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Synthesis, characterization, DNA binding and anticancer property of *cis* chlorodimethylsulphoxide(S)bis(1,10-phenanthroline) ruthenium(II) chloride

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ABSTRACT

The six coordinated Ruthenium complex of formula [Ru(phen)$_2$(dmso)Cl]$^+$Cl$^-$ (cis-chlorodimethylsulphoxide-S-bis(1,10-phenanthroline) ruthenium (II) chloride) has been prepared, and characterized structure on the basis of spectroscopic data, such as FT-IR, ^{1}H NMR and UV-Vis spectroscopy. The molecular structure of the complex determined by X-ray diffraction studies is found to be octahedral. Also the bond lengths, bond angles and dihedral angles are found complementary to octahedral structure. Further studies on the binding of this complex with Calf Thymus DNA (CT-DNA) have been carried out by using UV-visible spectroscopy, electrochemical and gel electrophoresis studies. The evidences of CT-DNA binding with this complex have been indicated from these studies. The anticancer activity of this compound against Dalton's lymphoma (in vitro and in vivo) is found promising.

Keywords: DNA, Ruthenium complex, Calf thymus, Anticancer activity, Dalton's Lymphoma.

INTRODUCTION

The transition metal complexes have been found useful in pharmaceuticals since the discovery of cisplatin [1-10]. Several water soluble metal complexes attracted considerable interest owing to their good anticancer or antibacterial properties [8-15]. Among the metal complexes reported, the ruthenium complexes have certain advantages because of its solubility in water as well as low toxicity [11-12]. Although there are several reports on the synthesis and medicinal properties of ruthenium complexes, the DNA targeted Ruthenium complexes with intercalating ligands may be important anticancer agent. The role of aromatic ligands may be prominent for enhancing biological properties as well as the DNA binding than the existing complexes.

The Imidazole(Im) and –NH_3 ligands have been used in the synthesis of [Ru(H_2O)(NH_3)$_5$], cis-[$RuCl_2(NH_3)_4$]Cl and trans-HIm[$RuCl_4Im_2$], which are DNA binding complexes. In most cases, DNA binding of drugs usually correlates with cytotoxicity [10-15]. The complex [Ru(H_2O)(NH_3)$_5$] binds selectively with guanine nucleobase of both single and double stranded DNA, but some Ruthenium complexes bind within adenine and cytosine residues of DNA [15-16]. There observed distinct coordination bond between Ru metal centre and guanine in the crystal structure of trans-[Ru(H_2O)(Py)(NH_3)$_4$] bonded DNA. The EDTA has been used as ligand in some Ru(III) and Ru (IV) complexes having anticancer activity, and also bind with DNA. Several compounds, cis-[$RuCl_2(NH_3)_4$]Cl, fac-[$RuCl_3(NH_3)_3$] and trans-Him[$RuCl_4(Im)_2$] can target the primary tumour cells, and are known for their anticancer activity [15]. Many complexes with 1,10 phenanthroline(phen) ligand have been known for their anticancer property. However low solubility in water is the major problem for such complexes, and DMSO ligand has been found in water soluble metal complexes. So, the solubility may be enhanced by using DMSO molecules as ligand in

ruthenium complexes along with phen ligand. The cis-[$RuCl_2(DMSO)_4$] acquires significant anticancer activity, and also relatively non toxic compared to other metal complexes [17-18]. The trans-[$RuCl_2(DMSO)_4$] can rapidly looses two DMSO molecules forming cis diaquo species, and also undergo chloride dissociation reversibly [19-20]. The basis of anticancer activity of these complexes is quite complicated. The dissociation of chloride is the primary factor for anticancer activity, and the chloride concentration in serum can also suppress the rapid dissociation of O-bonded DMSO molecules. But cisplatin can exist as neutral complex in blood serum that make it easier to cross the lipid bilayer, where the chloride lost and DNA binding could probably depend on the chloride concentration in intracellular medium [15-18]. All these complexes show almost similar anticancer activity, but not superior to cisplatin. Similarly, NAMI emerges out as antimetastatic agent, but only small fraction of the compound can reach the tumour target [21-23].

