Synthesis and antiproliferative activity of $[RuCp(PPh_3)_2(HdmoPTA)](OSO_2CF_3)_2$ (HdmoPTA = 3,7-H-3,7-dimethyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane)

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ABSTRACT: Complex $[RuCp(PPh_3)_2(HdmoPTA)](OSO_2CF_3)_2$ (**2**) was synthesized and characterized by elemental analysis, IR and NMR spectroscopy. Its crystal structure was also determined by single-crystal X-ray diffraction. The complex showed a more potent antiproliferative activity than *cis*platin against a representative panel of human cancer cells.

The development of effective anticancer drugs is mandatory for medicinal chemists. Cancer is one of the plagues of our time that has not a general and totally effective cure. The earliest studies by B. Rosenberg in 1965 on the antiproliferative activity of *cis*platin and its FDA-approval as a chemotherapeutic agent in 1979 led to this compound to be one of the most clinical useful anticancer drugs.[1] Nevertheless its value, *cis*platin is not active against all cancer forms and displays several undesirable side effects such as large toxicity.[2] Many attempts are being focused to obtain new valuable anticancer drugs, effective on a large classes of cancer varieties, less toxic and better tolerated by the human body. Some compounds containing metals different to Pt have showed comparable anticancer activity than *cis*platin but with fewer side effects, ruthenium complexes being one of the most currently interesting alternative.[3] Regarding platinum compounds ruthenium complexes exhibit lower systemic toxicity and specific accumulation in cancer cells.[3,6] The early experiments (1980s) with *fac*-$[Cl_3(NH_3)_3Ru]$, *cis*-$[Cl_2(NH_3)_4Ru]Cl$ (CCR) and (ImH)*trans*-$[(Im)_2Cl_4Ru]$ (ICR) showed that these compounds are active agents against the cervix cancer cell line HeLa with less toxicity than *cis*platin.[4] Since these initial findings, new anticancer ruthenium-based therapeutic agents such as NAMI-A, KP1019, NKP1339, KP418 or RAPTA derivatives (**Figure 1**) have been obtained.[3,5]

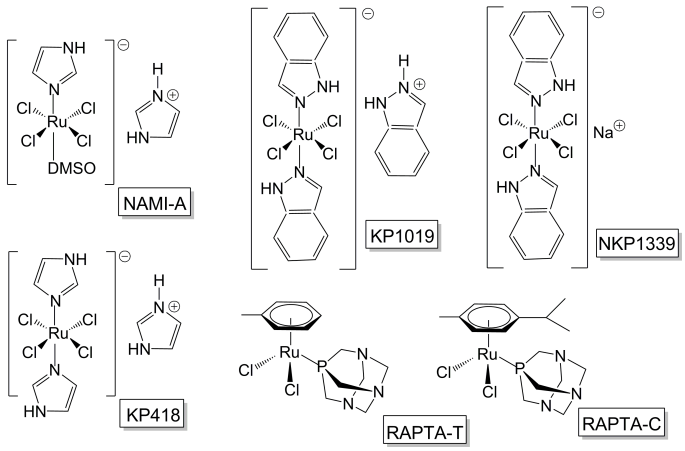


Figure 1. Some known ruthenium complexes with significant anticancer and antimetastatic activity.

In the past, we have been engaged actively in the synthesis of arene-ruthenium complexes $[RuCpX(L)(L')]^{n+}$ (X = Cl; L PPh_3; L' = PTA, mPTA) (PTA = 1,3,5-triaza-7-phosphaadamantane; mPTA = *N*-methyl-PTA) (**Figure 2**), which showed good water solubility and active cytotoxic properties particularly on *cis*platin resistant cells.[7] Their antiproliferative activities were related to ligands bonded to the metal, which modify the electronic properties of the complexes but also their partition coefficient (Log *P*). The outcome of those studies pointed out that the same basic structure with new PTA derivatives (**Figure 2**) could provide more active anticancer agents.

