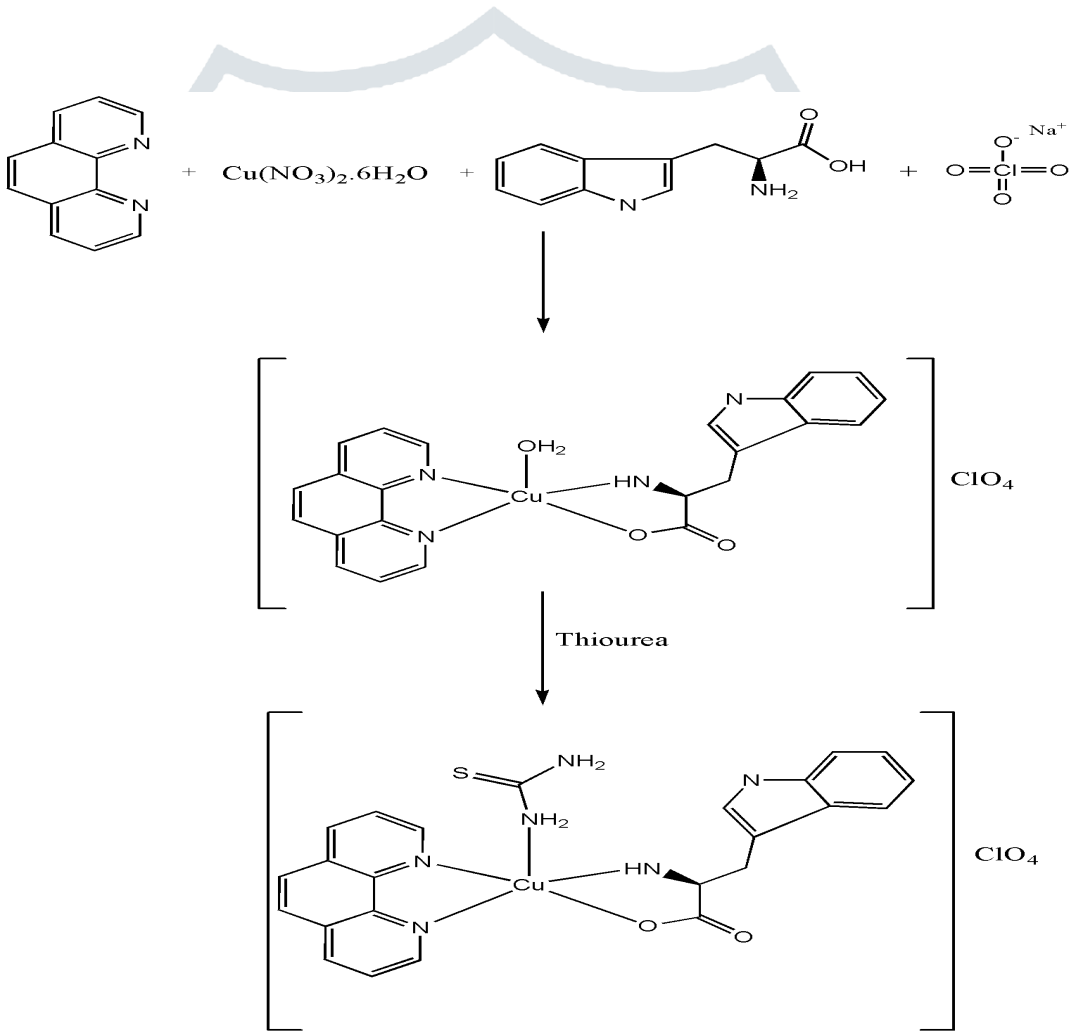
3.2 Electronic spectra

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 585 nm and 609 nm in addition to the ligands centered bands in the UV region of the electromagnetic spectra (Figure 1.1a and 1.1b). The electronic spectra of the complexes are in good agreement with the previously reported square pyramidal geometry of the complexes[29-31].