Furthermore, considerable interest has been given to synthesize ruthenium complexes with phen ligand [22-35]. The well known complex $Ru(phen)_3$ emerges as an important class of DNA binding anticancer agent [23]. Hence, the synthesis of various derivatives of this compound has been taken up. As part of our onging research on the synthesis of water soluble Ruthenium complexes, we performed the synthesis and characterization of [$Ru(phen)_2(dmso)Cl]Cl$ as a noval ruthenium complex. The complex contains two phen ligands coordinated to Ru, which lie at the same plane, and one S bound DMSO. The overall reaction steps followed in the synthesis of this complex is shown **scheme I**. Here, we report the structure, DNA binding and anticancer activity of $[Ru(phen)_2(dmso)Cl]^+Cl^-$ complex.

MATERIALS AND METHODS

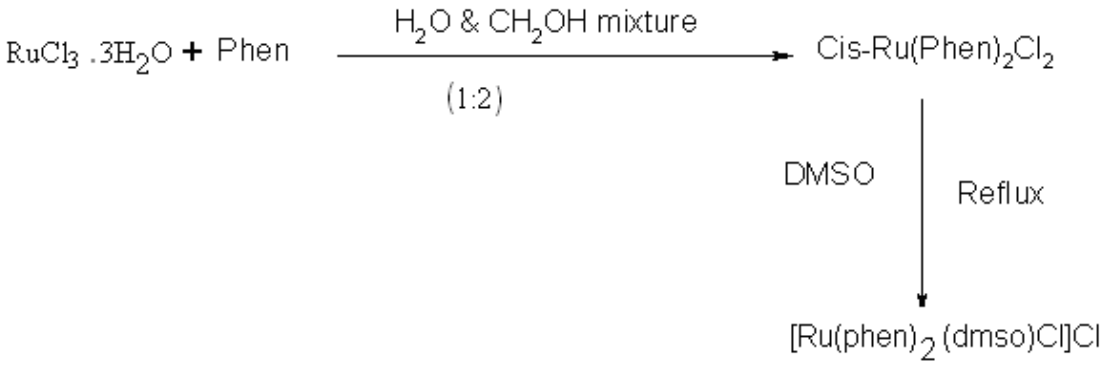
Experimental section:

Materials:

Analytical grade $RuCl_3.3H_2O$ was purchased from Sigma, and used without purification. Calf Thymus DNA (CT-DNA), Tris buffer and tetrabutylammonium perchlorate (TBAP) were obtained from Sigma-Aldrich, USA. The 1,10 phenanthroline(phen) and other solvents were used in the synthesis as received. CT-DNA was dissolved in Tris buffered saline at pH 7.6 (TBS), and dialyzed overnight against the same buffer so that A_{260}/A_{280} of the dialyzed solution should be >1.8.

Preparation:

Synthesis of chloro-dimethyl sulphoxide(s)bis(1,10 phenanthroline) Ruthenium II chloride(RuP): Initially, the compound cis-$Ru(phen)_2Cl_2.2H_2O$ (0.5 mM) was prepared by refluxing the solutions of $RuCl_3.3H_2O$ and phen ligand in ethanol and water mixture for 1 hour as per usual procedure [30]. The solution was mixed with DMSO (0.5 mM) after cooling, and again refluxed for half an hour. The solution was heated in a water bath to evaporate the solvent, and subsequently purified in column. The purity of the compound was checked by thin layer chromatography (TLC). Single crystal of RuP, suitable for X-ray diffraction was obtained by slow evaporation of the solution of the complex in ethanol/water mixture. A solid deep orange colored compound was collected, and the yield was found approximately 75%.



Scheme 1

Characterization procedure: The IR spectra of the compound have been recorded as KBr pellets on a Perkin-Elmer FT-IR spectrophotometer. The UV-visible spectra were taken in aqueous solution in a Shimadzu UV-2401 PC spectrophotometer. The ^{1}H NMR spectra was recorded on a Bruker Ultrashield 300 MHz NMR spectrometer using TMS as the internal standard.

Crystallography of $[Ru(phen)_2(dmso)Cl]^+Cl^-$ complex: Single crystal X-Ray diffraction data was obtained at 100 K with Bruker smart AXS diffractometer with graphite-monochromatised Mo-Kα radiation by ϕ-ω scans. We have used full matrix least square on F^2. The molecular graphic structure was analyzed by ORTEP plot program. The crystallographic data and refinement details are given in **Table SI** (supplementary). The structure was refined by using SHELXL-97, other materials were prepared by wingx publication routine (**Figure 1)** [31]. (Depository number: CCDC 772893)

Infrared spectra: The IR peaks with tentative assignments (ν_{max}/cm^{-1}) at 1646 (C=N aromatic), 1086 (S=O), 3097 (C-H, SP^2 Carbon), 2920, 2852 (C-H methyl) 1538, 1512, 1458 (C=C aromatic), 449, 414 (Ru-N and Ru-S) were observed.