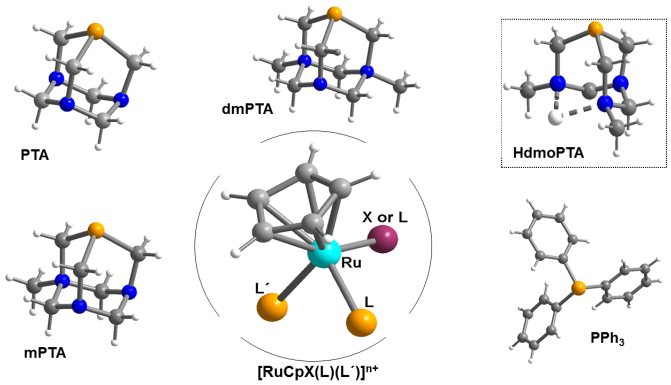
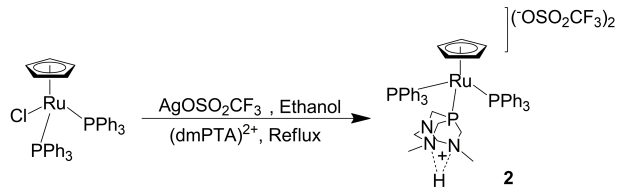


Figure 2. A careful selection of ligands, metal centre, and reaction conditions can confer control over the topology of the piano-stool complexes $[RuCpX(L)(L')]^{n+}$ (X = Cl; L = PPh_3; L´= PTA, mPTA; dmPTA; HdmoPTA) allowing modulation of the activity against human tumour cells.

With this aim, the ruthenium complex $[RuClCp(PPh_3)(HdmoPTA)](OSO_2CF_3)$ (**1**), containing the new PTA derivative 3,7-H-3,7-dimethyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (HdmoPTA), was obtained.[8] This ligand is able to be solubilized in water and organic solvents and its solubility could be modified easily by deprotonation.

Complex **1** was identified as an antiproliferative compound against a panel of representative human solid tumor cell lines with GI_{50} values in the range 1.5-2.6 μM (**Table 1**, *vide infra*). Nevertheless, it is important to stress that the antiproliferative properties of this complex were found to be clearly different to those of their parent complexes.[9]

Substitution of the proton in HdmoPTA by a metal provided bis-heterometal complexes $[RuClCp(PPh_3)$-μ-dmoPTA-1κP:2$\kappa^2 N,N'$-$MCl_2]$(M = Co, Ni, Zn),[10a] which showed similar antiproliferative activity than **1**.[9] This fact suggested that the biological activity of these complexes could implicate the exchange of the Cl bonded to the Ru, as for Pt complexes has been observed.[4] To investigate this possibility the new {CpRu} parent complex $[RuCp(PPh_3)_2(HdmoPTA)](OSO_2CF_3)_2$ (**2**), which does not contain Cl bonded to the metal, was synthesized (**see ESI**†) by the reaction of $[RuClCp(PPh_3)_2]$ first with $Ag(OSO_2CF_3)$ and then with $dmPTA(OSO_2CF_3)_2$ (**Scheme 1**) (dmPTA = *N,N´*-dimethyl-PTA; **Figure 2**).[8]



Scheme 1. Synthesis of $[RuCp(PPh_3)_2(HdmoPTA)](OSO_2CF_3)_2$ (**2**)

Complex **2** is soluble in organic solvents such as chloroform, acetone, methanol, DMSO and mostly insoluble in water (S_{25,H_2O}(mg/cm^3): 0.2). The complex remains unaltered in DMSO and DMSO/H_2O solutions under air for more than 2 h both at room temperature and 38 °C. Its ^{1}H NMR ($CDCl_3$) displays a characteristic η^5-Cp singlet at 4.90 ppm, which is shifted to low field with respect to its correspondent in **1** (4.56 ppm) in acetone-d_6. The PPh_3 signals (30 H) arise at typical aromatic range. The remaining signals belong to the HdmoPTA group, two contiguous broad singlets are due to both NCH_3 groups at 2.35 ppm and 2.36 ppm (6 H), which resemble those of the NCH_3 groups in **1** (2.49 ppm).[8] Finally, the multiplet at 1.25 ppm (1 H) corresponds to the hydrogen shared between both N_{CH_3} atoms. This suspicion was confirmed by a ^{1}H,^{1}H-2D COSY NMR experiment that showed how this signal is coupled with NCH_2NCH_3 and PCH_2NCH_3 groups (**Figure S1, ESI**†). The $^{31}P\{^1H\}$ NMR in $CDCl_3$ shows a doublet at 38.44 ppm (2P) and a triplet at -13.94 ppm (1P) that only could be assigned respectively to two PPh_3 and one HdmoPTA coordinated by the P atom despite of those chemical shifts are quite different to those in complex **1** (46.13 ppm; -1.80 ppm) in acetone-d_6.