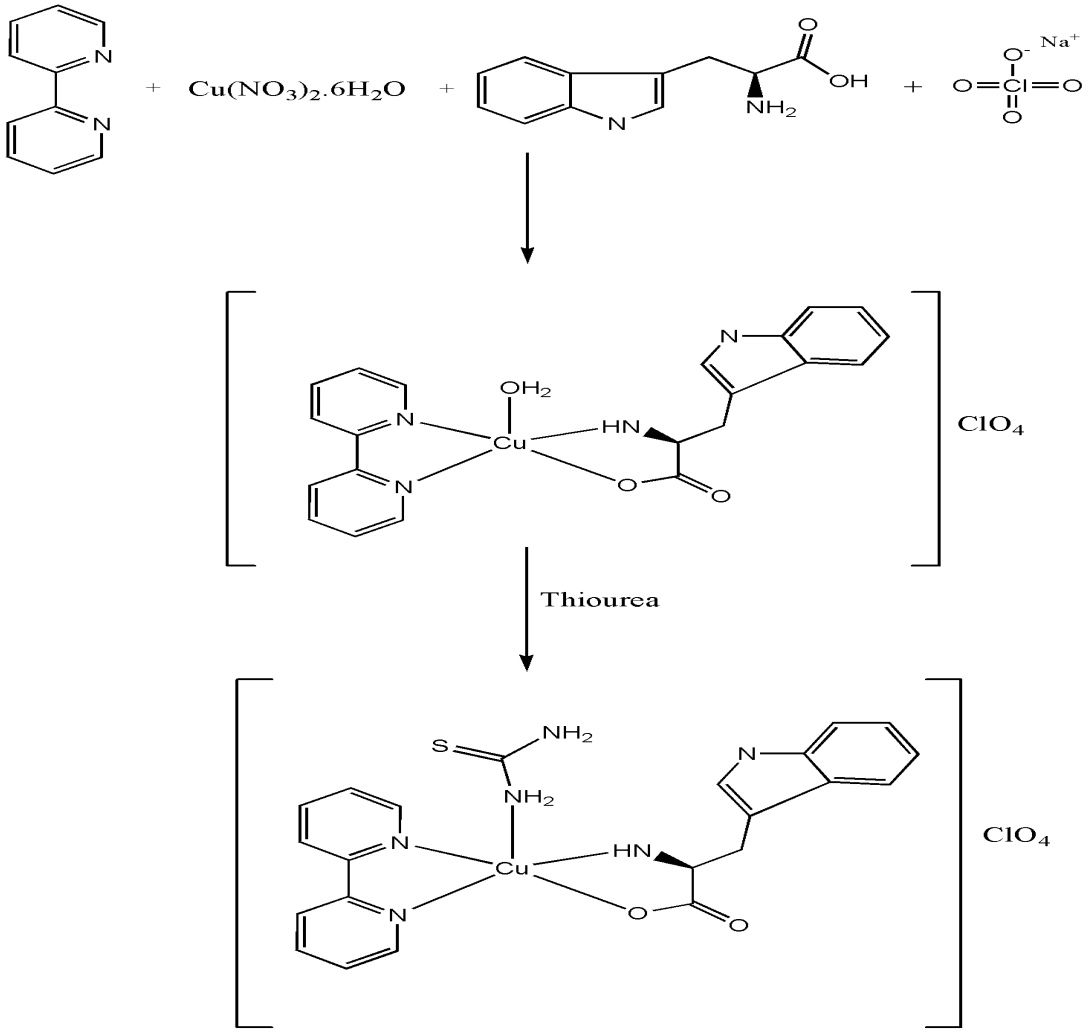
In the UV–Visible region, the intense absorption bands appeared from 240 to 300 nm is attributed to intraligand transitions. Another band which appeared around 271 nm and 249 nm is assigned to ligand field transitions[32]. The electronic absorption spectral data for Cu (II) complexes are given in the table 1.2

Table 1.1 Elemental analysis and molar conductance values of the complexes

Complex Name	Carbon %	Nitrogen%	Hydrogen%	Molar conductance $Ohm^{-1}cm^2\ mol^{-1}$
$[Cu(Phen)(L\text{-}Try)(TU)]ClO_4$	46.45(45.98)	13.54(13.40)	3.41(3.30)	88
$[Cu(Bipy)(L\text{-}Try)(TU)]ClO_4$	44.30(44.05)	14.09(14.00)	3.55(3.35)	94



Scheme 1. The synthetic route of the complex $[Cu(Phen)(L\text{-}Try)(TU)]ClO_4$ (1)



Scheme 2. The synthetic route of the complex [Cu(Bipy)(L-Try)(TU)]ClO_4 (2)