UV-visible: The UV-visible absorbance spectra of the solution of $[Ru(phen)_2(dmso)Cl]^+Cl^-$ complex in water shows two near visible region at λmax 340 nm and other at 262 nm.

^{1}H NMR: The RuP complex is diamagnetic in nature, and it exists as bivalent ruthenium (low spin d^6, S=0). ^{1}H NMR spectra of the complex was recorded in D_2O solution. We observed three signals at 8.42, 7.79 and 7.32 ppm, which correspond to phen ligands, and the highly intense peak appeared at around 2.04 ppm assignable to $-(CH_3)_2$ proton in DMSO.

DNA binding: The UV-Visible, Flourescence, Electrophoresis and Electrochemical studies of RuP complex with Calf Thymus DNA (CT-DNA) have been carried out. There observed distinct spectral shifts (UV-visible and Flourescence) after mixing the RuP complex with CT-DNA (**Figures 2a and 2b, 3**). Shifting of redox potential is another supporting evidence of CT-DNA binding. (**Figures 4a and 4b**). The variation of mobility and brightness of gel having different RuP concentrations in the Electrophoresis experiment some indications of CT-DNA binding by RuP(**Figure 5**).

UV-visible Absorption titration:
The UV-visible absorption spectra of the complex in the presence of CT-DNA at various concentrations are shown in **Figures 2a and 2b.** The binding of RuP complex with CT-DNA has been monitored from UV-visible absorption spectral shift. The experiment was performed with constant concentration of RuP and varying the concentrations of CT-DNA from $0.59X10^{-5}$ M to $4.1X10^{-5}$ M. The two distinct intense transitions at 340 nm and 262 nm in the absorption spectra are characteristic of Ru (d-d) and intra-ligand p-p* transitions. The spectral shifts from 340 nm to 375 nm in the visible region (λ_{max} 340 nm) have been observed after mixing with different concentrations of CT-DNA (**Table 1** and **Figure 2)**. The intrinsic binding constant (K_b) of the complex was estimated from the following equation [32-33],

$$\frac{\varepsilon_b-\varepsilon_f}{\varepsilon_a-\varepsilon_f} = \frac{1}{[DNA]K_b} + 1$$

where ε_a, ε_f and ε_b are the extinction coefficients of, observed solution, free complex and maximum CT-DNA mixing complex respectively. The K_b value of $3.46X10^4$ $M^{-1}$was obtained from the slope of the plot shown in **Figure 2b**.

Flourescence emission titration: Furthermore, fluorescence titration experiment has been performed to investigate the binding of RuP with CT-DNA. **Figure 3** shows the emission spectra of the complex with various concentrations of CT-DNA. The intensity of the complex increased steadily with the increase of CT-DNA concentrations from $0.59X10^{-5}$ M to $3.50X10^{-5}$ M (**Table 2**).

Electrochemistry : Cyclic voltammetric study for $[Ru(phen)_2(dmso)Cl]^+Cl^-$ complex has been carried out in DMSO solution(0.005 M) containing supporting electrolyte TBAP (0.1 M) by using Ag/Ag^+ as reference electrode, and a

glassy carbon as working electrode. The inert environment was maintained by passing N_2 gas through the solution to remove oxygen. The voltamogram shows distinct oxidation and reduction peaks of a reversible electron transfer reactions at scan rate of 100 mVs^{-1}. The shift of redox potential ($E_{1/2}$) from 152 mV to 188 mV in presence of CT-DNA is shown in **Figures 4(a)** and **4(b).**

Electrophoresis experiment: The binding of RuP complex with CT-DNA was further analyzed by electrophoresis experiment. The solution of the complex and CT-DNA were prepared in tris-HCl buffer at pH 7.6. The binding between the complex and CT-DNA was monitored by preparing three solutions with of the complex difference concentrations and incubated for 24 hours at 37ºC before running Gel Electrophoresis. The three solutions were placed at three different lanes 1, 2 and 3 in the gel having concentrations 6 mM, 3 mM and 2 mM respectively, and CT-DNA (5 mM) was placed in lane C. The samples were run for 4 hours at different voltages (half an hour at 50 V, 1 hour at 60 V, half an hour at 70V and 1hour at 80 V) on a 1% agarose gel in tris-borate EDTA. The gel was photographed under UV light. It has been found that lane C moves from –ve to + potential of the gel slightly faster than lanes 1, 2 and 3, and also the brightness of the bands decrease from lane 3 to 1 (**Figure 5**).