The crystal structure of **2** was determined by single-crystal X-ray diffraction and is showed in **Figure 3** (selected crystallographic parameters, distances and angles are display in **Table S1, ESI**†). The crystallographic study confirmed that the coordination sphere of the Ru is a distorted pseudo-octahedron constituted by a η^5-Cp, two PPh_3 and a HdmoPTA bonded by the P atom. The Cp ring is essentially planar (the larger separation from the overall Cp plane is 0.0089 Å (C84)), being the distance to the metal (Ru-$Cp_{cent.}$= 1.886 Å) similar to those found in parent Cp-piano-stool complexes.[8,10] The angle between the Cp plane and the plane defined by P1-Ru1-P3 (47.6°) and P2-Ru1-P3 (46.8°) are smaller than that in **1** (55.3°) while the angle P1-Ru1-P2 is found to be 103.3(4)°, which is near to that observed in similar complexes $[RuCpX(PPh_3)_2]$ (X = CN, 103.6(1)°; CNHCN, 102.5(1)°).[11] The $N_{CH_3}\cdots N_{CH_3}$ distance of 2.800 Å is somewhat larger than that for **1** ($d_{N1P\cdots N3P}$ = 2.702 Å) and the torsion angles for the cationic unit HdmoPTA (C75-N73-C73-P3 = -57.3° and C76-N71-C71-P3 = 51.6°) somewhat shorter than those in **1** (C5P-N1P-C3P-P2 = -54.5° and C4P-N3p-C1P-P2 = 58.9°).[8]

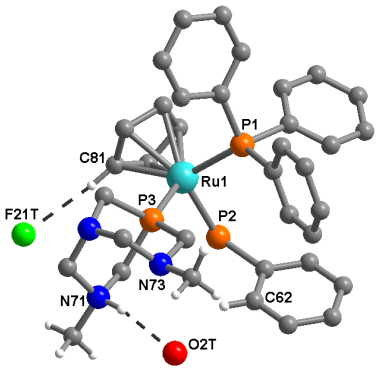


Figure 3. A perspective drawing of **2** with atom numbering. For the sake of clarity, the dashed lines N73···H71 (2.178(4) Å) and O2T···H62 (2.578(4) Å were omitted.

Furthermore, the O2T is located more than 3 Å from C62, well outside of normal H-bonding distance but at 2.814(6) Å from N71, bond length that supports the H-bond interaction N71-H71···O2T ($d_{H71\cdots O2T}$= 2.103(4) Å). Likewise, the crystal packing diagram is strengthened by another weak intermolecular interaction (C81-H81···F21 = 3.433(3) Å) and the C-H/π interactions[12] between the aromatic centroid and the adjacent phenyl-C-H groups (centroid-to-C-H distances from 3.183(5) to 4.039(5) Å, **Figure 4**).

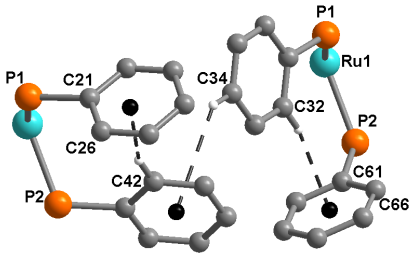


Figure 4. C-H/π interactions in **2**: $d_{centroid\text{-}to\text{-}C32\text{-}H32}$ = 3.183(5); $d_{centroid\text{-}to\text{-}C34\text{-}H34}$ = 4.039(5) and $d_{centroid\text{-}to\text{-}C42\text{-}H42}$ = 3.470(5).

