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Research Article

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Synthesis, characterization and DNA binding of copper(II) complexes with mixed ligands of 1, 10-phenanthroline / 2-2' bipyridyl, L-methionine and ethylamine: Studies on antimicrobial and anti-cancer activities

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Abstract

Ternary copper(II) complexes [Cu(phen)(L-met)EA)] **1** & [Cu(Bpy)(L-met)EA] **2** (phen = 1,10-phenanthroline Bpy = bipyridyl, L-Methionine and 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** and **2** displayed significant cytotoxicity when examined *in-vitro* on a panel of cancerous cell line - human liver cancer cell line - HepG-2 cells (IC50= 40.82 and 29.74 µg/ml). Further complexes **1** & **2** were tested for their antimicrobial activities and it was found to have good antimicrobial activities.

Keywords: Copper (II) Complexes, L-Methionine, Thiourea, DNA Binding & Cytotoxicity,

1. Introduction

The designed and synthesized polynuclear metal complexes have become an active area for the researches in the last few decades due to their interesting molecular structures, crystal packing and potential applications in the fields of bio-inorganic chemistry[1]. The first copper complex reported to show efficient DNA cleavage activity bis (1,10-phenanthroline) copper(I), and then the chemistry of metal complexes of 1,10 phenanthroline or modified ligand were developed as therapeutic agents[2]. In recent years, the coordination of drugs to transition metal ions has an important role in medicine and diagnostics[3].

Deoxyribonucleic acid (DNA) is a genetic material that acts as a form of memory storage for genetic information[4]. It is the target of some anti-tumor reagents which reacts with DNA and stop its replication and inhibiting the growth of tumor cells[5]. By changing both the metal ions and the ligands, it is possible to modify the mode of interaction of the nucleic acids with the complexes[6–8].

The designed co-ligand plays an important role in enhancing the DNA-metal complex interactions[9] as the modification from the previously reported works[10-12]. Thus, conveying the importance of the ligands like

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heterocyclic bases and amino acids in metal complexes, the same has been proved by experimental data reported in this work. Large planar ligands promote intercalative binding of the metal complexes to DNA[13,14], whereas the central metal ion plays a crucial role in the cleavage of DNA.

The need of new antibacterials with a novel mechanism of action to overcome the problem of resistance is needed urgently[15]. This made the researchers more and more turning their attention to folk medicine. They are all looking for the improved drugs against microbial infections. The copper(II) complexes of 1,10-phenanthroline and amino acids exhibit numerous biological activities, such as antitumor, anticancer and antimicrobial activities[16,17]. Substantial attention has been focused on the use of 1,10- phenanthroline and 2,2'- bipyridyl complexes as the intercalating agents of DNA and as artificial nucleases.

Thereby, in this study, we have synthesized and structurally characterized [Cu (phen)(L-met)(EA)]NO_3 & [Cu (bipy)(L-met)(EA)]NO_3 complexes of a heterocyclic bases with amino acid as ancillary ligand. Moreove

2. Experimental

2.1. Materials and Methods

We purchased the reagents like $Cu(NO_3)_2.3H_2O$, NaOH, $NaClO_4.H_2O$, 2,2'-bipyridyl, L-methionine, ethylamine, 1,10-Phenanthroline, CT DNA, Tris HCl, NaCl and ethidium bromide(EtBr) from Aldrich. The spectroscopic titration was carried out in the buffer (50 mMNaCl–5 mM Tris–HCl, pH 7.1) at room temperature. We recorded absorption spectra on a UV/VIS Shimadzu 2450 Spectrophotometer using cuvettes of 1-cm path length and emission spectra were recorded on JASCO FP 770 spectrofluorimeter. FT-IR spectra were recorded on a FT-IR Perkin Elmer spectrophotometer with samples prepared as KBr pellets. EPR spectra were recorded on Varian E-112 EPR spectrometer at room temperature, the field being calibrated with DPPH = 1, 10-diphenyl-2-picrylhydrazyl (g =2.0037).

Calf thymus DNA solution 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. We used Milli-Q water to prepare the solutions. Cyclic voltammetry studies were verified on CHI 602D (CH Instruments Co., USA) electrochemical analyzer under oxygen free conditions using a three-electrode cell in DMF solution with TBAP (0.1 M) as the supporting electrolyte.

2.2 Synthesis of [Cu(L-Met)(Phen)(EA)](NO_3) (1)

The complex [Cu(L-Met)(Phen)(H_2O)](NO_3) was prepared by literature method[18]. To the aqueous solution of parental complex (1 mmol), ethylamine (1 mmol) was added and stirred for 4 hrs resulting the color of the solution change from blue to bluish green. The resulting solution was filtered. The filtrate was kept for slow evaporation, after two weeks bluish green complex was separated out.

