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HETEROLEPTIC MONONUCLEAR RUTHENIUM(II) COMPLEXES: SYNTHESIS, CHARACTERIZATION, DNA CLEAVAGE, ANTIOXIDANT AND CYTOTOXIC ACTIVITIES

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ABSTRACT: Mononuclear ruthenium(II) complexes of the type $[Ru(bpy)_2(L)]$ $(PF_6)_2$, where L=4,5-bis(4-dimethyaminophenyl)-1*H*, 1 '*H*-2,2'-biimidazole (1) and 4,5-bis (4-fluorophenyl) - 1*H*, 1' *H*-2,2'-biimidazole (**2**) have been synthesized and characterized by elemental analyses and spectroscopic techniques such as UV-visible, IR and ESI-MS. The redox behavior of the complexes has been studied by cyclic and differential pulse voltammetry. Both the complexes show reversible electrochemical wave attributable to Ru(II)/Ru(III) couple. The complexes exhibit half-wave potential ($E_{1/2}$) values of +0.8698 V for the complex 1 and +0.8395 V for the complex **2** respectively. Electrophoretic studies showed that the complexes are able to cleave supercoiled plasmid DNA more effectively in the presence of light at the wavelength of 480 nm. The mode of action of DNA cleavage activity was studied using DMSO and histidine. DPPH method has been adopted to find the radical scavenging activity of the newly synthesized ligands and complexes. The cytotoxic activity of these complexes was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay against MCF7 breast cancer cell lines.

INTRODUCTION: Making use of different properties of metal ions, new anticancer agents are being developed in the field of medicinal inorganic chemistry.[1] Conversely, metal-based therapeutics finds some limitations thereby emerging the scientists to develop new drugs. The clinical success of cisplatin as an anticancer drug has promoted the research in this field to contribute more against cancerous cells.

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Among the non-platinum complexes developed, ruthenium complexes are of promising interest because these complexes show a lower toxicity with biologically accessible oxidation states than platinum-based drugs. [2-4] Over the past few decades ruthenium complexes with polypyridyl ligands have found applications as DNA structural probes and mediators of DNA cleavage reaction by utilising their photophysical and electrochemical properties. [5-8] Owing to their good anticancer or antibacterial properties, several water soluble metal complexes attracted considerable interest. On comparing the metal complexes reported, the ruthenium complexes have certain advantages because of its solubility in water as well as low toxicity.

In spite of several reports on the synthesis and medicinal properties of ruthenium complexes, the DNA targeted ruthenium complexes with intercalating ligands may be an important anticancer agent. [9-10] Since there has been considerable interest in the design and study of DNA binding and cleavage properties of mixed-ligand Ru(II) complexes, it is worthwhile to study these complexes as metallo-drugs. However, it is surprising that biimidazole based ruthenium complexes have not been investigated systematically. In this paper, we report the DNA cleavage, anticancer and antioxidant activities of the two biimidazole based ruthenium(II) complexes.

MATERIALS AND METHODS: Ruthenium chloride trihydrate, imidazole-2-carboxaldehyde, ammonium hexafluoro phosphate, 4,4'-difluorobenzil and 4,4'-bis(dimethylamino benzil) were purchased from Sigma-Aldrich. Acetic acid, ammonium acetate, methanol, acetonitrile and ethanol were purchased from SD Fine chemicals.

Absorption spectra were recorded on Shimadzu UV-160A UV-Visible spectrophotometer. Cyclic (CV) and differential pulse voltammetries (DPV) were performed by using CH instrument (USA) model CH-620 B electrochemical analyzer. A conventional three electrode system consisting of platinum disc as a working electrode, platinum wire as an auxiliary electrode and saturated calomel (SCE) as a reference electrode was used for the electrochemical measurements. 0.1 M tetrabutyl ammonium perchlorate (TBAP) was used as the supporting electrolyte for all the experiments. Elemental analyses were performed using Elementar Vario EL III at Sophisticated Test and Instrumentation Centre (STIC), Kerala. Positive ion electron ionization mass spectra of the complexes were obtained by using Thermo Finnigan LCQ 6000 advantage max ion trap mass spectrometer. IR spectra were recorded as KBr pellets in the 400 - 4000 cm^{-1} region using a Shimadzu FT–IR 8000 spectrophotometer.

