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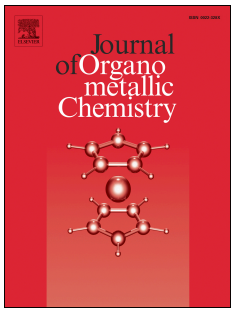

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Ionic η^5-Cp-Ruthenium (II) complexes as potential anticancer agents

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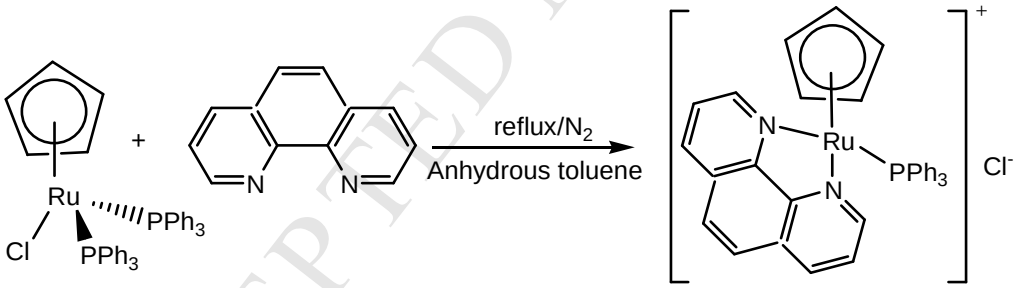
Abstract

Ionic organometallic ruthenium(II) complexes, [η^5-CpRu(PPh_3)(1,10-phenanthroline)]$^+Cl^-$ **1**, [η^5-CpRu(PPh_3)(4,7-dimethyl, 1,10-phenanthroline)]$^+Cl^-$ **2**, and [η^5-CpRu(PPh_3)(1,10-phenanthroline-5-amine)]$^+Cl^-$ **3** have been synthesized and characterized. The molecular structures of the complexes **1** and **2** were confirmed by single-crystal X-ray structure analysis. Cytotoxicity assays demonstrated that these compounds show significant toxicity against NIH3T3 and Raw 264 cancer cell lines at low concentration. These complexes have the property of DNA binding cleavage.



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Keywords: Ruthenium arene complexes, Crystal structure, phenanthrolines, DNA binding cleavage *in vitro* cytotoxicity.

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1. Introduction.

The platinum derived complexes, in particular cisplatin and carboplatin are extensively utilized for cancer treatment. However, drug resistance, the toxic side-effects, and lack of activity of platinum compounds against several types of cancers are serious drawbacks [1]. The shortcoming of platinum drugs inspired the search for anticancer activity of other transition metal complexes. Ruthenium complexes including organometallic complexes has received immense attention as anticancer agents [2, 3]. Early reports misconstrued that organometallic complexes were unstable to normal conditions, and until recently organometallic compounds have never been considered as suitable candidate as pharmaceuticals [4]. Consistent with recent studies, organometallic compounds are promising therapeutic agents with novel mechanistic activity [5-12], probably due to their great structural variety and by rational ligand design. Organometallic complexes have tremendous advantage with their wide spectrum of coordination numbers, coordination geometries, thermodynamic and kinetic preferences, redox activity, Lewis acidity, electrophilicity, access to ionic/radical species, flexible bond order, unique geometries, easily accessed structure/activity variations, and magnetic, spectroscopic, and radioactive signatures. These variations in organometallic compounds may overcome the cellular resistance problem common in platinum-related drugs and may suggest improvements in the discovery and development of new cancer drugs. Biological activity of Ru complexes is becoming increasingly important in both bioinorganic chemistry and anticancer chemotherapy [13-18]. Sadler's piano-stool organometallic compounds have contributed in the understanding of the mechanism of the interaction between the target biomolecule and the ruthenium complex [19,20]. Also, transition metal complexes are investigated comprehensively for biomedical applications [21]. In fact, the rapid development of ruthenium compound's in the field in the medicinal chemistry, especially in the development of chemotherapeutics with minimal side effects and immunity to drug resistance [22]. The most promising ruthenium complexes, NAMI-A and KP-1019, have successfully reached clinical trials [23]. Recently, Chi et al. reported the antitumor activity and cellular pharmacology of various metallacycles composed of arene-Ru acceptors and various pyridyl donors [24]. The studies on Ru-metallocycle suggested that larger metallacyles show higher activity in comparison with small metallacycles. This is probably in agreement with the hypothesis that a large macromolecules are more likely to be retained inside cancer cells. A recent review describing potential application of ferrocenyl secondary natural product conjugates in medicinal chemistry such as antimicrobial, antiparasite and anticancer agents [25, 26].