Yield: 62%; Anal. (%) Calc. for $C_{19}H_{25}CuN_5O_5S$: C, 45.73; H, 5.05; N, 14.03. Found: C, 43.44; H, 4.97; N, 13.72. IR (KBr pellet): 3416, 1625, 1580, 1516, 1424, 1143, 868cm^{-1}. UV-Vis (λ_{max} nm): 273, 612 nm.

2.3 Synthesis of [Cu(L-Met)(bpy)(EA)](NO_3) (2)

Synthesis was described in complex **1**, using [Cu(L-Met)(bpy)(H_2O)](ClO_4) (1 mmol) and thiosemicarbazide (1 mmol). Yield: 61%; Anal. (%) Calc. for $C_{17}H_{25}CuN_5O_5S$: C, 42.98; H, 5.30; N, 14.74. Found: 41.69; H, 5.22; N, 14.59. IR (KBr pellet): 3416, 1625, 1580, 1223, 1104, 868, 725 cm^{-1}. UV-Vis (λ, nm): 300 and 619 nm.

The DNA binding and antimicrobial activity experimental details were given in literature[19].

2.4 Copper analysis

Copper content in the copper(II) complexes was estimated by the following method[20]. A known weight of the complex (0.02 g) was dissolved in 2 ml of concentrated nitric acid. The solution was gently warmed. After being cooled, the pH of the solution was adjusted to > 5 with 6M NaOH. The solution was transferred into 10 ml volumetric flask and made upto the mark with aqueous NH_3. The absorbance of this solution was measured against a reagent blank. From the absorbance, the concentration of copper was calculated.

3. Results and Discussion

3.1 General Aspects

These complexes are synthesized by ligand substitution method; the synthetic strategy of the complexes is outlined in Scheme.**1** given below. The synthesized complexes are more stable and they are soluble in water and in other organic solvents. The elemental analysis data of the copper(II) complexes agree with the theoretical values.

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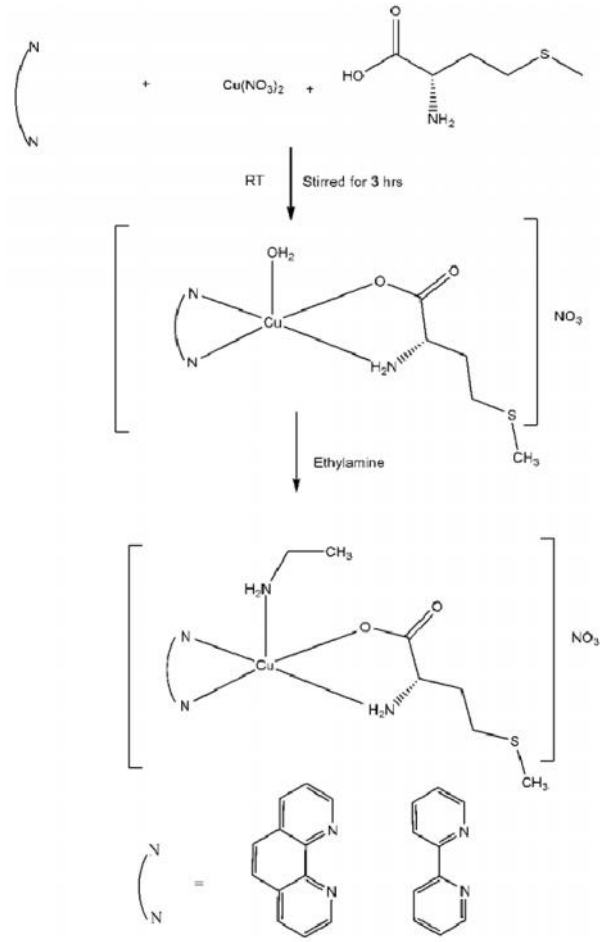

Scheme 1: Synthesis of complexes **1** and **2**.

3.2 Electronic absorption spectra

In the UV region, the complex presented in Fig 1.1, bands around 273 and 300 nm which can be attributed to π→π* transition of the coordinated phenanthroline ligand, and the complexes **1** and **2** exhibits d-d band at UV-Visible spectra. The complexes are in good agreement with the previously reported square pyramidal geometry of the complexes[20-22].