Biological studies of Chlorodimethylsulphoxide-S-bis(1,10phenanthroline) ruthenium(II) chloride complex :
1. Effect of Ru complex on the survival of Dalton's lymphoma cells *in vivo*:
Dalton's lymphoma cells were isolated from the peritoneal cavity of tumor bearing mice (control and treated with different concentrations of Ru complex). 2-3 ml of sterile phosphate buffered saline (PBS) was injected into the peritoneal cavity and the fluid containing the tumor cells was withdrawn, collected in sterile petridishes and incubated at 37^0C for 2h. The cells of macrophage lineage adhered to the bottom of petridishes to form a confluent monolayer. The non adherent population of lymhoma cells was gently aspirated out and washed repeatedly with PBS. The viability was tested by Trypan Blue Exclusion Test (**Figure 6**).

2. Effect of Ru complex on the survival of Dalton's lymphoma cells *in vitro*:
For cytotoxicity assay *in vitro*, Dalton's lymphoma cells were plated at high density ($8x10^7$ cells/dish) at time zero in DMEM containing fetal calf serum, 10mM $NaHCO_3$, 0.3% glutamine and different concentrations of Ru complex for a fixed treatment duration of 1h. Control dishes were treated with equal amount of PBS used as a solvent for Ru complex. At the end of drug treatment, cells were harvested and washed with PBS, resuspended in ADM with DFCS and incubated for 72h at 37^0C. After incubation cells were trypsinized and viable cells were counted by trypan blue exclusion test (**Figure 7**).

3. Effect of different concentrations of Ru complex on mice bearing Dalton's lymphoma:
Control and experimental animals were selected randomly and divided into groups of 10 mice each according to randomized block design. Each animal was transplanted with $3x10^6$ cells/mice. On day 4 post-tumor transplantation, experimental mice were treated with single i.p. injection of different concentrations of Ru complex. Control animals were injected with equal amount of PBS. In each group mean survival time, % increase in the life span, % of more than 60 day survivors and tumor free survivors were calculated. % increase in the life span was calculated as %ILS= [(T-C)/C] where T is the mean survival time of experimental mice and C is the mean survival time of Control mice. Each set was repeated thrice and the results were pooled together.

All the concentrations of Ru complex were able to increase the mean survival time of tumor bearing mice. Control animals could survive for 9 days whereas tumor bearing mice treated with 20-50 mg/kg Ru complex were able survive up to 56 days (Figure 8). The increase in the life span of tumor bearing animals was found to be 337-650% when treated with different concentrations of Ru complex (Figure 9).

It has been found that 40 and 50 mg/kg of RuP are the more effective doses. 30% mice treated with RuP appeared as tumor free survivors (Figure 10).

RESULTS AND DISCUSSION

The compound consists of $[Ru(phen)_2(dmso)Cl]^+$ cation and a chloride counter anion. **Figure 1** shows two phen ligands, one DMSO and a chlorine atom coordinated with Ru . The phen ligands are in cis configuration and coordinated with Ru through the nitrogen atoms at distances 2.097 Å, 2.092 Å, 2.094 Å and 2.067 Å, respectively. The S atom of DMSO and Cl are coordinated at distances 2.263 Å and 2.413 Å. The geometry around Ru of $[Ru(phen)_2(dmso)Cl]^+$ cation is found to be octahedral. The geometrical parameters supporting this structure are