Synthesis of Ligands:

Synthesis of 4,5-bis(4-dimethyaminophenyl)-1*H*,1'*H*-2,2'-biimidazole (L1):4,4'-bis (dimethyl amino)benzil (0.2 g, 0.67 mmol), imidazole-2-carboxaldehyde (0.068g, 0.71mmol) and ammonium acetate (2 g, 25 mmol) were dissolved in 15 mL acetic acid and heated to reflux for 3 h. After cooling, cold water (10 mL) was added to the solution, during which light green precipitate was appeared. It was filtered and recrystallized using ethanol (Yield 0.13 g, 48 %). EI-MS: m/z 373.5 $(M+1)^+$. Anal. Calc. for $C_{22}H_{24}N_6$: C, 70.94; H, 6.49; N, 22.56. Found: C, 70.89; H, 6.46; N, 22.52. IR, cm^{-1}(KBr pellet) 3479, 3088, 1618, 1587, 1381.

Synthesis of 4,5-bis(4-fluorophenyl)-1*H*,1'*H*-2,2'-biimidazole (L2): 4,5-bis(4-fluorophenyl)-1*H*,1'*H*-2,2'-biimidazole was synthesized by using the same procedure described above by reacting imidazole-2-carbaldehyde (0.081 g, 0.85 mmol) with 4,4'-difluorobenzil (0.2 g, 0.81 mmol) and ammonium acetate (Yield 0.12 g, 44 %). EI-MS: m/z 323.4 $(M+1)^+$. Anal. Calc. for $C_{18}H_{12}F_2N_4$: C, 67.08; H, 3.75; N, 17.38. Found: C, 67.05; H, 3.71; N, 17.32. IR, cm^{-1} (KBr pellet) 3435, 3072, 1616, 1590, 1413.

Synthesis of Complexes:

Synthesis of $[Ru(bpy)_2(L1)](PF_6)_2$ (1): A mixture of [*cis*-$Ru(bpy)_2Cl_2]\cdot 2H_2O$ (0.2 g, 0.38 mmol) and **L1** (0.14 g, 0.38 mmol) was suspended in an ethanol/water solvent mixture (3/1, v/v). The mixture was refluxed under an inert atmosphere for 4 h while vigorous stirring was maintained. The reaction mixture was cooled to room temperature; the solvent was reduced under vacuum to one-third of its initial volume. A saturated aqueous solution of NH_4PF_6 was added to precipitate $[Ru(bpy)_2(L1)]^{2+}$ as its hexafluorophosphate salt. The product was filtered and washed with water (3 × 10 mL) and then purified by column chromatography on neutral alumina using acetonitrile/toluene (1.5/1, v/v) as an eluent. Yield: 0.2739 g, 67 %. Anal. Calc. for $C_{42}H_{40}F_{12}N_{10}P_2Ru$: C, 46.89; H, 3.75; N, 13.02. Found: C, 46.86; H, 3.70; N, 12.99. EI-MS: *m/z* 1076.71 $(M+1)^+$; IR, cm^{-1}(KBr pellet) 3429, 3097, 1589, 1379, 1247, 840, 765. UV-Visible λ_{max}, nm (ε, $M^{-1}cm^{-1}$) 279(63740), 321(46680), 474(9220).

Synthesis of $[Ru(bpy)_2(L2)](PF_6)_2$ (2): The synthesis and purification of compound **2** were similar to those of **1** using $[Ru(bpy)_2Cl_2]\cdot 2H_2O$ (0.2 g, 0.38 mmol) and **L2** (0.12 g, 0.38 mmol). Yield:

0.2299 g, 59 %. Anal. Calc. for $C_{38}H_{28}F_{14}N_8P_2Ru$: C, 44.50; H, 2.75; N, 10.92. Found: C, 44.47; H, 2.71; N, 10.90. EI-MS: *m/z* 1026.23 $(M+1)^+$; IR, cm^{-1}(KBr pellet) 3394, 3074, 1666, 1598, 1415, 1232, 844, 759. UV-Visible λ_{max}, nm (ε, $M^{-1}cm^{-1}$) 283(38140), 329(54040), 478(6040).