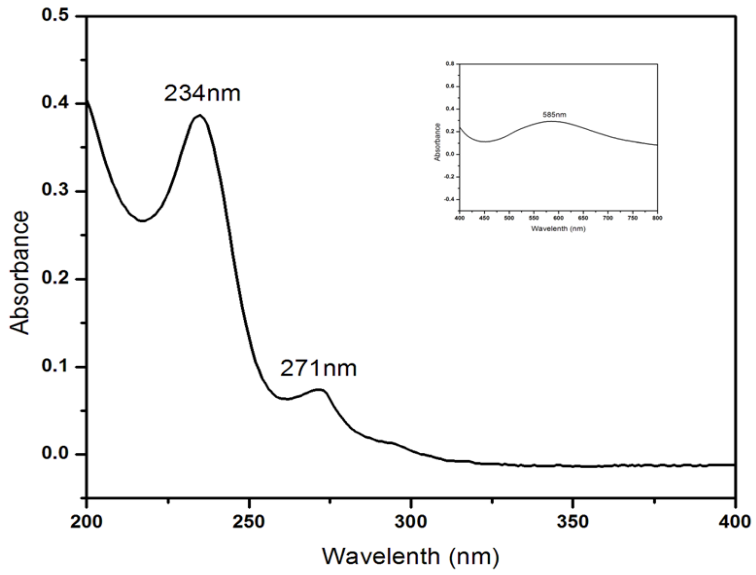


Figure 1.1a UV Visible spectra of [Cu(Phen)(L-Try)(TU)]ClO_4

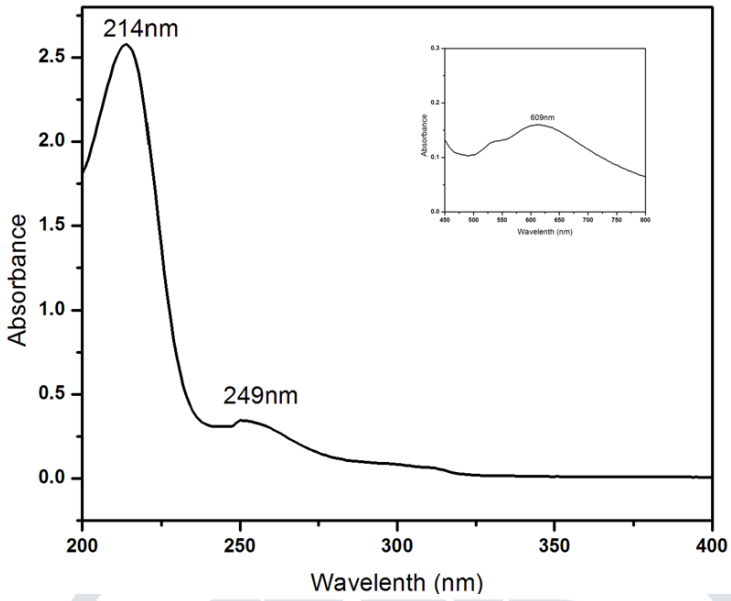


Figure 1.1b UV Visible spectra of [Cu(Bipy)(L-Try)(TU)]ClO_4

Table: 1.2 UV-Visible values of the copper (II) complexes

Complex Name	λ_{max}	ε_{max} ($M^{-1}cm^{-1}$)
[Cu(Phen)(L-Try)(TU)]ClO_4 (1)	234 271	38587 7679
[Cu(Bipy)(L-Try)(TU)]ClO_4 (2)	214 249	254680 34127

3.3 Infrared spectra

In the IR spectra, the N-H stretching vibrations were observed at 3206.60 cm^{-1} for complex 1, and 3599.17 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 1615 & 1369 cm^{-1}, in bipy at 1658 & 1379 cm^{-1}. The strong bands at 1112 cm^{-1} for complex 1 and 1085 cm^{-1} for complex 2 were assigned to ν (Cl-O) of ClO_4. The non ligand peaks at 720 and 633 cm^{-1} were assigned to ν (Cu-O) and ν (Cu-N) for complex 1 (for complex 2, 731 & 626 cm^{-1}) (Figure 1.2a and 1.2b)

3.4 Electron paramagnetic resonance

The solid state EPR spectra of the copper (II) complexes were recorded at X-band frequencies shows (Figure 1.3a and 1.3b). At liquid nitrogen temperature, complex 1 & 2 exhibits well defined single isotropic feature near g = 2.12 and g = 2.04 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.

3.5 DNA BINDING STUDIES

3.5.1 Electronic spectral studies

Electronic absorption spectroscopy was an effective method to examine the binding mode of DNA with metal complexes[33-35]. 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. Figure 1.4a and 1.4b shows the UV absorption spectral study of complexes (1 and 2) in the absence and presence of DNA.