given in supplementary data. The coordination distances, Ru-N between phen ligand and Ru ranges from 2.067 Å to 2.097 Å. The Ru-Cl and Ru-S distances (2.413 Å, 2.263 Å) are slightly larger than Ru-N distances. The recorded infrared spectra of the complex have been found at 1086 cm^{-1}, 449 cm^{-1} and 414 cm^{-1}. The potential bonds for the observed spectral data are assignable to γ (S=O), γ (Ru-N) and γ (Ru-S) respectively. The structure has been compared with the available complex, cis-[chloro (dimethylsulfoxide)bis (1,10-phenanthroline) ruthenium(II)]-tetraphenylborate ($[Ru(phen)_2(dmso)Cl]^+$ $B(ph)_4^-$)(35). The geometries of both the complexes are octahedral. The Ru-N in $B(ph)_4^-$ complex is different from that of RuP, and the bond lengths ranges from 2.03 Å to 2.105 Å . Also the Ru-Cl distances are 2.403 and 2.438 A°, and Ru-S distance is 2.256 A ° (Table 6 in supplementary data). The geometrical parameters of $[Ru(phen)_2(dmso)Cl]^+Cl^-$ is somewhat different from that of $[Ru(phen)_2(dmso)Cl]^+B(ph)_4^-$. Both the complexes are monoclinic, the $B(ph)_4^-$ complex crystallized as P21/c space group unlike that of P2 (1)/n space group for RuP.

The compound was prepared from the reaction of $RuCl_3.3H_2O$ and phen ligand by refluxing in ethanol, and adding DMSO after cooling. The mixture was again refluxed for half an hour. Although the mechanism of the reaction cannot be fully traced, it may proceed the reaction steps given in **Scheme I**. Initially, the two Cl atoms might be replaced by phen ligands, then the DMSO molecule further reacts with $[Ru(phen)_2(Cl)_2]$ replacing the inner Cl atom to give $[Ru(phen)_2(dmso)Cl]^+$. However, the crystalline compound was analyzed by XRD experiment, and the ORTEP structure is shown in **Figure 1**. The prominent bonds (UV-visible) at 340 nm and 262 nm correspond to Ru and phen ligands. The ^1H NMR of this complex showed bands at 8.42, 7.79, 7.32 and 2.04 ppm assignable to aromatic phen ligand and DMSO (methyl group). The presence of these ligands evidenced by ^1H NMR and IR studies are found consistent.

Further studies have been performed to understand the binding of RuP with CT-DNA. With the increase of DNA concentrations, there observed significant red shift from 340 nm to 375 nm in the UV-Visible spectra **(Table 1** and **Figure 2)**. This spectral shift is the characteristics of CT-DNA binding with $[Ru(Phen)_2(dmso)Cl]^+$ complex. The intrinsic binding constant (K_b) is found to be $3.46X10^4$ M^{-1}. There observed large fluorescence spectral shift from 33.8 nm to 137.8 nm that may be due to the binding of RuP with CT-DNA (**Figure 3)**. The redox potentials obtained from square wave voltammogram of the complex and in presence of CT-DNA were observed at +152 mV and +188 mV (**Figures 4(a)** and **4(b)).** The +ve potential shift (+36 mV) of the complex after mixing with CT-DNA shows some evidences of CT-DNA binding with the complex. Moreover, electrophoresis experiment has been conducted to analyze the binding of CT-DNA with this complex. Migration of lane C slightly faster than the lanes 1, 2 and 3 from –ve to +ve potential in the gel electrophoresis might be due to CT-DNA binding. The brightness of the bands have been significantly decreased with increase of complex concentrations from lane 3 to 1, which is a clear indication of CT-DNA binding with this complex(**Figure 5)**.

The biological studies (in vitro and in vivo) of this complex have been performed against Dalton's lymphoma. The effects of this complex on the Dalton's lymphoma isolated from the peritoneal cavity of tumor bearing mice are found efficient. The survival of Dalton's lymphoma (in vivo) with different concentrations of complex, 10, 20, 30, 40 and 50 mg/kg of body weight are shown in **Figure 6**. It has been found that the viability of lymphoma cells is directly proportional to concentrations of the injected complex. The LC_{50} was found to be 40 mg/kg **(Figure 6).** Similarly, in vitro experiment has been carried out to understand the survival of cells with increasing concentrations of the complex (**Figure 7**). There exists a linear correlation between the concentrations of RuP complex and % survival of lymphoma cells. The IC_{50} was found to be 20 µg/ml **(Figure 7).** The doses 40 and 50 mg/kg of the complex were found to be more effective. 50% mice appeared as tumor free survivors after treatment with 50 mg/kg RuP complex and are still surviving without tumor reappearance **(Figure 10).**

Table 1.The wavelengths and corresponding absorbance of complex with and without mixing CT- DNA at different concentrations.