The ruthenium-based drugs seem to be a good alternative to platinum drugs, and significant advances have been made in this regard [27-29]. Ru(III) complexes preferably bind to Fe(III) sites of the proteins lactoferrin and transferrin [30 ,31], which are responsible for the delivery of Ru(III) to cancer cells where they are taken up via receptor-mediated endocytosis [32]. The protein which delivers iron to cells, and transferrin receptors are overexpressed in cancer cells [29]. It is hypothesized that the Ru(III) complexes are reduced to Ru(II) *in vivo*, being kinetically more reactive than Ru(III) [2]. Nonetheless ruthenium(II) compounds also exhibit a low general toxicity, and since cancer cells can also become oxidizing at certain stages of their growth cycle, oxidation of the ruthenium cannot be excluded [33].

Ligands such as arenes and cyclopentadienyl may provide control of the hydrophilicity and hydrophobicity of the faces of the coordination complex (which influence cell uptake and targeting) [34]. Metallodrugs are mainly prodrugs, and control over ligand substitution is vital if the complex is to reach and react with its target site. The low-spin d^6 metal complexes are attractive for drug design since they are often kinetically inert. A number of organometallic compounds bearing η^5-cyclopentadienyl ligand capable of binding to the metal center through π interactions exhibit promising anticancer activity. Cyclopentadienyl rhodium [35, 36] and ruthenium complexes with potential therapeutic applications have also been reported.

In this paper we report synthesis of ionic cyclopentadienyl-ruthenium complexes with bidentate nitrogen donor ligands. All these complexes were isolated as chloride salts. These complexes (**1**, **2**) were fully characterized by X-ray diffraction and spectroscopic studies. These complexes were further studied for cytotoxicity and DNA binding.

2. Experimental

2.1 Materials and general methods. All reagents were of analytical grade. 1, 10-phenanthroline, 4,7-dimethyl, 1,10-phenanthroline, 1,10-phenanthroline-5-amine and $CpRuCl(PPh_3)_2$ and solvents were purchased from Sigma-Aldrich. All reactions were performed under inert atmosphere.

The IR spectra were measured on a CARY 630 FT- infrared spectrophotometer (Agilent Technology). UV-vis spectra were obtained on an Agilent 8453 spectrophotometer. Elemental analysis was performed by Atlantic Microlab, Norcross, Georgia. The diffraction data were collected at low temperature on a Bruker Kappa Apex-II DUO diffractometer equipped with Mo

Kα (λ = 0.71073 Å) radiation, a focusing monochromator, and an Oxford Cryostream low-temperature device. Data were measured at 100K for **1** and 180K for **2**. Absorption corrections were made by the multi-scan method. For **2**, disordered dichloromethane solvent contribution was removed using the SQUEEZE procedure. Crystal data and details of data collection and refinement are given in Tables 1-2. The NMR spectra were measured 400 MHz Varian/Joel spectrophotometer in a $CDCl_3$ solvent

2.2 Biological studies.

Plasmid DNA isolation and gel electrophoresis. pUC19 plasmid was introduced into DH5· competent cells based on manufacturer's protocol (Invitrogen Corporation, Carlsbad, CA). A single colony was selected from LB plate and cultured in 5.0 ml of LB medium at 37˚C in a shaker at a speed of 300 rpm for overnight. This starter cell culture was diluted 1:500 using freshly prepared LB medium and grew at 37˚C in a shaker at a speed of 300 rpm for 16-18 h. Cells were harvested at 4,000 rpm for 5 min. The plasmid DNAs were purified from the cell culture using a Qiagen plasmid purification column based on manufacturer's protocol (Qiagen Inc., Valencia, CA). LB medium and plates contained 100 µg/ml ampicillin. The concentration of plasmid DNA was determined by the absorbance at 260 nm using UV-Vis spectrophotometry. 1.0 µg of pUC19 plasmid DNA was incubated with the ruthenium complexes at the specified concentrations in a total 20 µl in a 37˚C water bath for 2-32 h. At the end of incubation, bromophenol blue loading buffer was added. The samples were then loaded on a 1.0% agarose gel containing ~2.0 µg/ml ethidium bromide. Gel electrophoresis was carried out at 150 V for ~20 min in Tris-Borate-EDTA (TBE) buffer. Bands were visualized by UV light and photographed by a Bio-Rad gel documentation system (Bio-Rad Laboratories, Hercules, CA) [37].

Culture of cell lines and cytotoxicity test.

