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# New Class of Half-Sandwich Ruthenium(II) Arene Complexes Bearing the Water-Soluble CAP Ligand as an in Vitro Anticancer Agent

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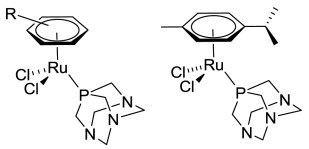
Supporting Information

**ABSTRACT:** Ruthenium(II) arene complexes of 1,4,7-triaza-9-phosphatricyclo[5.3.2.1]tridecane (CAP) were obtained. Cytotoxicity studies against cancer cell lines reveal higher activity than the corresponding PTA analogues and, in comparison to the effects on non-cancerous cells, the complexes are endowed with a reasonable degree of cancer cell selectivity.

Since the discovery of cisplatin in 1965,[1,2] interest in the application of coordination complexes to treat cancer and other diseases has continually increased.[3] In particular, when resistance to cisplatin developed,[4,5] certain classes of ruthenium complexes were found to be active,[6] including ruthenium(III) coordination complexes[7−9] and half-sandwich ruthenium(II) arene organometallic derivatives.[10−14] RAPTA-type compounds (Chart 1) were identified as promising anticancer agents,[15,16]

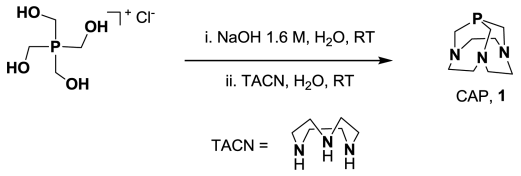
**Chart 1. Prototypical RAPTA-Type (R = H, Me, $Me_6$) and RAPTA-C Structures**




with their water solubility being given by the cage-like 1,3,5-triaza-7-phosphaadamantane (PTA) ligand, binding the metal in a $\kappa^1$-*P* fashion.[17−19] Several studies evaluating the antitumor activity of RAPTA-C revealed strong antiangiogenic and antimetastatic activities,[20,21] together with a good efficacy in inhibiting tumor growth even at moderate doses,[22] low general toxicity, and tolerance to low pH,[23,24] suitable for investigation as an orally administered drug. For this class of compounds, the reactivity and stability, uptake into cancer cells, target recognition, and overall cytotoxicity and cancer cell selectivity were found to heavily depend on the choice of phosphine. Indeed, modification of the PTA ligand often led to increased cytotoxicity, but at the same time caused the cancer cell selectivity to be lost.[25]

We have been interested in the application of Ru-PTA complexes not only as antitumor agents but also as selective catalysts for hydrogenation reactions.[26−33] Recently, the new ligand 1,4,7-triaza-9-phosphatricyclo[5.3.2.1]tridecane (CAP, **1**) was reported (Scheme 1).[34]

**Scheme 1. Modified Synthesis of Ligand 1**




CAP has a tris(homoadamantane) cage similar to PTA and was obtained by Mannich-type condensation of 1,4,7-triazacyclononane (TACN) and tris(hydroxymethyl)phosphine (THP).[35,36] CAP has a higher cage flexibility due to the presence of two $CH_2$ spacers between the N atoms. Electron density distribution analysis showed that the P and N atoms of CAP exhibit comparable electron donicity, bringing about different reactivities of CAP and PTA toward protonation at N sites and alkylation at N and P atoms.[37−39] In the search for new RAPTA-type compounds with potential anticancer activity, we decided to explore the coordination properties of CAP to ruthenium(II) arene moieties. The obtained complexes were evaluated in vitro against human ovarian (A2780 and A2780cis) cancer and human embryonic kidney (HEK) cell lines, and the preliminary results of these studies are presented here.