DNA Cleavage Activity: DNA cleavage experiment was performed by agarose gel electrophoresis method. The efficiency of DNA cleavage was measured by determining the ability of the complexes to form open circular (OC) and nicked circular (NC) DNA from its super coiled (SC) form. The supercoiled DNA in tris(hydroxymethyl)methane–HCl (Tris-HCl) buffer (pH 7.2) was treated with the metal complex (0–48 µM) followed by dilution with the buffer to the total volume of 25 µL. Each solution was incubated for 1 hour and then irradiated at 440 nm. The samples after irradiation were added to the loading buffer and the solution was finally loaded on 0.8% agarose gel(tris-boric acid-EDTA buffer, pH 8.0) containing 0.5 µg mL^{-1} ethidium bromide at 50 V for 2 h. The stained gel was illuminated under UV lamp and gel documented. In a separate experiment the DNA was incubated with 48 µM of the metal complex and 10 mM of histidine and irradiated at 440 nm. The irradiated solution was then subjected to electrophoresis.

Antioxidant Activity: The newly synthesized compounds were tested for their in vitro antioxidant activity by DPPH method.

DPPH free radical scavenging activity: 1,1-Diphenyl-2-picrylhydrazyl (DPPH) is a stable free radical having maximum optical absorbance at 517 nm. A stock solution (1 mg/mL) was diluted to final concentrations of 5-20 µg/mL. An ethanolic DPPH solution was added to sample solutions in DMSO at various concentrations (5-20 µg/mL). The test tubes were kept at an ambient temperature for 30 minutes. The absorbance of the sample solutions containing ligands and their ruthenium complexes were measured at 517 nm using UV-Visible spectrophotometer. These measurements were run in triplicate. The percentage of scavenging activity was calculated as follows:

Scavenging activity (%) = $[(A_{DPPH} - A_{TEST})/A_{DPPH}] \times 100$

Where, A_{DPPH} is the absorbance of DPPH without test sample (control) and A_{TEST} is the absorbance of DPPH in the presence of test sample.

***In vitro* Cytotoxicity Assay**: 3-[4,5-dimethylthiazol-2-yl] 2, 5 - diphenyltetrazolium bromide (MTT) is a yellow water soluble tetrazolium salt. A mitochondrial enzyme in living cells, succinate-dehydrogenase, cleaves the tetrazolium ring, converting the MTT to an insoluble purple formazan. Therefore, the amount of formazan produced is directly proportional to the number of viable cells.

The human breast cancer cell line (MCF 7) was obtained from National Centre for Cell Science (NCCS), Pune and grown in Eagles Minimum Essential Medium (EMEM) containing 10 % fetal bovine serum (FBS). All cells were maintained at 37ºC, 5 % CO_2, 95% air and 100 % relative humidity. For screening experiments, the cells were seeded into 96-well plates in 100 mL of the respective medium containing 10 % FBS, at a plating density of 10 000 cells/well and incubated at 37ºC, 5 % CO_2, 95 % air and 100 % relative humidity for 24 h prior to the addition of compounds. The compounds were dissolved in DMSO and diluted in the respective medium containing 1 % FBS.

After 24 h, the medium was replaced with the respective medium with 1 % FBS containing the compounds at various concentrations and incubated at 37°C, 5 % CO_2, 95 % air and 100 % relative humidity for 48 h. Experiments were performed in triplicate and the medium without the compounds served as control. After 48 h, 15 µL of MTT (5 mg mL^{-1}) in phosphate buffered saline (PBS) was added to each well and incubated at 37 °C for 4 h. The medium with MTT was then removed and the formed formazan crystals were dissolved in 100 mL of DMSO and the absorbance measured at 570 nm using a micro plate reader. The % cell inhibition was determined using the following formula, and a graph was plotted between % of cell inhibition and concentration. From this plot, the IC_{50} value was calculated. The % cell inhibition was determined using the following formula.

% cell Inhibition = 100- Abs (sample)/Abs (control) ×100.

Nonlinear regression graph was plotted between % Cell inhibition and Log concentration and IC_{50} was determined using GraphPad Prism software.

RESULTS AND DISCUSSION:

Synthesis and Characterization: The mixed ligand ruthenium(II) complexes with formula $[Ru(bpy)_2(L)](PF_6)_2$ (where L=4,5-bis(4-dimethy aminophenyl)-1*H*,1'*H*-2,2'-biimidazole (**1**) and 4,5-bis(4-fluorophenyl)-1*H*,1'*H*-2,2'-biimidazole (**2**)) have been isolated from an aqueous ethanolic solution containing $[Ru(bpy)_2(Cl)_2].2H_2O$ as the starting material. Both the complexes were obtained in good yield and were characterized by using elemental analysis, UV-Vis, EI-MS and IR spectral techniques. The positive ion electron ionization mass spectra of the ruthenium(II) complexes **1** and **2** showed a major peak at 1076.71 and 1026.23 respectively.