The murine cell lines: NIH3T3 and Raw 264 were maintained in either T25 or T75 flasks containing DMEM medium supplemented with 10% fetal bovine serum, 1% glutamine, and 1% penicillin and streptomycin (Invitrogen) in the standard 3T3 protocol. The cells were grown at 37˚C in a 5% CO_2 incubator. 1.0 x 10^5 cells (cell culture day 0) were plated in T25 flasks for investigating effects of the ruthenium complexes on the murine cell lines. Specifically, the ruthenium complexes dissolved in DMSO, filter-sterilized, were added into a growth medium using 1:1000 dilution to avoid the toxic effects of DMSO after the cells were plated for 24 h (cell culture day 1). At the end of incubation with ruthenium complexes from 0 h (day 1), 24 h (day 2), 48 h (day 3), 72 h (day 4), and 96 h (day 5), cells were removed from flasks by trypsin-EDTA

solution (Invitrogen). Cell viability was determined by the trypan blue staining, and cell number was counted using a haemocytometer [38]. The experiment was independently repeated for four times. IC_{50} values for each ruthenium complexes were calculated by normalizing survival rate of the treated cells to that of control (DMSO treated) cells.

As stated earlier, the cells were incubated with the compounds for 0, 1, 2, 3, 4 and 5 days. At the end of incubation with the compound each day, cell viability was determined by the trypan blue staining, and cell number was counted using a haemocytometer. At the longest incubation (5 days), nearly all cells were killed by 10.0 μM of the compounds, the highest concentration in our study. Significant fraction of the cells were still alive in the culture media with low concentration, for example 0.080 μM, of the compounds.

3. Synthesis of complexes

3.1 Synthesis of [η^5-CpRu(PPh_3)(1,10-phenanthroline)]$^+Cl^-$ **1**. In a 100 mL Schlenk flask provided with magnetic stirrer and a condenser under nitrogen, $CpRuCl(PPh_3)_2$ (0.1g, 0.138 mmol) and anhydrous 1,10-phenanathroline (0.027g, 0.151 mmol) were dissolved in anhydrous toluene (6 mL) and was stirred for 3 h at room temperature to get a thick red solution. An orange solid was obtained on cooling at -20^{0}C, which was filtered and vacuum dried. Yield 45 mg, 45 %. Anal. Calcd. for $C_{35}H_{28}N_2PRuCl{\cdot}CH_2Cl_2{\cdot}H_2O$ (747.03): C, 57.88; H, 4.32; N, 3.75. Found: C, 58.50; H, 4.15; N, 3.86. Selected IR absorption bands (cm^{-1}): ν_{SO}1096 (S-TMSO) and, $\nu_{C=N}$ (pyz) 1401. UV-vis (H_2O): 364 nm (ε = 3260 $L.mol^{-1}.m^{-1}$); 426 nm (ε = 1060 $L.mol^{-1}.m^{-1}$). ^1H NMR (400MHz ,$CDCl_3$) δ = 9.66 (d, *J = 5.5 Hz, 2 H), 8.34 (d, J = 8.2 Hz, 2 H), 7.87 - 7.83 (m, 2 H), 7.75 (dd, J = 5.3, 8.0 Hz, 2 H), 7.23 - 7.18 (m, 3 H), 7.14 - 7.07 (m, 6 H), 6.90 - 6.83 (m, 6 H), 4.85 (s, 5 H).*