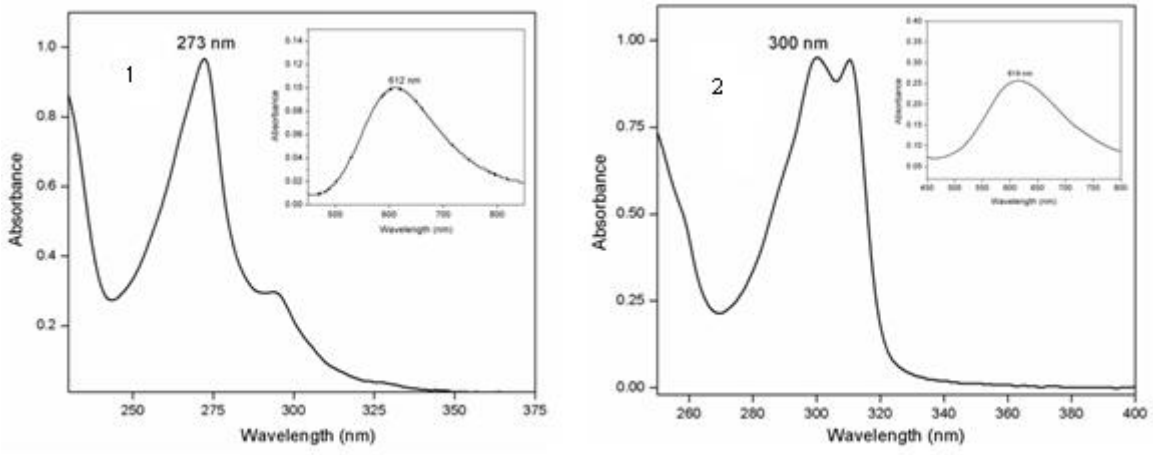

Fig 1.1: UV-Visible spectra of complexes **1** and **2**

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3.3 Infrared spectra

In the IR region, for complexesthe band around 3419 cm^{-1} and 3421cm^{-1} can be assigned to γ (N-H) stretching frequency of amino acid. The coordination of nitrogen atoms of heterocyclic base with copper metal ion can be examined by δ(C-H) for phenanthroline 853 cm^{-1} and 737 cm^{-1} is shifted to 825 cm^{-1} and 777 cm^{-1} and the band around 1383 cm^{-1} and 1384 cm^{-1} has been assigned for γ(N-O) of nitrate ion (Fig 1.2).