The synthesis of **1** was slightly modified compared to that in the literature. As for PTA,[40] the air-stable and commercially available tetrakis(hydroxymethyl)phosphonium chloride (THPC; 80% aqueous solution) was first treated with a NaOH solution (1.6 M), producing in situ THP [P-$(CH_2OH)_3$], which was reacted without isolation with an aqueous solution of TACN at room temperature (Scheme 1). After extraction of the aqueous phase with $CHCl_3$ and recrystallization of the crude product from hot ethanol (EtOH), **1** was obtained as a white crystalline solid in high purity. Also in our case, formation of the unidentified amorphous solid originally observed could not be avoided.[34] Our procedure has the advantage of using the less expensive and easier-to-handle THPC instead of air-sensitive THP and a

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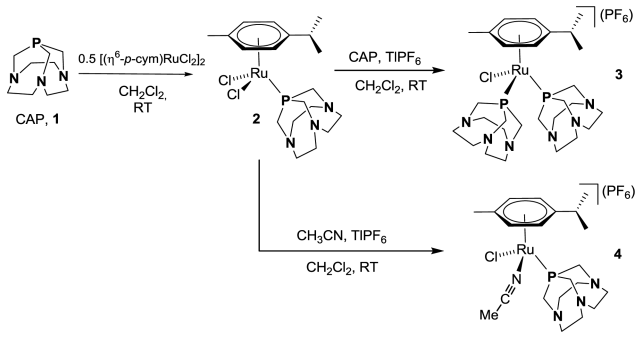
facile workup consisting of a simple extraction and recrystallization.

The RAPTA-C analogue $\kappa^1$-*P*-[($\eta^6$-*p*-cymene)$RuCl_2$(CAP)] (**2**, RACAP-C) was obtained by reacting [($\eta^6$-*p*-cymene)-$RuCl_2$]$_2$ with 2 equiv of CAP in $CH_2Cl_2$ at room temperature,

**Scheme 2. Syntheses of RACAP-Type Complexes 2−4**




affording **2** in 87% yield after purification (Scheme 2). The $^{31}P\{^1H\}$ NMR spectrum of **2** in $CDCl_3$ shows a singlet at 52.83 ppm, a rather different chemical shift than RAPTA-C (−36.63 ppm)[19] and in line with the gold(I) CAP derivative [(CAP-$H_2$)$_3$Au]$^{7+}$ (50.99 ppm).[34] The substantial $^{31}P\{^1H\}$ NMR downfield shift is not unexpected because of the different P-donor properties of **1**.[37] In the corresponding $^1H$ NMR spectrum, the cage protons of coordinated CAP give a multiplet in the range 3.07−2.92 ppm for N($CH_2$)$_2$N and a doublet centered at 3.70 ppm ($^2J_{HP}$ = 7.2 Hz) due to P$CH_2$N. This assignment was verified by $^1H\{^{31}P\}$ NMR spectroscopy, with the doublet turning into a singlet upon P decoupling. The aromatic protons of the *p*-cymene ring give a broad singlet at 5.48 ppm, similar to the signal at 5.46 ppm reported for [($\eta^6$-*p*-cymene)$RuCl_2$(PTA)].[19] In the $^{13}C\{^1H\}$ NMR spectrum of **2**, the $\eta^6$-coordinated arene ring affords two doublets for the aromatic *C*H C atoms at 88.55 and 83.97 ppm with $^2J_{CP}$ = 2.5 and 3.4 Hz, respectively. The proposed structure of **2** was also confirmed by electrospray ionization mass spectrometry (ESI-MS), with a peak envelope centered at *m*/*z* 470.2 corresponding to the cation [($\eta^6$-*p*-cymene)RuCl(CAP)]$^+$, i.e., the expected [M − Cl]$^+$ ion.