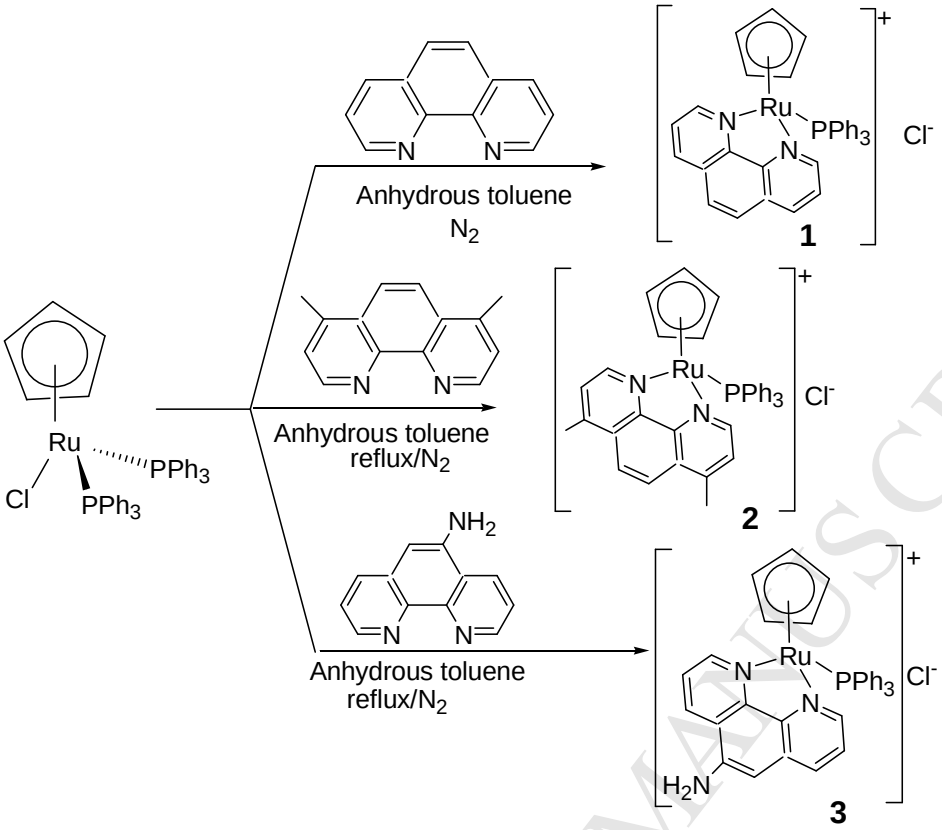
3.2 Synthesis of [η^5-CpRu(PPh_3)(4,7-dimethyl-1,10-phenanthroline)]$^+Cl^-$ **2**. This compound was prepared following a method analogous to that described for **1** starting from compound $CpRuCl(PPh_3)_2$ (0.1g, 0.138 mmol) and 4,7-dimethyl-1,10-phenanthroline (0.031 g, 0.151 mmol) in anhydrous toluene except that the reaction mixture were reflux for 3 h. The flask was placed in a refrigerator overnight. An orange colored crystalline compound was obtained. Yield: 66 mg 62%. Anal. Calcd. for $C_{35}H_{32}N_2PRuCl{\cdot}H_2O{\cdot}CH_2Cl_2$ (775.127): C, 58.88; H, 4.68; N, 3.61. Found: C, 58.08; H, 4.04; N, 3.51. Selected IR absorption bands (cm^{-1}): ν_{SO}1113 (S-TMSO), ν_{SO} 880 (O-TMSO) and, $\nu_{C=N}$ (pyz) 1401. UV-vis (H_2O): 364 nm (ε = 3260 $L.mol^{-1}.m^{-1}$); 426 nm (ε =

1060 L.mol^{-1}.m^{-1}). ^{1}H NMR (400MHz ,$CDCl_3$) δ = 9.48 (d, *J = 5.1 Hz, 2 H), 7.94 (s, 2 H), 7.55 (d, J = 5.5 Hz, 2 H), 7.6 (5,4 Hz, 2H), 7.21 - 7.15 (m, 2 H), 7.11 - 7.04 (m, 6 H), 6.91 - 6.82 (m, 6 H), 4.78 (s, 5 H), 2.80 (s, 6 H).*

3.3 Synthesis of [η^5-CpRu(PPh_3)(1,10-phenanthroline-5-amine)]$^+$Cl$^-$ **3.** This compound was prepared following a method analogous to that described for **2** starting from compound $CpRuCl(PPh_3)_2$ (0.1g, 0.138 mmol) and 1,10-phenanthroline-*5-amine* (0.031 g, 0.151 mmol) in anhydrous toluene. The flask was placed in the refrigerator for overnight. A orange colored crystalline compound was obtained. Yield: 66 mg 62%. Anal. Calcd. for $C_{35}H_{28}N_3PRuCl$ (658.094): C, 63.87; H,4.28; N, 6.38. Found C, 64.17; H, 4.04; N, 6.62. Selected IR absorption bands (cm^{-1}): ν_{SO}1113 (S-TMSO), ν_{SO} 880 (O-TMSO) and, $\nu_{C=N}$ (pyz) 1401. UV-vis (H_2O): 364 nm (ε = 3260 L.mol^{-1}.m^{-1}); 426 nm (ε = 1060 L.mol^{-1}.m^{-1}). ^{1}H NMR (400MHz ,$CDCl_3$) δ = 9.32-9.30 (d, *J = 5.1 Hz, 2 H), 8.94 (d, 2 H), 7.72-7.27 (m, J = 5.5 Hz, 2 H), 7.25 (d, 2H), 7.4-6.96 (m, 3 H), 6.83 – 6.81 (m, 6 H),6.79 - 6.38 (m, 6 H), 4.68 (s, 5 H), 1.80 (s, 3 H).*

4. Results and Discussion

4.1 Synthesis of complexes. The reaction of $CpRuCl(PPh_3)_2$ with phenanthrolines in anhydrous toluene at room temperature to refluxing temperature gave ionic complex [η^5-CpRu(PPh_3)(1,10-phenanthroline)]$^+$Cl$^-$ **1**, η^5-CpRu(PPh_3)(4,7-dimethyl, 1,10-phenanthroline)]$^+$Cl$^-$ **2**, and [η^5-CpRu(PPh_3)(1,10- phenanthroline-5-amine)]$^+$Cl$^-$ **3** as microcrystalline orange solids (Scheme 1). The elemental analysis, IR, and NMR analysis support the proposed structure for **1**, in which a ruthenium atom is coordinated to a η^5-Cp, 1,10-phenanthroline and triphenyl phosphine ligands, acting as an cation and Cl$^-$ as anion.