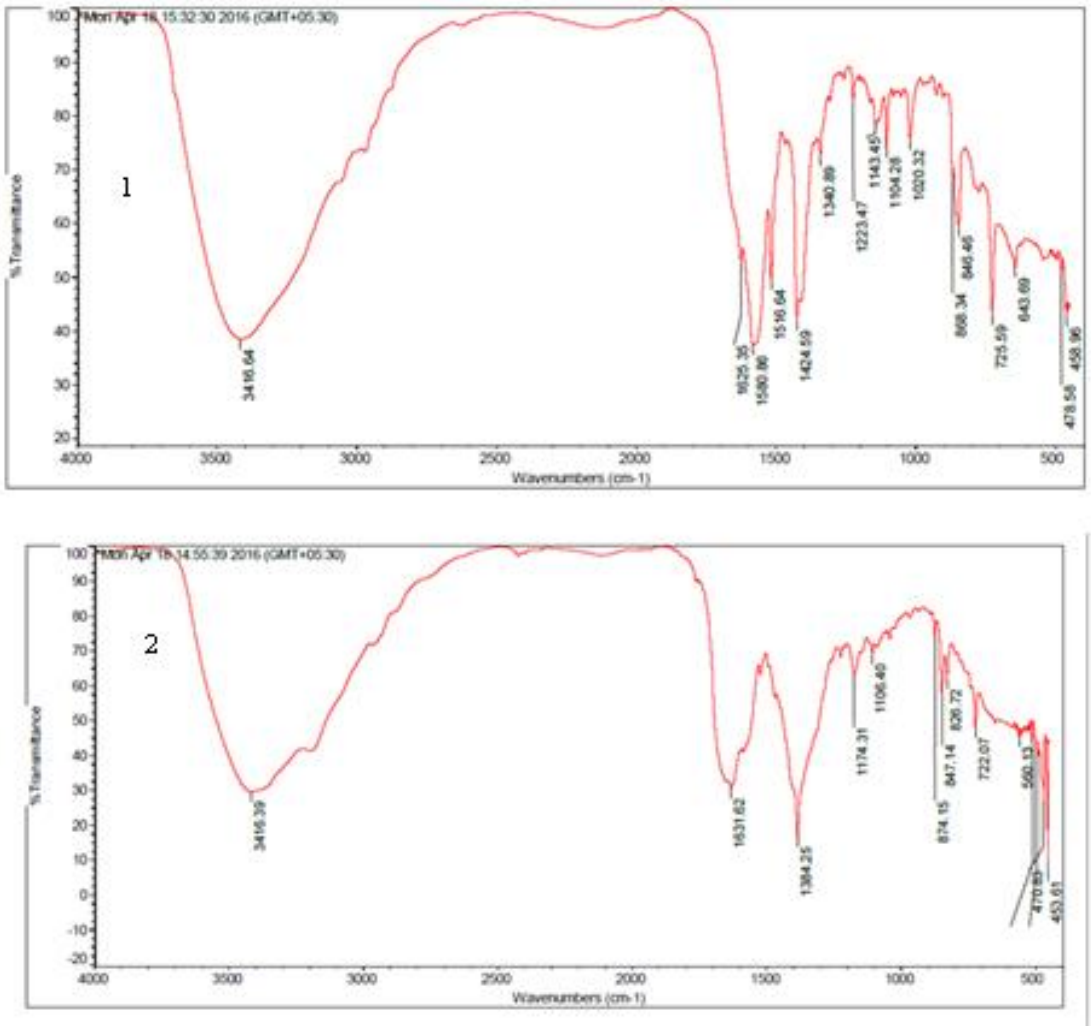

Fig 1.2: Infrared spectra of complexes **1** and **2**

3.4 Electron Paramagnetic Resonance

The solid state EPR spectra of the copper (II) complexes were recorded in X-band frequencies (Fig. 1.3). At room temperature, complexes **1** and **2** exhibit well defined single isotropic lines. 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.EPR spectra of mononuclear complexes copper(II) species with S=1/2, those with two signals ($g_{\perp}$and $g_{\parallel}$), on comparing these two signals $g_{\perp}(x,y) > g_{\parallel}(z)$ ($B_{\perp}(x,y) < B_{\parallel}(z)$) representing the elongated axial symmetry of the spin tensor.

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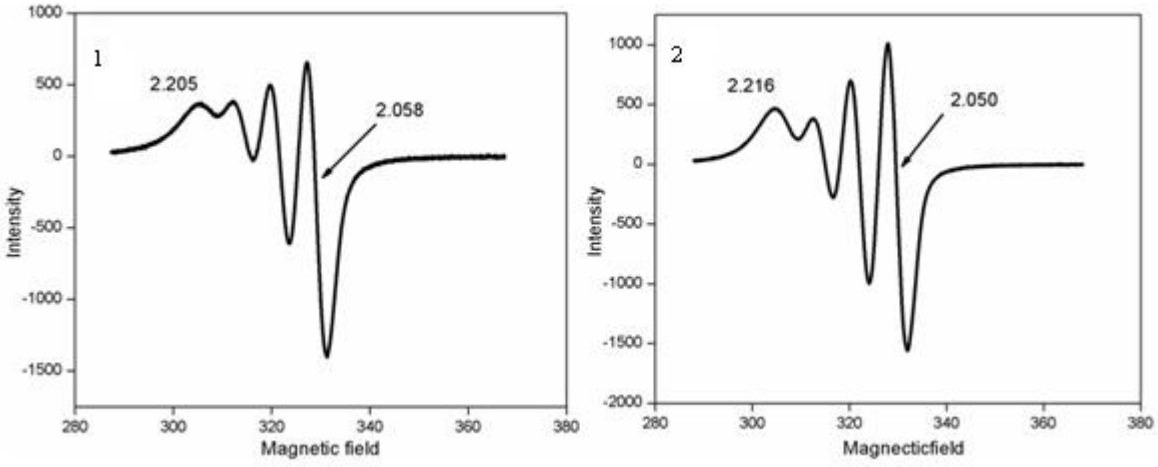

Fig 1.3: EPR spectra of complexes **1** and **2**

4. DNA binding studies

4.1 Electronic spectral studies

Electronic absorption spectroscopy was an effective method to examine the binding mode of DNA with metal complexes. In general, hypochromism and red shift are associated 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 1.4 shows the UV absorption spectral study of copper (II) complex in the absence and presence of DNA. The absorption intensity of the complex **1** increased (hyperchromism and blue shift) evidently after the addition of DNA, which indicated the interactions between DNA and the complex through intercalative mode.

We have observed blue shift along with significant hypochromicity for complex **2**. On comparing the Kb values (1.28 X 10^4 M^{-1} (**1**) and 1.05 X 10^4 M^{-1}) of complexes, complex **1** have higher value than complex **2**. So binding propensity of the phen complex **1** is high 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 phenanthroline ligand to the minor groove while the other phen making favourable contacts within the groove[24, 25].