	Name	Wavelength(nm)	Absorbance
a	**DNA**	**260**	**0.061**
b	**Complex**	**340**	**1.208**
c	**Complex +0.59X10^{-5}M DNA**	**355**	**1.396**
d	**Complex +1.10X10^{-5}M DNA**	**358**	**1.727**
e	**Complex +1.78X10^{-5}M DNA**	**362**	**1.780**
f	**Complex +2.37X10^{-5}M DNA**	**364**	**1.903**
g	**Complex +2.96X10^{-5}M DNA**	**365**	**2.016**
h	**Complex +4.10X10^{-5}M DNA**	**370**	**2.067**

Table 2.The emission apex and fluorescence intensities of complex with and without mixing CT- DNA at different concentrations.

	Name	Apex(nm)	Intensity
a	DNA	563	33.8
b	Complex	560	88.0
c	Complex +0.59X10^{-5}M DNA	560	116.9
d	Complex +2.37X10^{-5}M DNA	560	125.0
e	Complex +3.50X10^{-5}M DNA	560	137.8

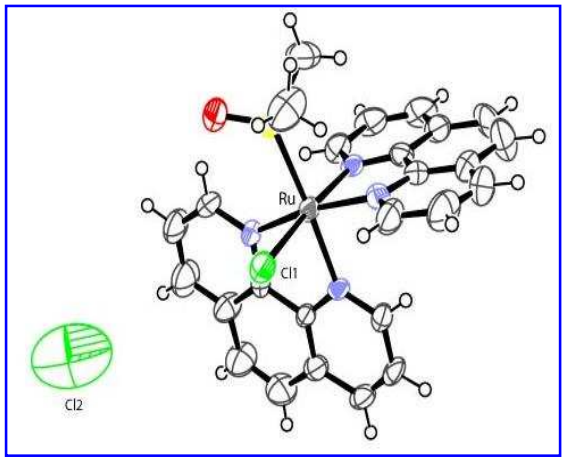
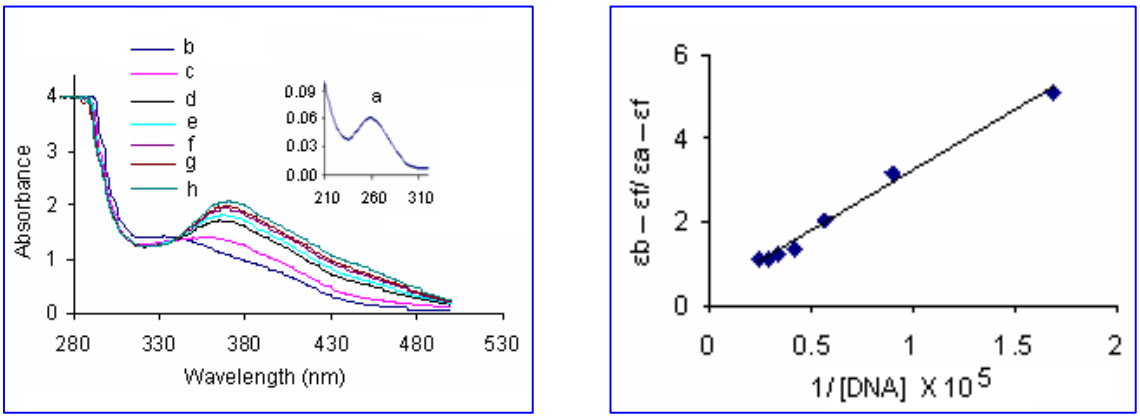


Figure 1. Structure of *cis* chlorodimethylsulphoxide-*S*-bis(1,10 phenanthroline) ruthenium(II) chloride.



(a) **(b)**

Figure 2. (a). UV-Visible spectra of RuP complex with and without mixing CT-DNA at different concentrations, along with simple CT-DNA and (b). plot of $\varepsilon_{b-}\varepsilon_{f}/\varepsilon_{a-}\varepsilon_{f}$ against reciprocal of concentration of CT- DNA (1/[DNA]).