Scheme 1. *Synthetic scheme for [η^5-CpRu(PPh_3)(1,10-phenanthroline)]$^+Cl^-$* ***1****, [η^5-CpRu(PPh_3)(4,7-dimethyl, 1,10-phenanthroline)]$^+Cl^-$* ***2****, and [η^5-CpRu(PPh_3)(1,10-phenanthroline-5-amine)]$^+Cl^-$* ***3***

The asymmetric units of both **1** and **2** include one cationic complex, one chloride as a counter-anion, one water molecule and one CH_2Cl_2 molecule, although the dichloromethane in 2 was removed by SQUEEZE. The structures of compounds **1** and **2** are represented in Fig. 1 and 2 respectively. Details of crystallographic data are given in Table 1, 2, and significant bond lengths and bond angles are listed in Table 3. Cations of both compounds **1** and **2** consist of a ruthenium atom coordinated to the cyclopentadienyl ligand, to the two nitrogen atoms of bidentate 1,10-phenanthroline ligand or 4,7-dimethyl-1,10-phenanthroline, and one triphenylphosphine, with chloride as counterion. In these complexes the coordination geometry of ruthenium is pseudo-tetrahedral (piano-stool complexes). The Ru-C(Cp) distances are in the range 2.158(2) - 2.2149(16) Å. The average value agrees with those of 2.177(5) and 2.185 A, respectively, reported for the $[CpRu(PMe_3)(CH_3CN)_2]^+$ and $[CpRu\ (PCy_3)(CH_3CN)_2]^+$ monomeric complex cations [39]. The Ru–N distances of compounds **1** and **2** agree well and are in the

range 2.0858(18) - 2.1002(18) Å. Ru–P distances also agree well, having values of 2.2997(4) Å in **1** and 2.3060(6) Å in **2**. The presence of the N-coordinated phenanthroline is evidenced by the characteristic IR spectrum absorption at 698 cm^{-1}. The band detected at 1430 cm^{-1} are characteristic of triphenylphosphine.

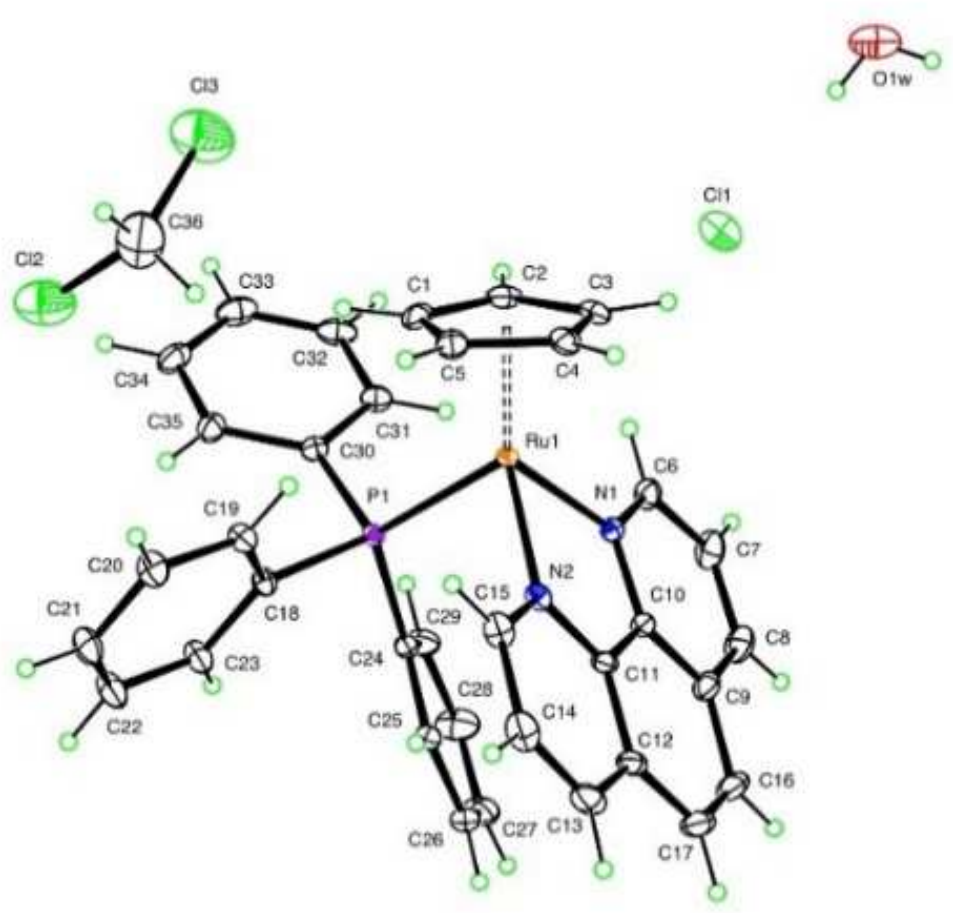


Figure 1. *ORTEP diagram and labelling scheme of complex **1.** 50%* thermal ellipsoids plotted.