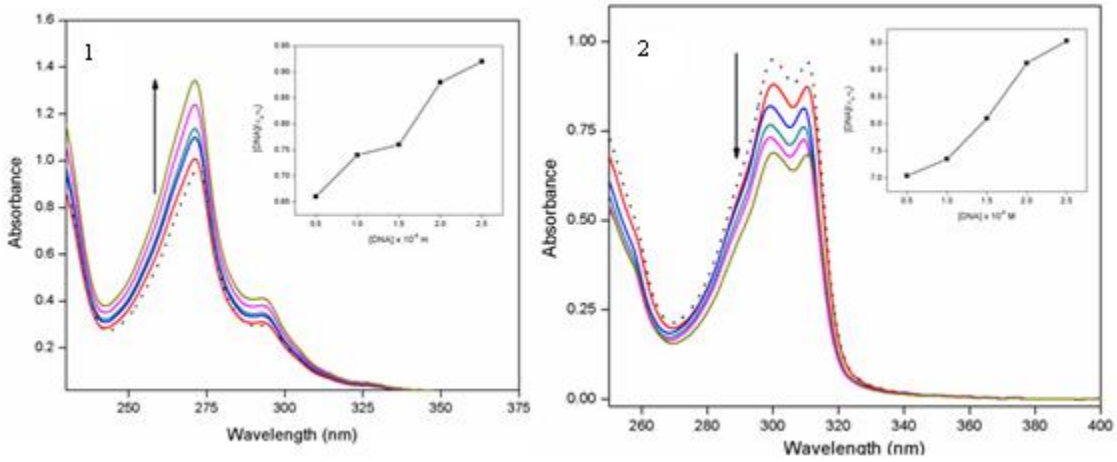

Fig 1.4: Absorption spectral traces on addition of CT DNA to complexes **1** and **2** (shown by arrow). Inset plot of [DNA]/(ε_a-ε_f) vs [DNA] for absorption titration of CT DNA with complex at 271 nm.

5. Fluorescent spectral studies

As the copper (II) complexes are non-emissive, competitive binding studies with EtBr 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 EtBr ([DNA]/ [EtBr] = 1) and then measurement of intensity of emission. The observed enhancement in emission intensity of EtBr bound to DNA is due to intercalation

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of the fluorophore in between the base pairs of DNA and stabilization of its excited state (Fig 1.5)[26]. Addition of all the complexes to CT-DNA incubated with EtBr decreases the DNA induced enhancement in emission to the same extent. This suggests that the complexes displace DNA-bound EtBr and bind to DNA at the intercalation sites with almost the same affinity, which is consistent with the above spectral results suggesting partial intercalation of the phenanthroline ring.

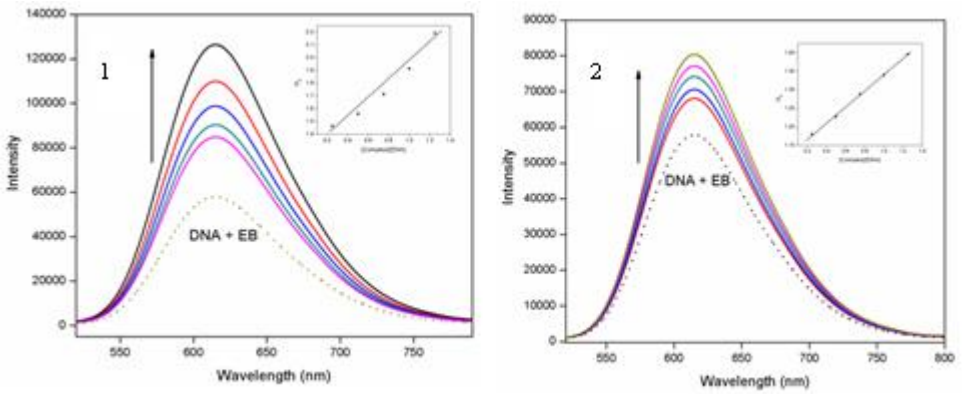

Fig 1.5: Emission spectra of EB bound to DNA in the absence (dotted line) and the presence (dashed line) of complexes **1** and **2**. Arrow shows the intensity changes upon increasing the concentration of the complex. Inset: Stern–Volmer quenching curves.

6. Viscosity measurements

To further explore the binding mode of the copper(II) complex with DNA, viscosity measurements were carried out. Since the relative specific viscosity (η/η_0) (η and η_0 are the specific viscosities of DNA in the presence and absence of the complex, respectively) of DNA reflects the increase in contour length associated with separation of DNA base pairs caused by intercalation, a classical intercalator such as ethidium bromide could cause a significant increase in viscosity of DNA solutions. In contrast, a partial and/or non-classical intercalation of the ligand could bend or kink DNA, resulting in a decrease in its effective length with a concomitant increase in its viscosity[27, 28], while the electrostatic and groove binding cause little or no effect on the relative viscosity of DNA solutions. Therefore viscosity measurements, which are sensitive to the changes in the contour length of DNA, are useful to probe for DNA intercalation by complexes.