The ruthenium(II) complex $\kappa^1$-*P*-[($\eta^6$-*p*-cymene)RuCl-(CAP)$_2$]$PF_6$ (**3**) was obtained in ca. 77% yield by reacting **2** with 1 equiv of CAP and a stoichiometric amount of $TlPF_6$ (Scheme 2). The $^{31}P\{^1H\}$ NMR spectrum of **3** in acetone-$d_6$ contains a singlet at 51.60 ppm, corresponding to the two equivalent phosphines and a septet at −144.26 ppm ($J_{PF}$ = 707.5 Hz) attributable to the $PF_6^-$ counterion (confirmed by the IR peak at 841.95 cm$^{-1}$, KBr). In the $^1H$ NMR spectrum, two doublets at 6.55 and 6.26 ppm ($J_{HH}$ = 6.4 Hz) corresponding to the aromatic protons of the arene ligand were observed, and the protons of P$CH_2$N give two sets of multiplets in the range 3.85−3.67 ppm, which afford a defined AB system ($J_{HAHB}$= 16.0 Hz) in the $^1H\{^{31}P\}$ NMR spectrum (see the Supporting Information). In line with the data obtained for the PTA analogue,[41] the ESI-MS spectrum of **3** contains a peak at *m*/*z* 669.3 consistent with the ion [($\eta^6$-*p*-cymene)RuCl(CAP)$_2$]$^+$ and a peak of lower relative intensity at *m*/*z* 470.2 corresponding to [($\eta^6$-*p*-cymene)RuCl(CAP)]$^+$, due to the loss of one phosphine ligand.

The complex $\kappa^1$-*P*-[($\eta^6$-*p*-cymene)RuCl(MeCN)(CAP)]$PF_6$ (**4**) was obtained from **2** by chloride abstraction with $TlPF_6$ and ligand substitution with $CH_3CN$ (Scheme 2). The $^{31}P\{^1H\}$ NMR spectrum of **4** exhibits a singlet at 48.17 ppm corresponding to the P atom in the CAP ligand and a septet at −144.27 ppm ($J_{PF}$ = 707.8 Hz) corresponding to the $PF_6^-$ ion (IR peak at 839.16 cm$^{-1}$). The presence of coordinated acetonitrile in **4** was confirmed by the singlet at 2.52 ppm in the $^1H$ NMR spectrum and by the two singlets at 128.55 and 3.91 ppm in the $^{13}C\{^1H\}$ NMR spectrum, with the the former attributed to *C*≡N and the latter to *C*$H_3$CN.[42] The $^1H$ NMR spectrum of **4** showed two well-distinguished doublets centered at 1.26 and 1.25 ppm ( $^3J_{HH}$ = 6.8 Hz) for the arene $CH_3$ isopropyl groups upon loss of symmetry in the piano-stool geometry. The solubilities of **2**−**4** in water were determined at 20 °C. Complex **2** was found to be much less water-soluble than RAPTA-C, with $S(H_2O)_{20\ °C}$ = 0.86 versus 10 g/L. The ionic complexes **3** and **4** were slightly more soluble than **2**, with values of 1.2 and 1.1 g/L, respectively.

The thermal stability of **2** in $D_2O$ was determined by variable-temperature NMR experiments. No changes were observed in the corresponding $^{31}P\{^1H\}$ NMR spectra (singlet at 57.48 ppm) in the temperature range 25−60 °C for a total of 30 h of experiment.

The stabilities of complexes **2**−**4** under pseudopharmacological conditions were also determined in aqueous NaCl/$D_2O$ (100 mM) at 37 °C for 72 h, monitoring every 24 h by $^1H$ and $^{31}P\{^1H\}$ NMR (see the Supporting Information). Complex **2** was stable under these conditions; i.e., the NMR spectra remained unchanged after 72 h, showing a $^{31}P\{^1H\}$ NMR singlet at 57.31 ppm. Complex **3** showed after 7 h the presence of singlets at 56.77 ppm (ca. 47% by integration), due to the original complex, and at 57.31 ppm (ca. 30%), due to the formation of **2** upon CAP-$Cl^-$ exchange. Two less intense singlets were also observed at 58.46 ppm (10%) and 54.44 ppm (13%). After 48 h, the **3**:**2** ratio reached ca. 1:1, and it was maintained until the end of the experiment. Similarly, complex **4**, characterized by a $^{31}P\{^1H\}$ NMR singlet at 54.30 ppm, immediately underwent MeCN−$Cl^-$ exchange to form complex **2** (ca. 60%). The ratio between **2** and **4** remained constant during the following 72 h (Figures S16−S21 in the Supporting Information).