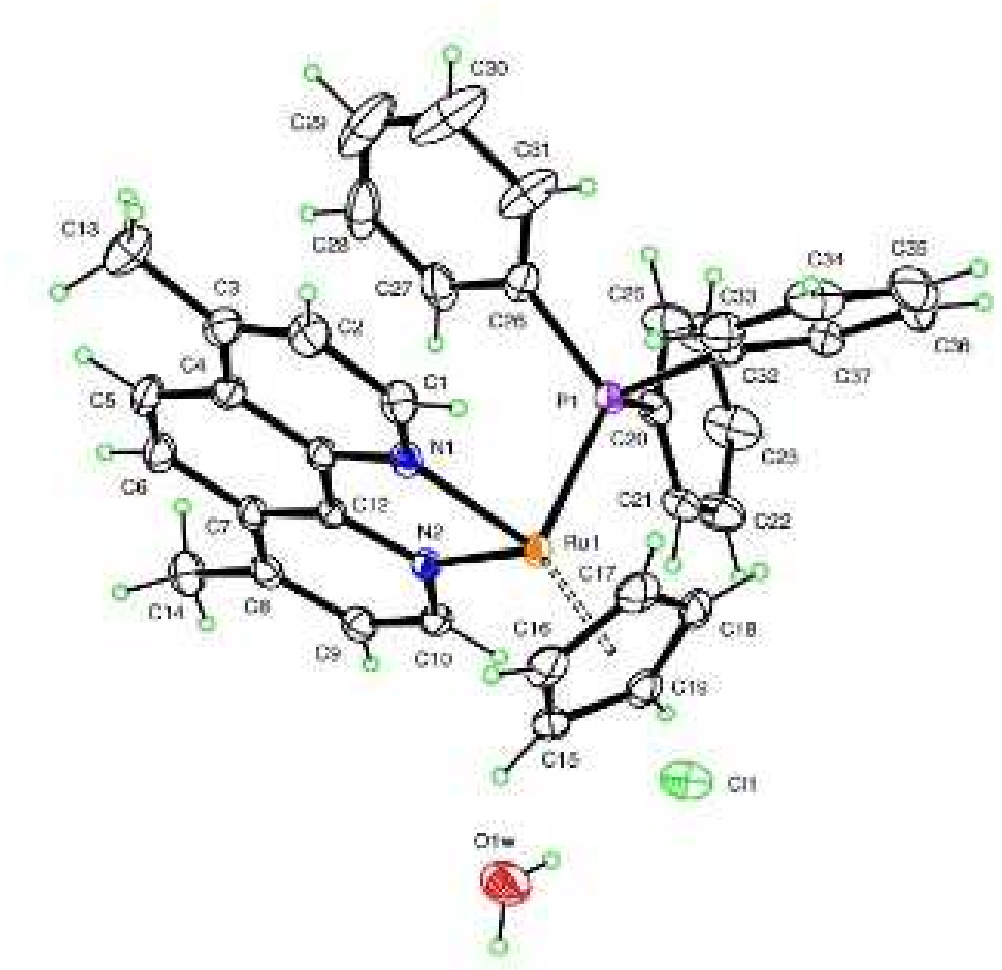


Figure 2. *ORTEP diagram and labelling scheme of complex* ***2.*** *50%* thermal ellipsoids plotted.

5. ***Effects on cell viability by the ruthenium complexes*** **1, 2 and 3*.*** A number of ruthenium complexes were reported to have anti-metastatic activity. Specifically, certain ruthenium complexes with heterocycles coordinated to the ruthenium center through nitrogen have been shown to act as cytostatic and cytotoxic drugs on colorectal tumor cells both *in vivo* and *in vitro*. In the present work, the effects of the ruthenium complexes on cell growth were investigated using two murine cell lines (NIH3T3 and Raw264). Three compounds at high concentration have cytotoxicity activities. Raw264 is more sensitive to ruthenium complexes than NIH3T3

cells. There are measurable differences in cytotoxicity of these three complexes: **2** has a slightly greater effect than **1**, which has a higher effect than **3**.