The plots of relative specific viscosities versus 1/R = ([Complex]/[DNA]) are shown in Fig 1.6. The relative specific viscosity increases with increasing concentration of the complex. However, the increase in the viscosity was much less compared to that of classical intercalators like ethidium bromide in the same DNA concentration range. This observation supports the above spectral studies which suggest that the complex **1** intercalates with the DNA base pairs and complex **2** involve through groove binding. Intercalation results in lengthening of the DNA helix due to base pairs being separated to accommodate the binding ligand, leading to an increase in viscosity of the solution[29, 30].

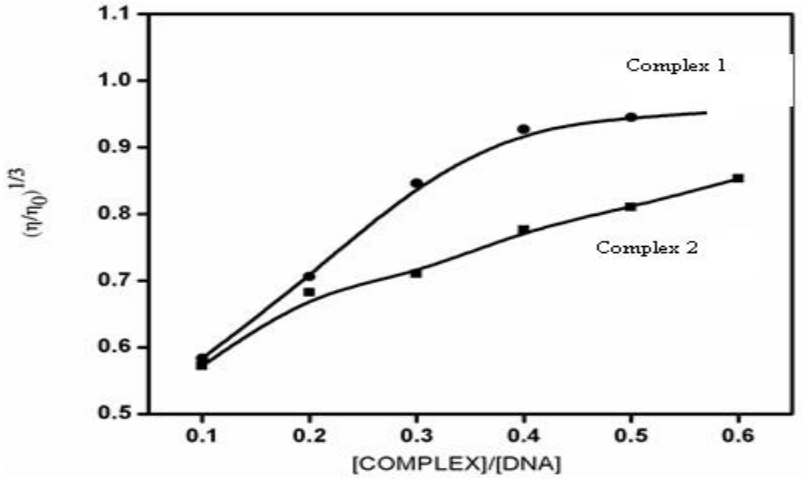

Fig. 1.6: Effect of increasing amounts of complexes (**9** and **10**) on the relative viscosities of CT DNA at 25^0C.

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7. Cyclic voltammetry studies

The cyclic voltammetric (CV) response for complexes **1** and **2** in Tris–HCl buffer (pH 7.28) in the presence and absence of CT DNA is shown in Fig 1.7. In the forward scan, a single cathodic and anodic peak was observed, which corresponds to the reduction and oxidation of complexes, which indicates that the process is reversible. When CT-DNA is added to a solution of complexes, marked decrease in the peak current and potential values were observed. The cyclic voltammetric behavior was not affected by the addition of very large excess of DNA, indicating that the decrease of peak current of complexes after the addition of DNA due to the binding of complex to the DNA[31]. When concentration of DNA increased, the changes in peak current and potential become slow. This reveals that the complexes were interact with Calf thymus - DNA.

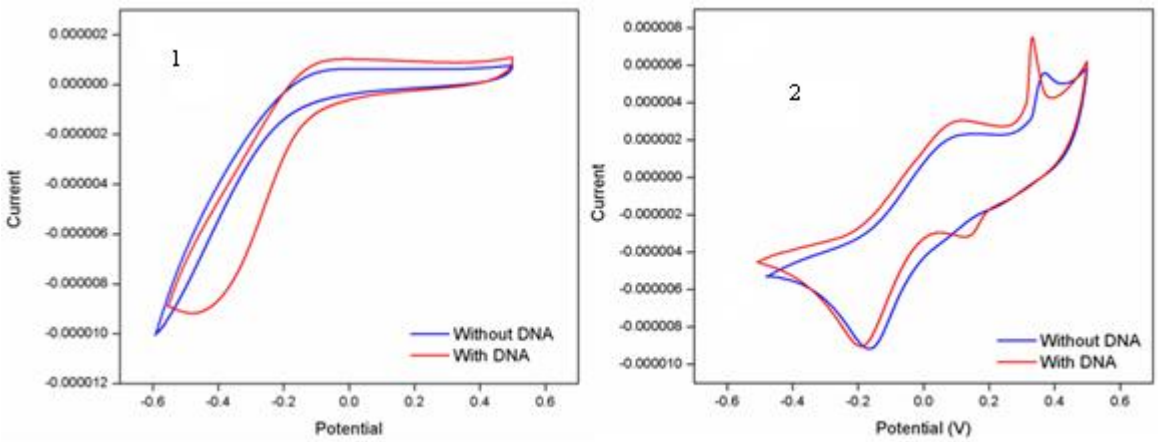

Fig 1.7: Cyclic voltammogram of complexes (**1** and **2)** in the absence (dashed line) and presence (dotted line) CT DNA.