Suitable crystals for single-crystal X-ray diffraction of **2** and **3** were obtained from the slow diffusion of dry EtOH in a $CH_2Cl_2$ solution of each complex. The molecular structure of **2** (Figure 1) consists of a $Ru^{II}$ center coordinated by a $\eta^6$-*p*-cymene unit, two Cl atoms, and a $\kappa^1$-*P* CAP ligand. The CAP ligand does not experience significant changes of the [333] conformation observed in the free ligand.[43] Accordingly, the intramolecular P···N ($d_{PN}$) and N···N ($d_{NN}$) distances of CAP in **2** range from 2.824 to 2.808 Å and from 3.028 to 3.064 Å, respectively (comparable to that found for uncoordinated CAP, i.e., an average $d_{PN}$ of 2.886 Å and an average $d_{NN}$ of 3.1132 Å).[37] The Ru−P bond length in **2** is significantly longer compared to that observed in the analogous PTA structure [i.e., 2.3180(5) vs 2.296(2) and 2.298(2) Å].[19] The same applies to the Ru−C(*p*-cymene) bond lengths [i.e., 2.198(2) and 2.275(2) Å in **2** versus 2.179(9) and 2.210(10) Å in the PTA analogue].[19]

The replacement of one $Cl^-$ in **2** by a CAP ligand, to give the monocationic ruthenium species **3** (Figure 2), leads to an elongation of the Ru−P [i.e., 2.3180(5) Å (**2**) vs 2.3254(7) and 2.3353(7) Å (**3**·2MeOH·$H_2O$)] and Ru−C(*p*-cymene) [i.e., 1.709 Å (**2**) vs 1.768 Å (**3**·2MeOH·$H_2O$)] bonds compared to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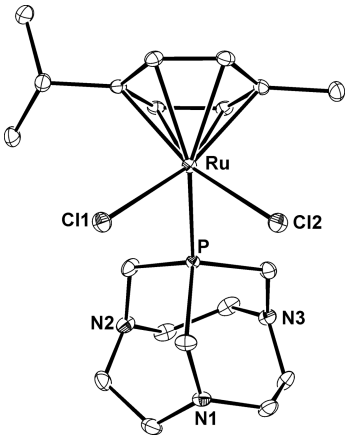


**Figure 1.** Molecular structure of **2**. Thermal ellipsoids are presented at a 30% probability level, and H atoms are omitted for clarity. Selected bond distances (Å) and angles (deg): Ru−Cl1 = 2.4184(5), Ru−Cl2 = 2.4205(5), Ru−P = 2.3180(5), Ru−centroid (C1−C6) = 1.709; Cl1−Ru−Cl2 = 87.601(19), Cl1−Ru−P = 86.937 (19), Cl2−Ru−P = 83.775(18).

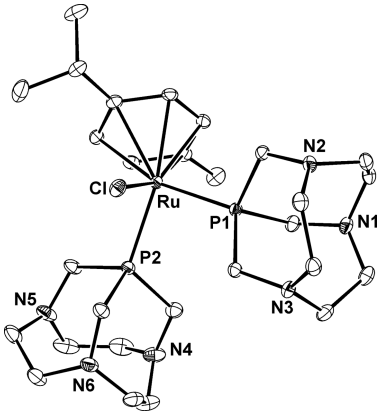


**Figure 2.** Molecular structure of **3**·2MeOH·$H_2O$. Thermal ellipsoids are presented at a 30% probability level, and H atoms, counteranions, and solvent molecules are omitted for clarity. Selected bond distances (Å) and angles (deg): Ru−Cl = 2.4026(7), Ru−P1 = 2.3254(7), Ru−P2 = 2.3353(7), Ru−centroid (C1−C6) = 1.768; Cl−Ru−P1 = 83.59(2), Cl−Ru−P2 = 87.90(3), P1−Ru−P2 = 93.37(3).