The antiproliferative activity of **2** was studied in a panel of representative human solid tumour cell lines.[13] Thus, cells were exposed to the compound for 48 h and the results expressed as GI_{50} are given in **Table 1**. Overall, the GI_{50} values of **2** against all cell lines were in the range 0.17-0.29 μM, which are significantly lower than those for the reference anticancer drug *cis*platin and complex **1**. Significant differences between antiproliferative activity of **2** and *cis*platin were observed for T-47D (*ca.* 70:1) and WiDr (> 100:1) cells, which are more *cis*platin resistant.[9]

It is important to point out that the GI_{50} values of **2** are larger than those for **1**.[9] To the best of our knowledge the antiproliferative activity of **2** against human solid tumour cell lines is among the largest known.[14]

The main structural difference between **1** and **2** is the presence of one or two PPh3 groups, respectively. The enhancement of the biological activity due to the addition of PPh3 ligands has been reported for other ruthenium complexes.[15] This result is consistent with the reported findings for **1** and **2**, and with our previous observations of the parent PTA and HPTA complexes RuCp(DMSO-κS)(PTA)2](OSO2CF3), [RuCp(DMSO-κS)(HPTA)2]Cl3·2H2O and [RuClCp(HPTA)2]Cl2·2H2O,[10b] which were tested against HeLa, SW1573, T-47D and WiDr cells, resulting inactive (GI50 > 100 μM) in all cell lines (*unpublished results*). Noteworthy, the presence of PPh3 groups is not always enough for ensuring an antiproliferative effect. Solubility of the complexes plays also a crucial role. For instance, {CpRu} precursor [RuClCp(PPh3)2] is insoluble under the NCI protocol requirements (40 mM in DMSO) and therefore could not be tested.[13]

Table 1. GI_{50} values of complexes **1**,[a] **2** and *cis*platin against human solid tumor cells lines.[b]

	Cell line (*origin*)				
	A549 (lung)	HeLa (*cervix*)	SW1573 (*lung*)	T-47D (*breast*)	WiDr (*colon*)
1[a]	-	2.6 (±0.2)	1.5 (±0.1)	1.9 (±0.5)	1.7 (±0.4)
2	0.29 (±0.09)	0.17 (±0.04)	0.20 (±0.02)	0.25 (±0.04)	0.20 (±0.03)
*cis*platin	4.9 (±0.2)	1.8 (±0.5)	2.7 (±0.4)	17 (±3.3)	23 (±4.3)

[a] $[RuClCp(PPh_3)(HdmoPTA)](OSO_2CF_3)$ (**1**)[9]
[b] Values are given in μM and are means of at least three experiments (±standard deviation).

Next, we examined cell cycle phase distribution by flow cytometry[13] to determine whether cell growth inhibition caused by compound **2** involved cell cycle changes (**Figure 5, Table S6, ESI**†). Contrary to *cis*platin, which induces the accumulation in S-phase of A549, SW1573 and WiDr cells, we found that ruthenium complex **2** produced the accumulation at G1 phase of the cell cycle. However, in HeLa cells, *cis*platin is known to induce accumulation at G1 phase.[16] Interestingly, compound **2** produced an increase of the G2/M compartment in HeLa. These results clearly indicate that the mechanism of action of the new compound differs from that of *cis*platin.

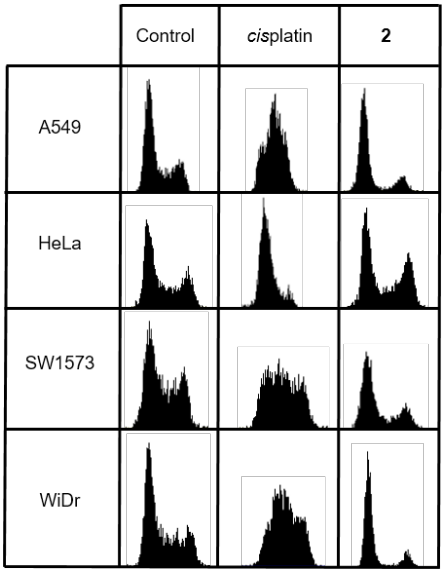


Figure 5. Histogram of untreated cells (C) and cells treated (drug dose in μM) for 24 h with cisplatin (CDDP) and complex **2**. Cells were exposed to *cis*platin at 10 μM (A549, HeLa and SW1573) or 20 μM (WiDr), and to complex **2** at 0.5 μM.