8. Antibacterial and antifungal activity

The copper (II) complexes were screened in vitro for its microbial activity against certain pathogenic bacterial and fungal species using disc diffusion method. The complex was found to exhibit considerable activity against bacteria and the fungus. The test solutions were prepared in double distilled water and the results of the antimicrobial activities are summarized in Table 1.1. Zoroddu et al., 1996[32] have reported that copper complex show any significant activity against the Gram positive and Gram negative bacteria. Recently Patel et al[33], 2005, have indicated that the copper (II) complex with L-phenylalanine has exhibited considerable activity against some human pathogens.

Table 1.1: Antimicrobial activity of complexes **1** and **2**.

S.No	Name of microorganism	Complex 1	Complex 2	Disc (Ciprofloxacin/Amphotericin - B)
Antibacterial activity				
1	*Staphylococcus epidermidis*	20	22	14
2	*Streptococcus fecalis*	14	31	20
3	*Bacillus subtilis*	24	33	13
4	*Klebsiella pneumoniae*	23	29	19
5	*Escherichia coli*	25	17	21
6	*Proteus vulgaris*	20	34	21
Antifungal activity				
1	*Aspergillus niger*	8	11	12
2	*Aspergillus flavus*	7	10	9
3	*Candida tropicalis*	9	7	10
4	*Aspergillus fumigatus*	8	8	9
5	*Aspergillus terreus*	13	11	11
6	*Candida albicans*	12	10	10

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In our biological experiments, using copper(II) complexes, we have observed good antibacterial and antifungal activity (Fig 1.8).

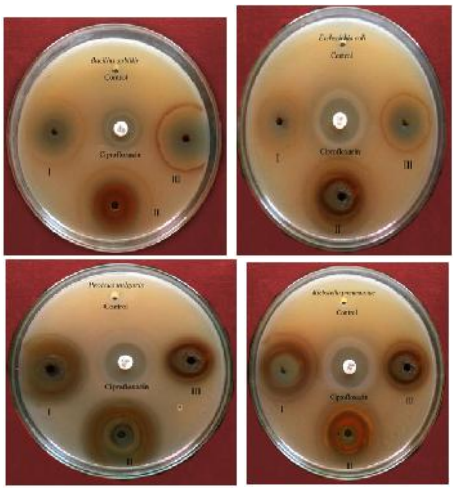

Fig 1.8: Antimicrobial activity of complexes **1** and **2**.

Particularly, complex **2** has very high biological activity against *Bacillus subtilis* (Table 1.1). Complexes **1** and **2** have good antifungal activity against *Aspergillus terreus*. It may be concluded that our copper (II) complexes inhibits the growth of bacteria and fungi to a greater extent.

9. *Anticancer activity*

The cytotoxicity of the complex to be used as chemotherapeutic agents was studied using MTT assay. The ability of the complex on HepG2 cells was tested with or without various concentrations (10–50 µg/mL) of the complex for 24 h. Cells incubated with different concentration of Doxorubicin served as positive control. After incubation period, MTT assay was carried out to calculate the cell death percentage. For each concentration of the complex cells were incubated in triplicate. The (**Figure. 1.9**) clearly illustrates that there is a clear decrease in the live cells number in the cells incubated with complex in a concentration dependent manner. Viability of cells incubated without any compound was considered as 100% and the percentage of live cells incubated with compounds are given as relative to the control. The IC50 values of the complex is 91.82µgm/ml respectively.