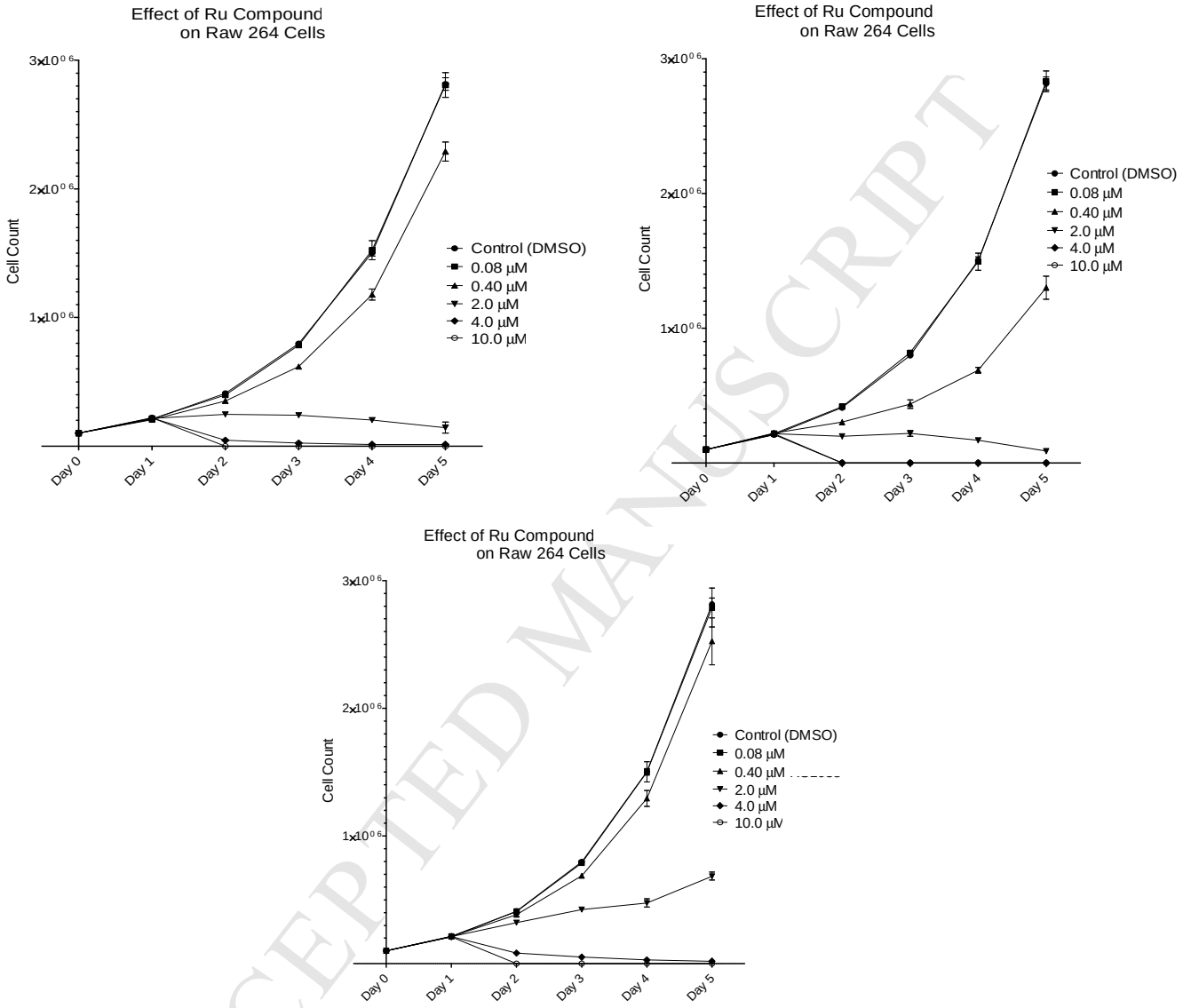


Figure 3. *Effects of the Ru complexes 1, 2 and 3 on cell viability. The mouse Raw 264 and NIH 3T3 cell lines were incubated with varying concentrations [0 (control), 0.080. 0.40, 2.0, 4.0 and 10.0 µM] of the complexes.*

5.1. DNA binding activity by the ruthenium complexes 1, 2 and 3. Ruthenium (II) complexes have been reported to have DNA binding properties. The observed cell growth inhibition of complexes 1, 2 and 3 made us hypothesize that the complexes might have the property of either DNA binding, or cross-linking, or cleavage. Our gel electrophoresis results

show that intensity of plasmid forms I and II is proportionally decreased in dose-dependent manner when DNAs were incubated with the compounds (Figure 4). This observation indicates that ruthenium compounds especially at high concentration gradually replace ethidium bromide, and cause decreased intensity under UV light. Taken all together, our DNA binding experiments suggest that the complexes could function as intercalating agents.