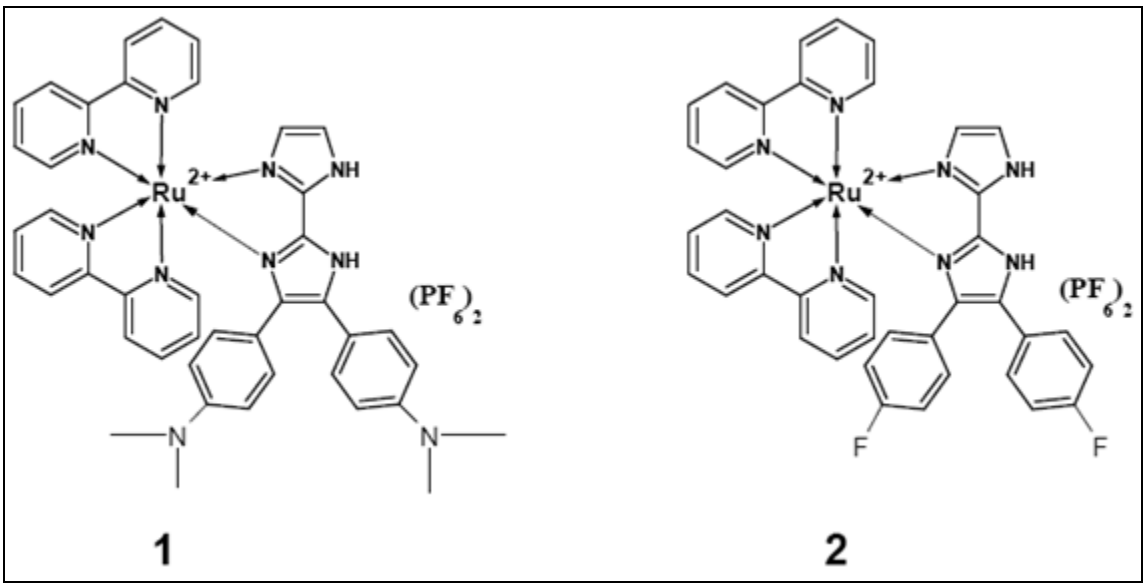

FIG. 1: STRUCTURE OF MONONUCLEAR RUTHENIUM(II) COMPLEXES

The analytical and mass spectral data are consistent with the proposed formula of the ruthenium(II) complexes. The IR spectra of the free ligands and their ruthenium(II) complexes were compared. In the IR spectrum of both complexes, absorption bands appeared in the region 1379 – 1462 cm^{-1} indicates the presence of aromatic skeleton. The IR spectra show the characteristic peaks for the imidazole N-H stretch at 3429 and 3394 cm^{-1} for the complex **1** and **2** respectively. In the IR spectra of free ligands **L1** and **L2**, the bands due to νNH absorption appeared at 3479 and 3435 cm^{-1} respectively.

TABLE 1: ELECTRONIC AND ELECTROCHEMICAL DATA OF MONONUCLEAR RUTHENIUM(II) COMPLEXES IN ACETONITRILE SOLUTION AT 25 ± 0.2 °C

Complex	λ_{max}, nm (ε, $M^{-1}cm^{-1}$)	$E_{p,a}$(V)	$E_{p,c}$(V)	ΔE_p(mV)	$E_{1/2}$ Ru^{II}/Ru^{III} *vs* SCE CV (V)	DPV (V)
$[Ru(bpy)_2(L1)](PF_6)_2$ (**1**)	474 (9220) 321(46680) 279(63940)	+0.9095	+0.8301	79	+0.8698	+0.8687
$[Ru(bpy)_2(L2)](PF_6)_2$ (**2**)	478 (6040) 329(54040) 283(38140)	0.8770	+0.8019	75	+0.8395	+0.8311

The ground state of ruthenium(II) (t_{2g}^6 configuration) is $^1A_{1g}$. For a hexacoordinate ruthenium(II) complex, four transitions corresponding to $^1A_{1g} \rightarrow {}^3T_{1g}$; $^1A_{1g} \rightarrow {}^3T_{2g}$; $^1A_{1g} \rightarrow {}^1T_{1g}$ and $^1A_{1g} \rightarrow {}^1T_{2g}$ are possible. The electronic spectra of the complexes showed high intensity π–π* transitions in the 279-283 nm range for bipyridine ligand. The peaks observed in the region 321-329 nm were attributed to the ligand molecules **L1** and **L2**.