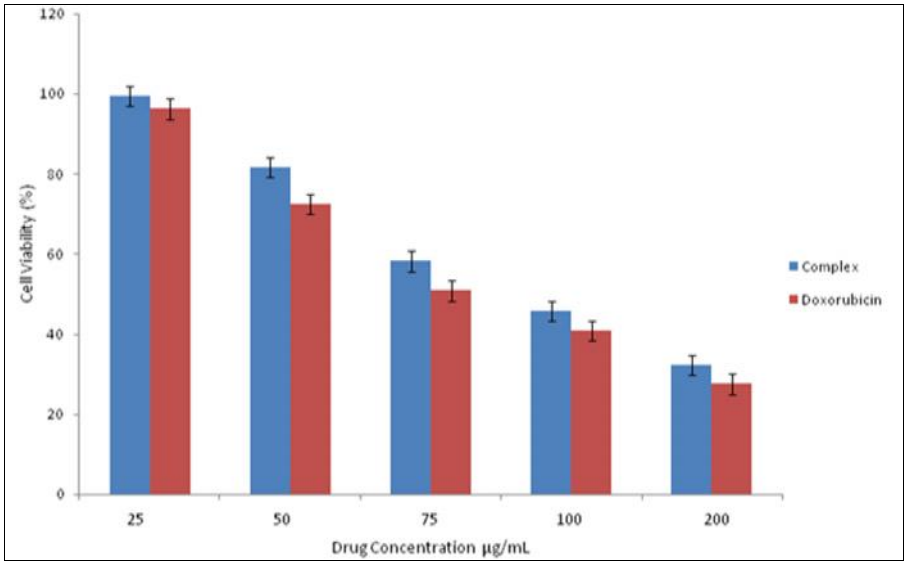

Figure 1.9: Cell Viability of $HepG_2$ cells after treatment with complex at different concentration at 24 hours.

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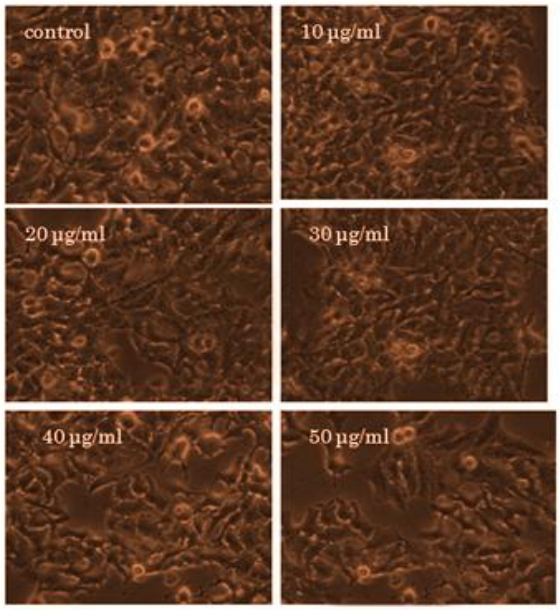

Figure 1.10: Morphological changes after treating complex **1** with HepG2cell after an incubation period of 24 hours.

Thus, interestingly, the phenanthroline complexes show lower cell killing activity than the bipyridyl complexes, which more strongly bind and cleave DNA. Also, the higher cytotoxicity is consistent with its stronger DNA binding and more efficient oxidative DNA cleavage. Further, the cell killing activity of mixed ligand Cu(II) complexes containing phen co-ligand depends on the primary ligands, Furthermore, we have already shown that the mixed ligand Cu(II) complexes of amino acid co-ligands exhibit cell killing activity higher than the covalently DNA binding Cu(II) complexes[34]. Thus, the present complexes containing phen as co-ligand, which involves in non-covalent DNA interaction, show better cytotoxicity than 1:1 metal:ligand complexes.

Very recently, mixed ligand copper(II) complexes have been found to exhibit prominent anticancer activity by inducing apoptosis and, interestingly, they are found to strongly bind and cleave DNA[35-37]. In general, redox-active agents that damage DNA in vitro are thought to exhibit apoptotic activities in live cells by inducing oxidative stress and/or DNA damage[38]. Sigman and his co-worker have shown that copper complexes of 1,10-phenanthroline act as effective chemical nucleases with a high preference for double-stranded DNA in the presence of molecular oxygen and a reducing agent[39,40]. Reedijk and co-workers have found that [CuII(pyrimol)Cl] brings about efficient self-activated DNA cleavage and cytotoxic effects toward L1210 murine leukemia and A2780 human ovarian carcinoma cell lines[41]. Sadler and diimines as co-ligands exhibit cytotoxic and antiviral activities. Burstyn and coworker have found that copper(II) complexes of macrocyclic triamines promote the hydrolytic cleavage of plasmid DNA[42]. Chakravarty and his coworkers[43] have reported several Cu(II) complexes that could show photoinduced DNA and protein cleavage activity for their potential application as photodynamic therapy and anti-metastasis agents. Several Cu(II) complexes, which possess biologically active ligands, demonstrate high nucleobase affinity and nuclease activity and are found to have the potential to serve as anticancer agents[44]. Interestingly, phen complexes exhibit stronger DNA binding, more efficient DNA cleavage ability and also more potent cytotoxicity than the bipyridyl complexes.

10. Conclusion

We described here about our new copper (II) complexes. Further characterization of the complexes was achieved through physico-chemical and spectroscopic methods. The effectiveness of binding of complex is being confirmed by means of hyperchromism and hypochromism in the electronic spectral studies and increase in the intensity of emission in the case of emission spectral studies. Besides that, the effectiveness of binding is also confirmed by the viscometric and cyclic voltametric studies. This shows that the complex **1** is intercalative and complex **2** is electrostatic or groove binding. Both the complexes exhibit good antibacterial and antifungal activity.

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