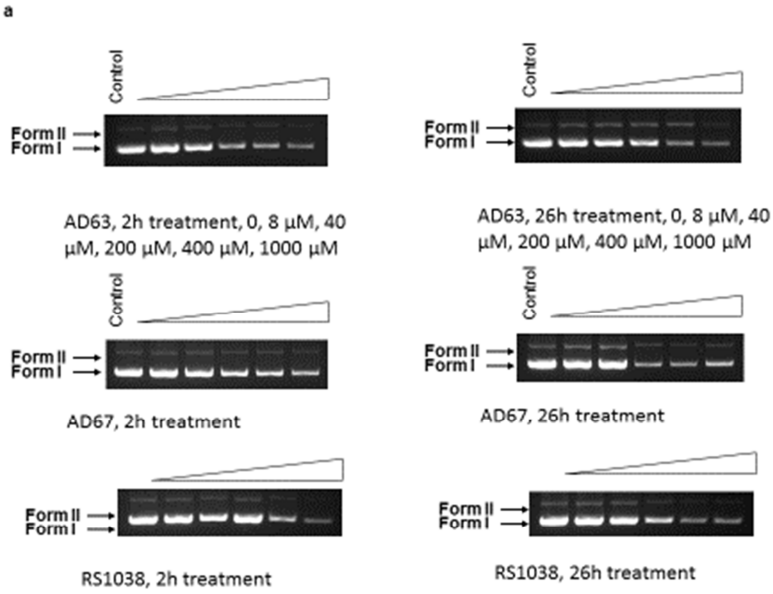


Figure 4. *Plasmid DNA binding by complexes 1, 2 and 3. Plasmid DNA (1.0 µg) was incubated with varying concentrations (0.80, 40, 200, 400 and 1,000 µM) of the complexes in 1.0 mM Tris-Cl buffer, pH 7.0 at 37˚C.*

Supplementary material

Crystallographic data for the structure analyses have been deposited with the Cambridge Crystallographic Data Center, CCDC 1584250 and 1584251 for compounds **1-2**. Copies of this may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336-033; email: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Acknowledgement

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Table 1. Crystallographic data and structure refinement for compounds **1**, and **2**.

	1	**2**
Formula	$C_{35}H_{28}N_2PRuCl.CH_2Cl_2.H_2O$	$C_{37}H_{32}N_2PRu.Cl.H_2O.CH_2Cl_2$
Formula weight	747.03	775.08
Crystal system	Triclinic	Triclinic
Space group	PI	PI
T (K)	100	180
a (Å)	9.8122 (3)	9.9987 (3)
b (Å)	10.1176 (3)	10.636 (3)
c (Å)	16.8761 (4)	17.4832 (6)
α (°)	99.883 (2)	100.284 (2)
β (°)	97.574 (2)	92.954 (2)
γ (°)	97.546 (2)	91.062 (2)
V ($Å^3$)	1615.67 (8)	1727.96 (9)
Z	2	2
Dx (Mg m^{-3})	1.536	1.490
μ (mm^{-1})	0.82	0.77
Crystal size (mm)	0.18 x 0.11 x 0.09	0.20 x 0.19 x 0.09
R [$F^2>2\sigma(F^2)$]	0.093	0.035
R_{int}	0.039	0.025
wR(F^2)	0.093	0.084

Table 2. Selected bond lengths (*Å*) and angles (°) for complexes **1**and **2.**

	1		**2**
Ru1-N1	2.0882(13)	Ru1-N1	2.0858(18)
Ru1-N2	2.0922(13)	Ru1-N2	2.1002(18)
Ru1-C1	2.1715(16)	Ru1-C15	2.208(2)
Ru1-C2	2.1793(16)	Ru1-C16	2.203(2)
Ru1-C3	2.1938(16)	Ru1-C17	2.175(2)
Ru1-C4	2.2149(16)	Ru1-C18	2.158(2)
Ru1-C5	2.2050(16)	Ru1-C19	2.193(2)
Ru1-P1	2.2997(4)	Ru1-P1	2.3060(6)
N1-Ru1-N2	77.52(5)	N1-Ru1-N2	77.45(7)
N1-Ru1-C1	142.87(6)	N1-Ru1-C18	142.79(9)
N2-Ru1-C1	139.56(6)	N2-Ru1-C18	139.61(9)
N1-Ru1-C2	106.31(6)	N1-Ru1-C17	106.89(9)
N2-Ru1-C2	163.11(6)	N1-Ru1-C17	159.94(9)
N1-Ru1-P1	91.36(4)	N1-Ru1-P1	89.82(5)
N2-Ru1-P1	90.11(4)	N2-Ru1-P1	912.45(5)

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Highlights

- We have synthesized three new organometallic complexes.
- All the complexes have half sandwich geometry.
- All the complexes are significantly toxic against NIH3T3 and Raw 264 cancer cell lines at low concentration.
- These complexes have the property of DNA binding cleavage.