H. Liu and P. Sadler[17] have shown that the insertion of a coordinated aromatic ligand able to intercalate into DNA provides some metal complexes with a dual mode of binding, that is, intercalation between the DNA bases and metal coordination to a DNA base. Ru-arene complexes with such a dual mode of binding exhibit stronger cytotoxicity toward cancer cells than the non-intercalating counterparts.[18]

Cell cycle experiments together with our previous finding for complex **1**,[9] allow us to discard DNA as the main biological target for compound **2**. It has been described that ruthenium compounds might directly interfere with proteins.[14b] At present, this extent has not been confirmed for complex **2**.

Another interesting point to study is the role of the positively charged complex, which might be essential to force interaction with the negatively charged cell membrane. The geometries of complexes **1** and **2** were modelled by DFT[19,20] (**see ESI**†) with the aim of obtaining information of how it changes from those in crystal and to know how the charges are distributed in molecules, which could justify their different antiproliferative activity. The modelled structures of both complexes retain the disposition of the ligands around the metal as in the crystal. The HOMO-LUMO energy gap is very similar in both complexes (3.840 eV for **1**, 3.858 eV for **2**), being the HOMO/LUMO energies of **1** the higher (**1**: HOMO = -10.267 eV, LUMO = -6.427 eV; **2**: HOMO = -7.333 eV, LUMO = -3.475 eV). For both complexes the largest bond distance differences respecting those in crystal structures were found for Ru-P bonds: +8.7% for Ru1-P1 in **1** and +10.5% for Ru1-P2 in **2**.

The charge distribution on the phenyl rings of **1** and **2** do not differ significantly. Therefore, the electronic distribution in both complexes is similar and could not justify the large antiproliferative activity differences between them. Nevertheless, the separation (from 3.951 to 3.871 Å) between both almost parallel (4.73°, **Figure S4, ESI**[†]) phenyl rings C21-C26 and C61-C66 (**Figure 4**), which could be the responsible of the exceptional antiproliferative activity of **2**.[21] Nonetheless, other possible mechanisms have been identified to justify the biological activity of ruthenium complexes[14] and therefore, further studies outside the scope of this work will be necessary to depict the mechanism of action of **2**.

In conclusion, complex **2** displays a high antiproliferative activity largely bigger than most of the known platinum drugs and ruthenium complexes. Experimental and theoretical studies are in progress to determine the specific mechanism of action of complex **2** against cancer cells. The synthesis of parent ruthenium complexes containing the ligand HdmoPTA and its derivatives is also in progress as well as the study of their biological activity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information **ESI**[†] is available free of charge on the ACS Publications website at DOI:

Experimental procedures, NMR spectroscopic data and Figure S1 giving ^{1}H,^{1}H-2D COSY NMR of **2**; Growth inhibition assays of compound **2**, Table S1 giving selected X-ray crystallographic data of compound **2;** Tables S2-S5 and Figures S2 and S3 giving the DFT details for complexes **1** and **2**, respectively and Figure S4 giving optimized structure of **2** including planes containing the aryls C21-C26 and C61-C66, angle between them and separation between rings and facing planes (**PDF**); Table S6 summarize the histograma of human solid tumour cells after exposure to compounds for 24 h.

X-ray crystallographic data of complex **2** (CCDC 1465060) (**CIF**).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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The complex $[RuCp(PPh_3)_2(HdmoPTA)](OSO_2CF_3)_2$ showed more potent antiproliferative activity than *cis*platin against a representative panel of human cancer cells.