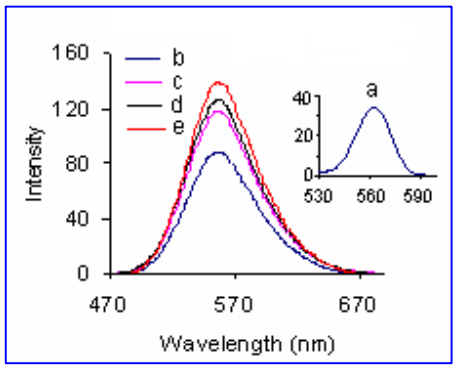
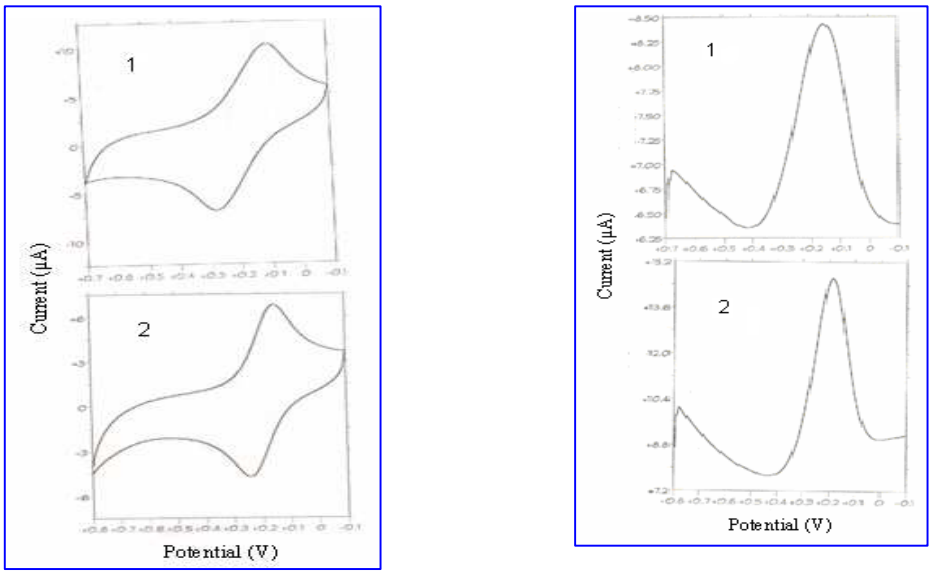


Figure 3. Fluorescence intensity of RuP complex with and without mixing CT-DNA atdifferent concentrations, along with simple CT-DNA.



(a) **(b)**

Figure 4. (a) Cyclic voltammogram and (b). Square wave voltammogram (1. and 2. for the RuP complex with and without mixing CT-DNA at different concentrations, respectively).

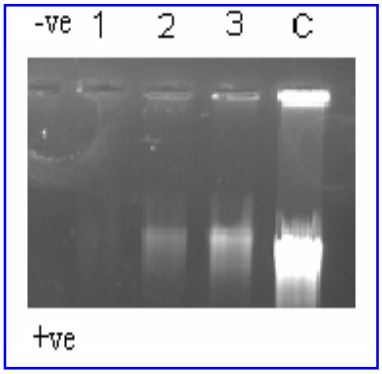


Figure 5. Gel electrophoresis of RuP complex with CT-DNA studied in tris-HCl buffer at pH 7.6 (concentrations decreases from Lane 1-3 respectively).

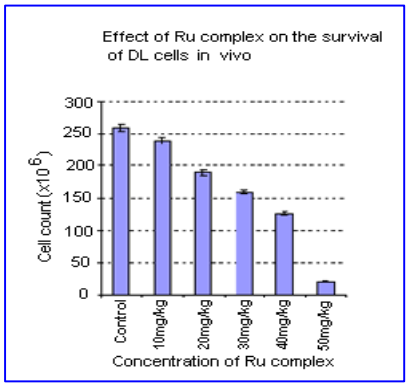


Figure 6. Effect of RuP on the survival of Dalton's lymphoma cells in vivo. The results are an average of five (n=5) independent experiments in triplicate and represented as mean ± SE. $p < 0.05$ vs control.

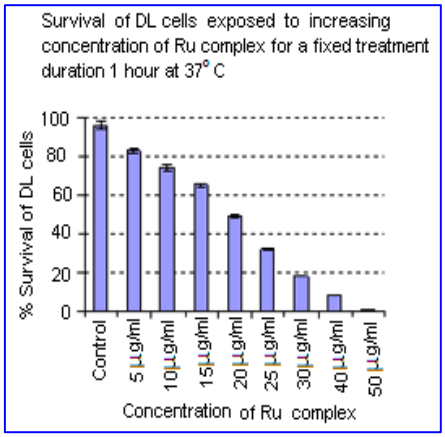


Figure 7. The results are an average of five (n=5) independent experiments in triplicate and represented as mean ± SE. p < 0.05 vs control.