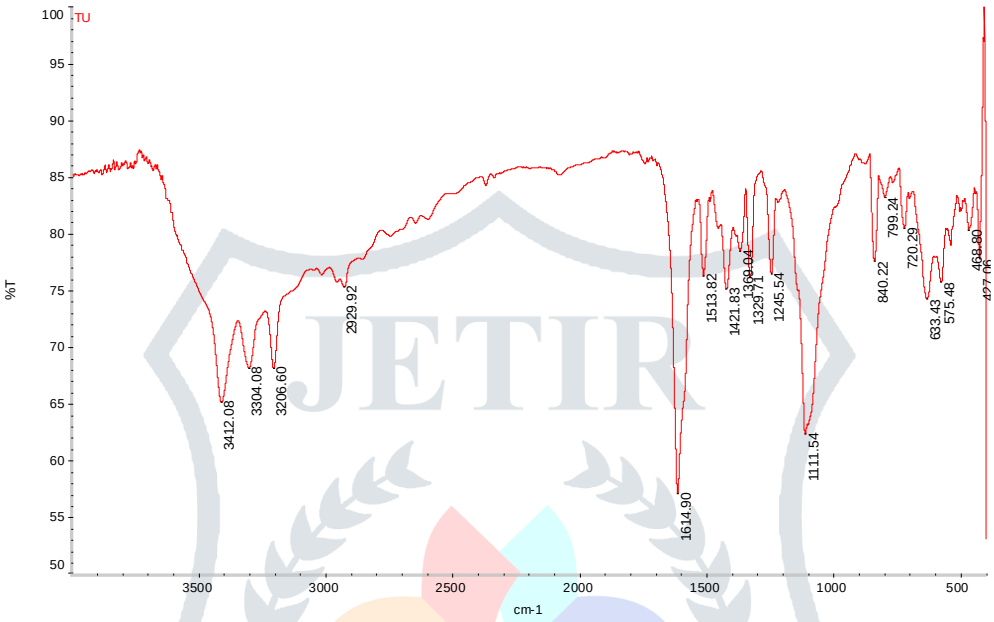


Figure 1.2a – IR spectra of [Cu(Phen)(L-Try)(TU)]ClO_4

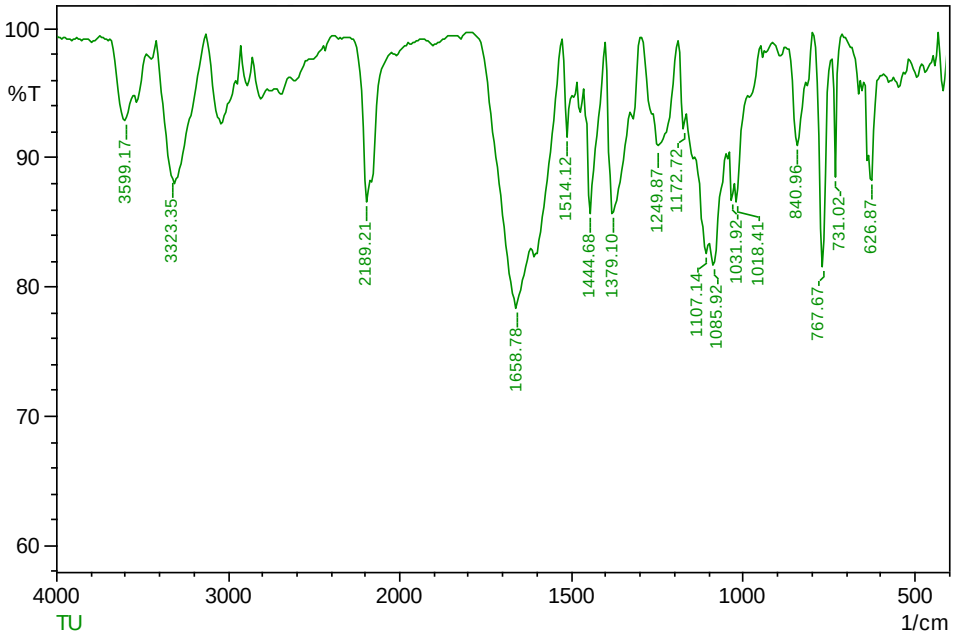


Figure 1.2b – IR spectra of [Cu (Bipy)(L-Try)(TU)]ClO_4

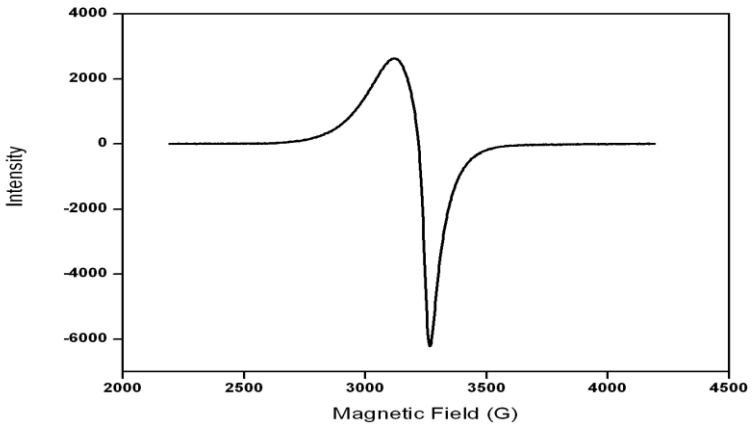


Figure1.3a EPR spectra of [Cu (Phen)(L-Try)(TU)]ClO_4 in DMSO at liquid nitrogen temperature.

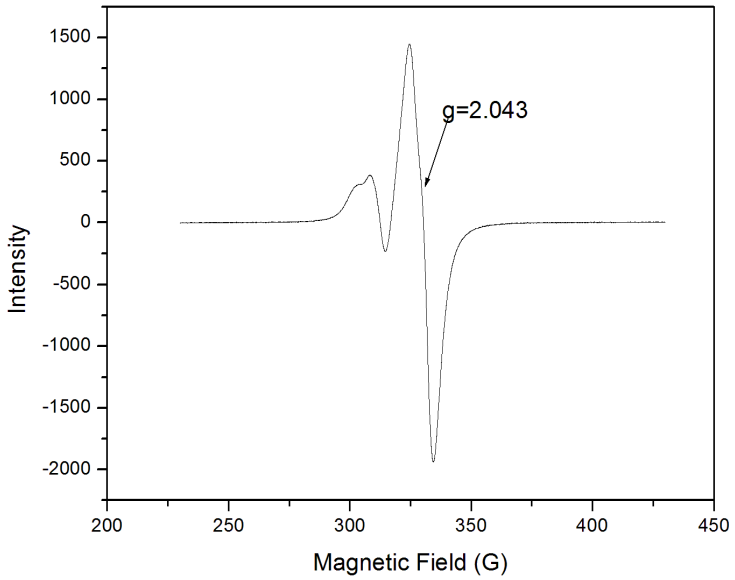


Figure 1.3b EPR spectra of [Cu (Bipy)(L-Try)(TU)]ClO_4 in DMSO at liquid nitrogen temperature.