The visible region of both complexes exhibited weak and broad absorption bands which are due to ruthenium(II) d−π* MLCT in the 474-478 nm range. This data suggests octahedral geometry for both ruthenium(II) complexes.

Electrochemical studies were performed for both in non-aqueous medium, and the relevant electrochemical results are gathered in **Table 1**. Both the complexes show reversible electrochemical wave attributable to Ru(II)/Ru(III) couple. The half-wave potential ($E_{1/2}$) has been found to be +0.8698 V for the complex **1** and +0.8395 V for the complex **2.** During the forward scan **1** shows a quasi-reversible anodic peak at +0.9095 V and cathodic peak at +0.8301 V with the peak separation of 79 mV. On the other hand complex **2** exhibits anodic peak at +0.8770 V and cathodic peak at +0.8019 V with the peak separation of 75 mV. These peaks are due to one electron Ru(II)/Ru(I) redox couple. Based on the analytical and spectral data, both the complexes are proposed to have octahedral geometry.

DNA Cleavage Activity of Ruthenium(II) Complexes: Agarose gel electrophoresis method was employed to monitor the degree of DNA cleavage by the newly synthesized compounds. **Fig. 2** show that the present complexes did not exhibit any cleavage activity in the absence of light. On the other hand, on irradiating the compounds in the presence of light at the wavelength of 480 nm, cleavage of supercoiled plasmid DNA has been observed even at a concentration of 24 µM.

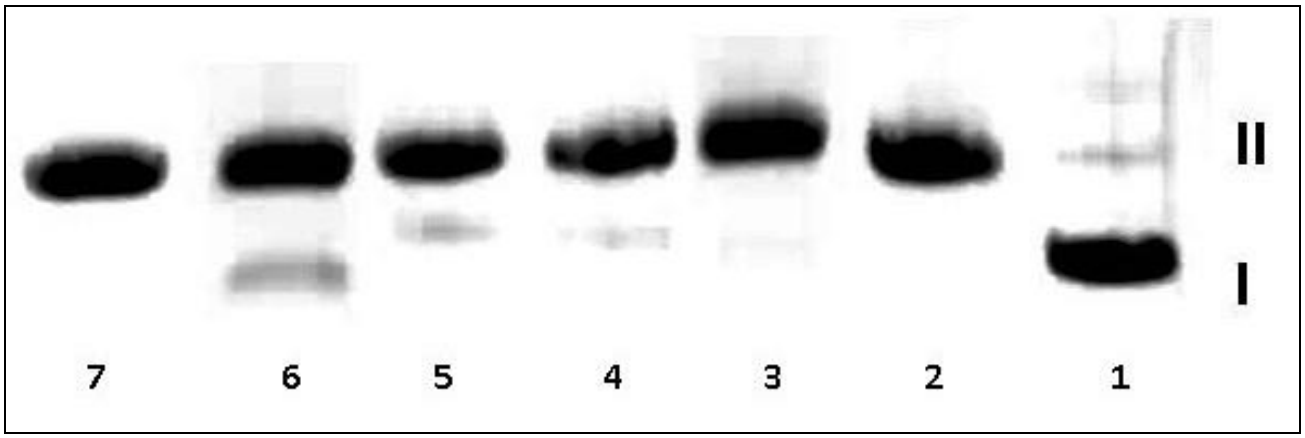

FIG. 2: CLEAVAGE OF SUPERCOILED PUC19DNA BY THE COMPLEXES (1 AND 2) IN THE PRESENCE OF LIGHT AT THE WAVELENGTH OF 480 nm (LANE 2-7). Lane 1: DNA alone; Lane 2: DNA+24 µM complex **1**; Lane 3: DNA+24 µM complex **2**; Lane 4: DNA+24 µM complex **1 +** Histidine (10 mM); Lane 5: DNA+24 µM complex **1**+DMSO (10 mM); Lane 6: DNA+24 µM complex **2 +** Histidine (10 mM); Lane 7: DNA+24 µM complex **2**+DMSO (10 mM).

In order to find out the reactive species involved in the cleavage mechanism, a control experiment with DMSO (hydroxyl radical scavenger) and histidine (singlet oxygen quencher) has been carried out. From the **Fig. 2** it has been observed that both the quencher molecules did not affect the cleavage of DNA brought about by photo irradiated complexes **1** and **2**. This clearly shows that the complexes cleave the DNA by direct guanine oxidation rather than through singlet oxygen.