**2**, whereas the Ru−Cl bond shortens from 2.4205(5) Å (**2**) to 2.4026(7) Å (**3**·2MeOH·$H_2O$). The overall conformation of the coordinated CAP is essentially identical with that found in **2**. The significantly different Ru−P bond lengths found for **2** and **3**·2MeOH·$H_2O$ correlate with the slightly higher positive $^{31}P$ coordination shift found for **2** in solution [i.e., 52.83 ppm, $d_{RuP}$= 2.3180(5) Å for **2**, vs 51.60 ppm, $d_{RuP}$ = 2.3254(7) and 2.3353(7) Å for **3**·2MeOH·$H_2O$]. The stronger Ru−*p*-cymene interaction in **2** compared to **3**, observed in the solid state, is thus maintained in solution. Accordingly, the aromatic $^1H$ NMR signals assigned to *p*-cymene in **2** are shifted upfield compared to **3**. In addition, the $^{13}C\{^1H\}$ NMR signals of the aromatic C atoms of *p*-cymene in **2** have small $^2J_{CP}$ values of 2.5 and 3.4 Hz, whereas in **3**, only $^{13}C\{^1H\}$ NMR singlets are observed.

Compounds **1**−**4** were tested for their cytotoxicity to human ovarian A2780 carcinoma cells and the A2780cisR variant with acquired resistance to cisplatin as well as against noncancerous HEK293 cells, using MTT assay (Table 1). All complexes

**Table 1. Cytotoxicity ($IC_{50}$, $\mu$M, 72 h) of 1−4 to A2780 and A2780cisR Cancer Cells and Non-cancerous HEK293 Cells**

| compound | A2780 | A2780cisR | HEK293 |
|---|---|---|---|
| **1** | >200 | >200 | >200 |
| **2** | 55.3 ± 18.6 | 108 ± 10 | 102 ± 26 |
| **3** | 48.1 ± 2.2 | 99.2 ± 15.9 | 80.7 ± 12.4 |
| **4** | 65.2 ± 18.0 | 70.6 ± 3.1 | 163 ± 46 |
| RAPTA-C[a] | 230 | 270 | >1000 |

[a]Values taken for comparison from ref 45.

induced a dose- and cell-dependent decrease in the cell viability, with **1** exerting only minor cytotoxic effects (not reaching the $IC_{50}$ value in the tested concentration range). The similar $IC_{50}$ values of the complexes are likely due to the same species formed by **3** and **4** in aqueous solution after ligand exchange reactions leading to **2**. Compared to RAPTA-C, the compounds are considerably more cytotoxic toward all cell lines. However, only complex **4** shows essentially equal cytotoxicity toward both the A2780 and A2780cisR cells. In comparison to complexes with other PTA-type ligands, complexes **2**−**4** maintain their cancer cell selectivity by a 2-fold stronger growth inhibition effect on A2780 cancer cells compared to noncancerous HEK293 cells. Usually modification of the PTA ligand has often led to more cytotoxic complexes but at the same time reduces the cancer cell selectivity.[30,44]

In conclusion, novel ruthenium(II) arene half-sandwich complexes bearing the cage-type CAP were prepared and characterized. Compared to RAPTA-C, the direct CAP analogue **2** is more cytotoxic to cancer cells and exhibits a reasonable degree of cancer cell selectivity. Other PTA-type ligands previously studied have not maintained the desirable cancer cell selectivity exhibited by the CAP derivatives.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.7b00915.

General methods and materials, synthetic procedures, NMR and MS spectra, tables for X-ray crystal structure determination, stability tests, and details of in vitro cytotoxicity tests (PDF)

X-ray crystallographic data in CIF format (CIF)

X-ray crystallographic data in CIF format (CIF)

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### Author Contributions

All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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## REFERENCES


(1) Rosenberg, B.; Van Camp, L.; Krigas, T. Inhibition of Cell Division in Escherichia Coli by Electrolysis Products from a Platinum Electrode. *Nature* **1965**, *205*, 698−699.