In the ultraviolet region from 240 to 300 nm, the complex 1 had strong absorption peaks at 266 nm, for complex 2 the absorption peak at 298 nm. The absorption intensity of the complexes (1 and 2) increased (hyperchromism) evidently after the addition of DNA, which indicated the interactions between DNA and the complexes. We have observed a minor blue shift along with significant hyperchromicity for the complex. The intrinsic binding constant, Kb, was determined by using the following equation[36]:

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

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 of the complex 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 complexes (1 and 2) are 2.12 x 10^{-5} and 1.32 x 10^{-5}. The binding propensity of the phen complex due to the presence of extended planar aromatic ring in phen. Earlier studies on bis-phen copper complex 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[37-39]. The nature of binding of the phen complex is proposed to be similar as observed for the bis-phen species.

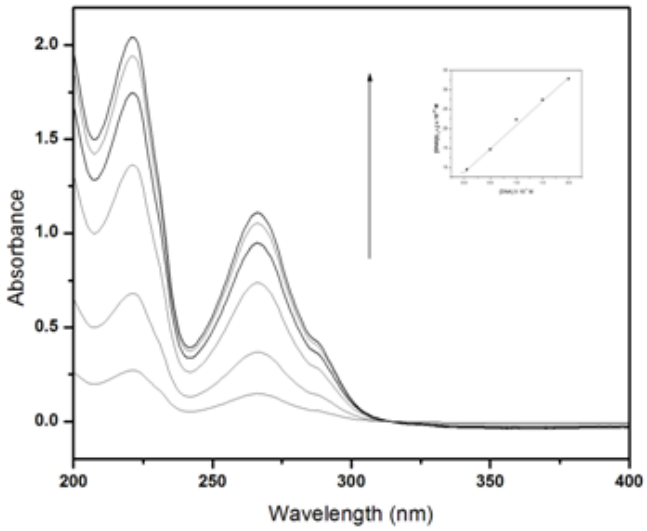


Figure 1.4a Absorption spectra of Complex-1. In the absence and in the presence of increasing amounts of DNA concentrations. [Complex] = 15 µM. [DNA] = (5, 10, 15, 20, 25) µM. The Arrow shows the absorbance changes upon increasing DNA concentrations.

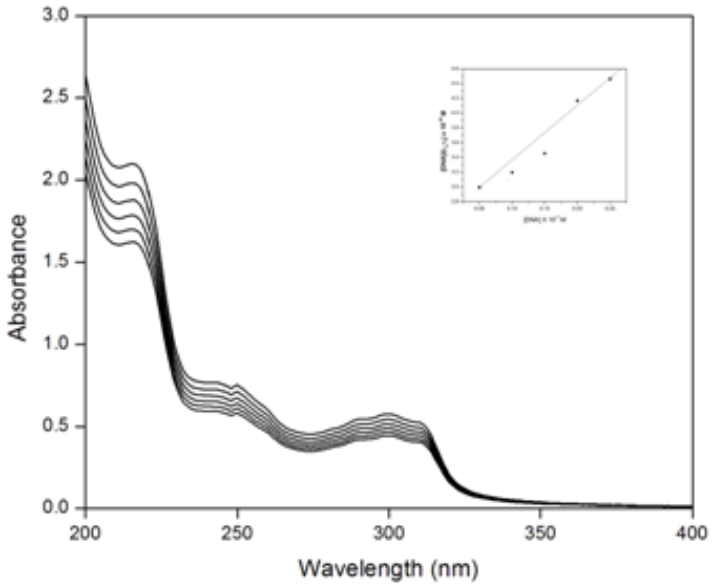


Figure 1.4b Absorption spectra of Complex-2. In the absence and in the presence of increasing amounts of DNA concentrations. [Complex] = 15 µM. [DNA] = (5, 10, 15, 20, 25) µM. Spectra shows the absorbance changes upon increasing DNA concentrations.

3.5.2 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 emission intensity of EthBr bound to DNA is due to intercalation of the

fluorophore in between the base pairs of DNA and stabilization of its excited state (Figure 1.5a and 1.5b)[40]. The addition of the complex to DNA pretreated with EB causes appreciable reduction in the emission intensity. This behaviour can be analyzed through the Stern–Volmer equation[41], $I_o/I = 1 + K_{sv}r$, where I_o and I are the fluorescence intensities in the absence and the presence of complex, respectively. K_{sv} is a linear Stern–Volmer quenching constant, r is the ratio of the total concentration of complex to that of DNA. The quenching plot (Figure 1.5a and 1.5b) 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} value for complexes (1 and 2) is 1.8 and 1.6, which is higher than that for ordinary transition metal copper complex[42]. This suggests that copper (II) complexes bind strongly with DNA, which is also consistent with our absorption spectral results.