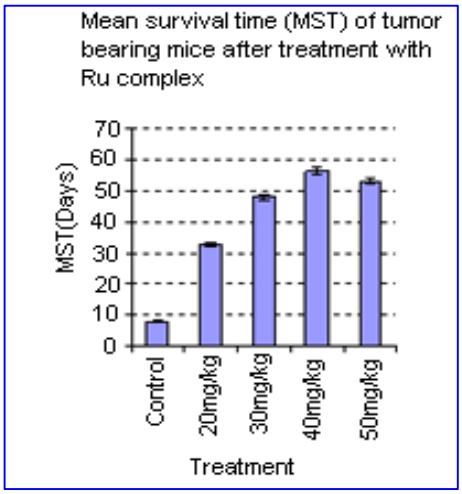


Figure 8. Mean survival time of tumor bearing mice after treatment with different concentrations of RuP.

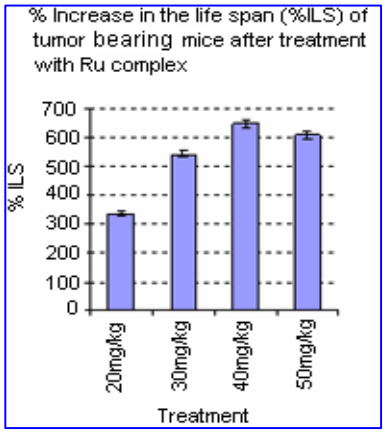


Figure 9. % increase in the life span of tumor bearing mice after treatment with different concentrations of RuP.

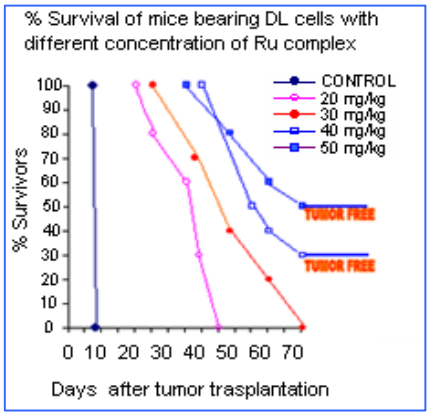


Figure 10. Effect of RuP on mice bearing Dalton's lymphoma. 30% and 50% tumor bearing mice became tumor free after treatment with 40 and 50 mg/kg of the complex respectively. Rest of the animals also exhibited significant (p< 0.05) increase in their life span compared to control.

Experimental data

Crystal data

Identification code	a-1-a	
Empirical formula	C26 H22 Cl2 N4 O Ru S	
Formula weight	610.51	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 15.2452(13) Å	□= 90°.
	b = 12.3301(11) Å	□= 113.827(5)°.
	c = 17.9292(17) Å	□ = 90°.
Volume	3083.0(5) $Å^3$	
Z	4	
Density (calculated)	1.315 Mg/m^3	
Absorption coefficient	0.772 mm^{-1}	
F(000)	1232	
Crystal size	0.50 x 0.30 x 0.20 mm^3	
Theta range for data collection	2.07 to 28.45°.	
Absorption correction:		
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7474 / 0 / 319	
Goodness-of-fit on F^2	1.000	
Final R indices [I>2sigma(I)]	R1 = 0.1209, wR2 = 0.3488	
R indices (all data)	R1 = 0.1754, wR2 = 0.4042	
Extinction coefficient	0.0000(12)	
Largest diff. peak and hole	1.012 and -1.711 e.$Å^{-3}$	

Data collection:

Crystal structure solution and refinement are carried out with SHELXTL Ver. 6.12 (SHELXL-97)in W95/98/NT/2000/ME, Bruker AXS (2001).

CONCLUSION

The study depicts the synthesis, characterization and biological evaluation of Ru complex. The structure analyzed by single crystal XRD study shows six coordinated octahedral geometry. On the basis of spectroscopic shifts, the intrinsic binding constant ($3.46X10^4$ M^{-1}), electrochemical $E_{1/2}$ shift, and electrophoresis band shifts, the complex is expected to bind with CT-DNA. The results characterized by various techniques indicate clear evidences of CT-DNA binding. The biological properties, IC_{50} and cytotoxic activity are promising. The findings may be useful for designing new potential anticancer drugs.

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