Investigation of Antioxidant Activity: The free radical scavenging ability of the metal complexes was determined by their interaction with the stable free radical 2, 2'-diphenyl-1-picryl hydrazyl.

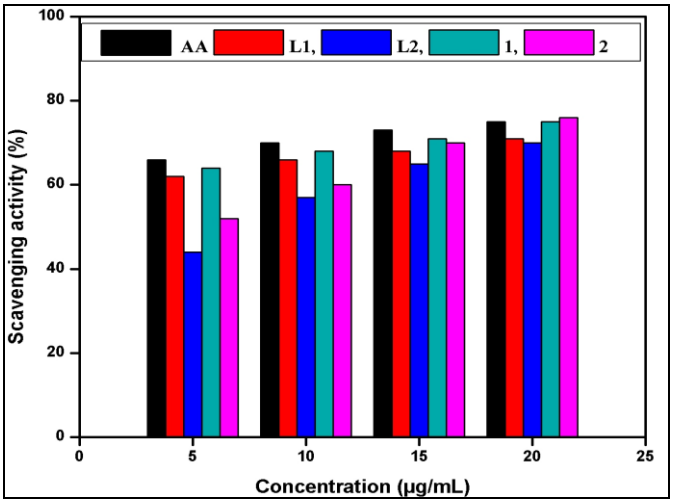

FIG. 3: ANTIOXIDANT ACTIVITY OF LIGANDS AND THEIR RUTHENIUM(II) COMPLEXES

The synthesized ligands and their metal complexes were screened for the reduction of DPPH at the concentrations of 5-20 µg/mL. Among them complexes showed good activity in DPPH scavenging comparable with the ligands. The antioxidant activity results are shown at **Fig. 3** and compared with the control standard AA. Lower absorbance values of the reaction mixture indicated higher free radical scavenging activity. A graph may be plotted with % scavenging effects on the y-axis and concentration (µg/mL) on the x- axis. Out of the two synthesized complexes, complex **2** showed a significant scavenging activity than **1**. This might be attributed to the presence of more electron withdrawing fluoride moiety in the complex **2**. The radical scavenging activity of the present complexes follows the order **2** > **1**.

Antiproliferative Activity of Ruthenium(II) Complexes: The present study examined the efficacy of ruthenium(II) complexes to inhibit the human breast cancer cell line (MCF-7) as determined by MTT assay. The cells were treated with five different concentrations ranging from 0.25 to 100 µM. The complexes suppressed the growth of breast cancer cell lines in a dose dependent manner. The maximum cell inhibitions of 95.10 and 77.22 % at 100 µM concentration were determined for **2** and **1** respectively and minimum inhibitions (4.48 and 11.69 %) at 0.25 µM concentration were observed for **2** and **1** respectively.

From the results presented in **Table 2**, it is clear that several ruthenium complexes exhibited a marked inhibitory effect on the proliferation of MCF-7 cancer cells. The IC_{50} values for complexes treated with MCF-7 cells were obtained at 16.42 and 18.25 µM for **1** and **2** respectively. Out of the two complexes tested, IC_{50} value for **1** is found to be less, suggesting that **1** could exert very strong anti-proliferative effect when compared to complex **2** tested with breast cancer cell lines at low doses. The complexes exhibited higher cytotoxic effects on breast cancer cells with lower IC_{50} values indicating their efficiency in killing the cancer cells even at low concentrations.

TABLE 2: *IN VITRO* CYTOTOXIC ACTIVITY OF SYNTHESIZED RUTHENIUM(II) COMPLEXES IN HUMAN BREAST CANCER CELL LINE(MCF7)

S.No.	Compound	IC_{50} value (µM)
1	$[Ru(bpy)_2(L1)](PF_6)_2$	16.42
2	$[Ru(bpy)_2(L2)](PF_6)_2$	18.25

CONCLUSIONS: Biimidazole based ligands derived from substituted benzils and imidazolde aldehyde and their corresponding ruthenium(II) complexes have been synthesized and characterized using various spectroscopic and electrochemical techniques. The electrochemical properties of the complexes have been found to be quasi-reversible. The complexes are able to cleave DNA in the presence of light radiation. Also they exhibit a better antioxidant and anticancer activities against MCF-7 breast cancer cell lines.

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CONFLICT OF INTEREST: The authors have no potential conflict of interest.

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