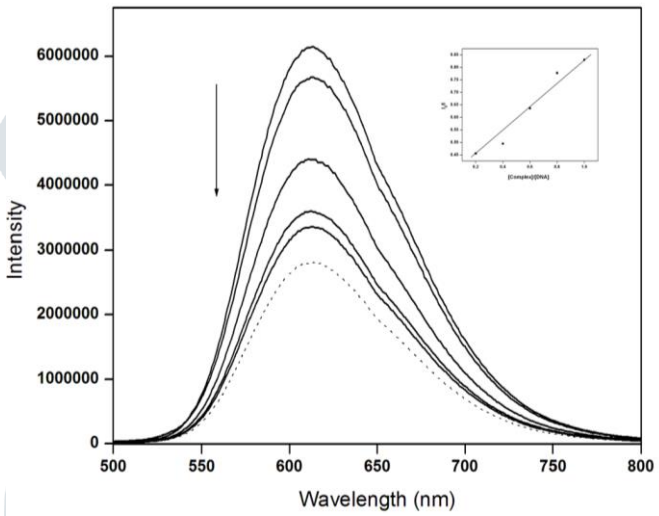


Figure 1.5a Emission spectra of EB bound to DNA in the absence (a) and in the presence of [Cu(Phen)(L-Try)(TU)]ClO_4. [complex] = 8,16,24,32,40 x 10^{-6} M. [DNA] = 3 x 10^{-5} M, [EB] = 3 x 10^{-5} M. The Arrow shows the intensity changing upon increasing complex concentrations.

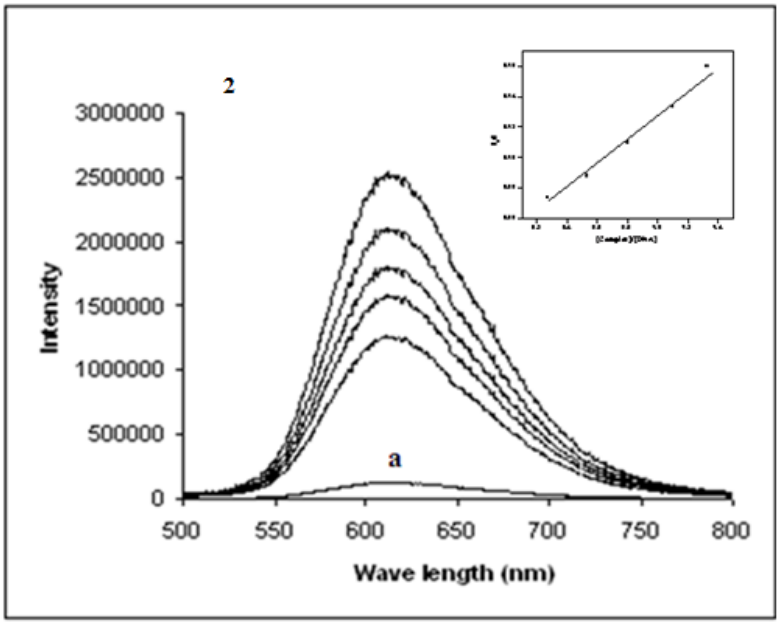


Figure 1.5b Emission spectra of EB bound to DNA in the absence (a) and in the presence of [Cu(Bipy)(L-Try)(TU)]ClO_4. [complex] = 8,16,24,32,40 x 10^{-6} M. [DNA] = 3 x 10^{-5} M, [EB] = 3 x 10^{-5} M. The Arrow shows the intensity changing upon increasing complex concentrations.

3.5.3 Viscosity studies

To explore further the interaction between the copper (II) complexes and DNA, viscosity measurements were carried out on CT-DNA by varying the concentration of the complexes. Spectroscopic data are necessary, but insufficient to support an intercalative binding mode. Hydrodynamic measurements which are sensitive to length increases (i.e. Viscosity, sedimentation et. al) are regarded as the least ambiguous and the most critical tests of binding on a solution in the absence of crystallographic structure data[43]. 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 non-classical intercalation of ligand would reduce the DNA viscosity[44]. The effects of the complexes (1 and 2) on the viscosity of the CT-DNA solution are given in figure 1.6a and 1.6b. The plot shows that the complex had a reverse effect on the relative viscosity of the CT-DNA. With the addition of the complex, 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[45,46]. Similarly, the same results were obtained from complex 2 (Figure 1.6a and 1.6b).

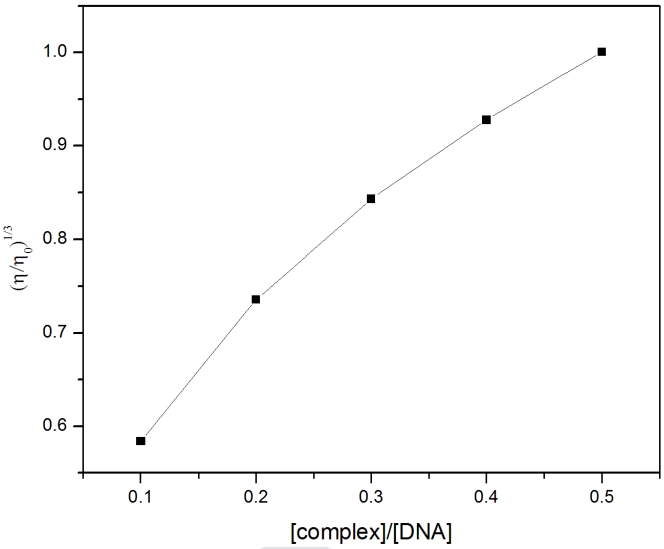


Figure 1.6a Effect of increasing amount of [Cu(Phen)(L-Try)(TU)]ClO_4 (1,15,20,25,30,35,40,45,50 µM) on the relative viscosity of calf thymus DNA (15 µM) in 5mM Tris-HCl/50mM NaCl buffer.

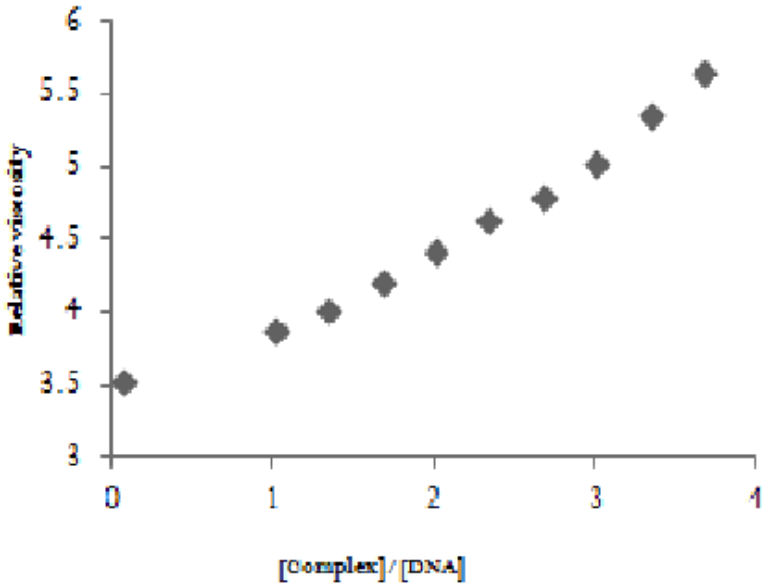


Figure 1.6b Effect of increasing amount of [Cu(Bipy)(L-Try)(TU)]ClO_4 (1,15,20,25,30,35,40,45,50 µM) on the relative viscosity of calf thymus DNA (15 µM) in 5mM Tris-HCl/50mM NaCl buffer.

3.5.4 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 (Figure 1.7a and 1.7b). 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[47], E_{pc} of -0.10 V and

anodic peak potential, E_{pa} of -0.14 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 = -0.040 V for 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 -0.14 V in the absence of DNA for complex 1 and -0.067V in the absence of DNA for complex 2 respectively.

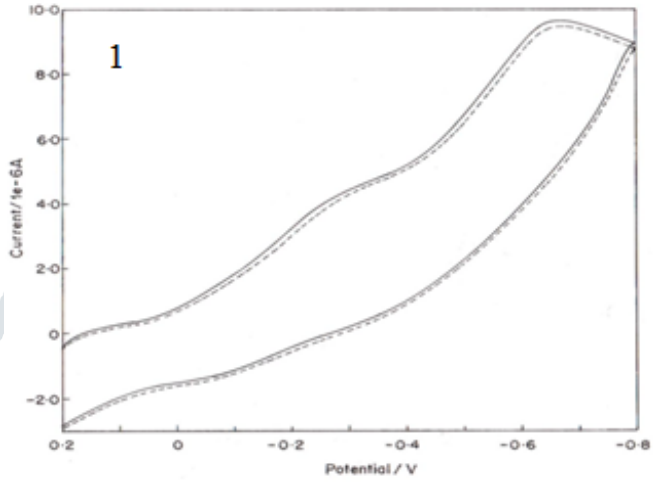


Figure 1.7a Cyclic voltammogram of [Cu(Phen)(L-Try)(TU)]ClO_4 (1 mM) complexes in the absence (—) and in the presence (….) of CT-DNA (1.5 x 10^{-5} M). 5 mM in buffer containing 50 mM NaCl–5 mM Tris–HCl, pH 7.2. Scan.

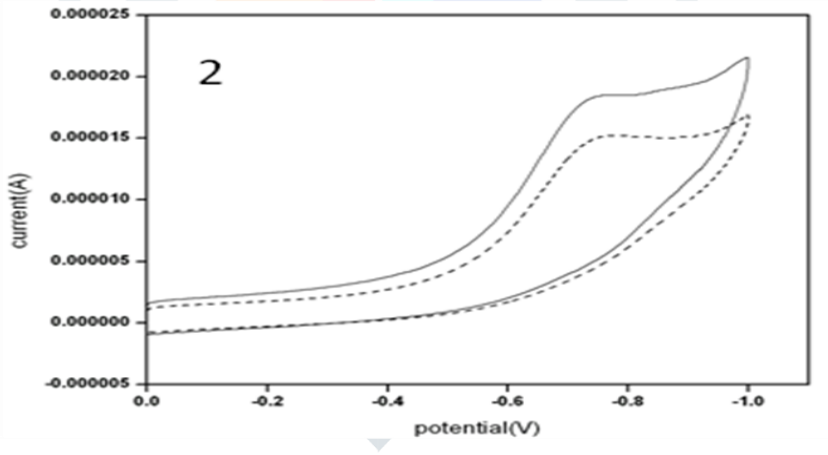


Figure 1.7b Cyclic voltammogram of [Cu(Bipy)(L-Try)(TU)]ClO_4 (1 mM) complexes in the absence (—) and in the presence (….) of CT-DNA (1.5 x 10^{-5} M). 5 mM in buffer containing 50 mM NaCl–5 mM Tris–HCl, pH 7.2. Scan.

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 $E_{1/2}$ ($E_{1/2}$ = -0.112 V for complex 1 and $E_{1/2}$ = -0.065 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[48], and this result also proves the results obtained from viscosity and absorption spectrum studies again.

3.6 Antibacterial and antifungal screening

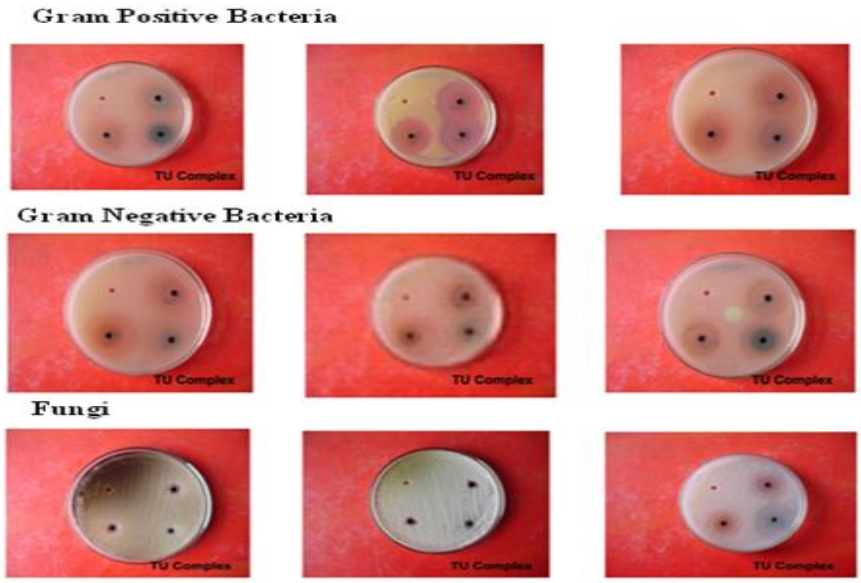


Figure 1.8a Antimicrobial screening of complex 1

The copper (II) complexes were screened in vitro for its microbial activity against certain pathogenic bacterial and fungal species using disc diffusion method (Figure 5.8a and 5.8b). The complexes were 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. Zoroddu et al.[49] 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) complexes with L-Tryptophan have exhibited considerable activity against some human pathogens[50]. In our biological experiments, using copper (II) complexes (1 and 2), 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) complexes are 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.

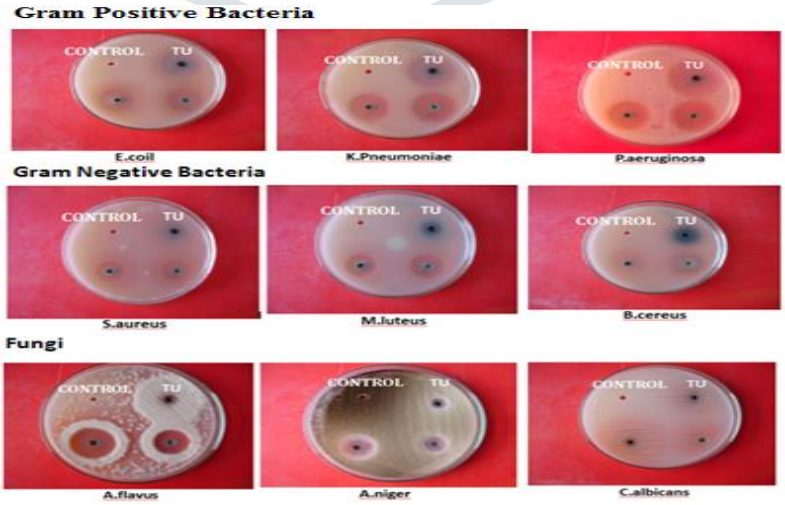


Figure 1.8b Antimicrobial screening of complex 2

4 CONCLUSIONS

The new mixed-ligand copper (II) complexes has been synthesis and characterization was achieved through physico-chemical and spectroscopic methods. The effectiveness of the binding of the complexes is being confirmed by means of hyperchromism 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 were exhibit good antimicrobial activity.

5. ACKNOWLEDGEMENTS

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