(2) Rosenberg, B.; Van Camp, L.; Trosko, J. E.; Mansour, V. H. Platinum Compounds: A New Class of Potent Antitumour Agents. *Nature* **1969**, *222*, 385−386.

(3) Martins, P.; Marques, M.; Coito, L.; Pombeiro, A. J. L.; Baptista, P. V.; Fernandes, A. R. Organometallic Compounds in Cancer Therapy: Past Lessons and Future Directions. *Anti-Cancer Agents Med. Chem.* **2014**, *14*, 1199−1212.

(4) Hambley, T. V. The Influence of Structure on the Activity and Toxicity of Pt Anti-Cancer Drugs. *Coord. Chem. Rev.* **1997**, *166*, 181−223.

(5) Guo, Z.; Sadler, P. J. Metals in Medicine. *Angew. Chem., Int. Ed.* **1999**, *38*, 1512−1531.

(6) Clarke, M. J. Ruthenium Metallopharmaceuticals. *Coord. Chem. Rev.* **2003**, *236*, 209−233.

(7) Hartinger, C. G.; Zorbas-Seifried, S.; Jakupec, M. A.; Kynast, B.; Zorbas, H.; Keppler, B. K. From Bench to Bedside − Preclinical and Early Clinical Development of the Anticancer Agent Indazolium *trans*-[tetrachlorobis(1*H*-indazole)ruthenate(III)] (KP1019 or FFC14A). *J. Inorg. Biochem.* **2006**, *100*, 891−904.

(8) Hartinger, C. G.; Jakupec, M. A.; Zorbas-Seifried, S.; Groessl, M.; Egger, A.; Berger, W.; Zorbas, H.; Dyson, P. J.; Keppler, B. K. KP1019, A New Redox-Active Anticancer Agent - Preclinical Development and Results of a Clinical Phase I Study in Tumor Patients. *Chem. Biodiversity* **2008**, *5*, 2140−2155.

(9) Bergamo, A.; Gaiddon, C.; Schellens, J. H. M.; Beijnen, J. H.; Sava, G. Approaching Tumour Therapy beyond Platinum Drugs: Status of the Art and Perspectives of Ruthenium Drug Candidates. *J. Inorg. Biochem.* **2012**, *106*, 90−99.

(10) Aird, R. E.; Cummings, J.; Ritchie, A. A.; Muir, M.; Morris, R. E.; Chen, H.; Sadler, P. J.; Jodrell, D. I. In Vitro and in Vivo Activity and Cross Resistance Profiles of Novel ruthenium(II) Organometallic Arene Complexes in Human Ovarian Cancer. *Br. J. Cancer* **2002**, *86*, 1652−1657.

(11) Novakova, O.; Kasparkova, J.; Bursova, V.; Hofr, C.; Vojtiskova, M.; Chen, H.; Sadler, P. J.; Brabec, V. Conformation of DNA Modified by Monofunctional Ru(II) Arene Complexes: Recognition by DNA Binding Proteins and Repair. Relationship to Cytotoxicity. *Chem. Biol.* **2005**, *12*, 121−129.

(12) Morris, R. E.; Aird, R. E.; del Socorro Murdoch, P.; Chen, H.; Cummings, J.; Hughes, N. D.; Parsons, S.; Parkin, A.; Boyd, G.; Jodrell, D. I.; Sadler, P. J. Inhibition of Cancer Cell Growth by Ruthenium(II) Arene Complexes. *J. Med. Chem.* **2001**, *44*, 3616−3621.

(13) Aliende, C.; Pérez-Manrique, M.; Jalón, F. A.; Manzano, B. R.; Rodríguez, A. M.; Cuevas, J. V.; Espino, G.; Martínez, M. Á.; Massaguer, A.; González-Bártulos, M.; de Llorens, R.; Moreno, V. Preparation of New Half Sandwich Ruthenium Arene Complexes with Aminophosphines as Potential Chemotherapeutics. *J. Inorg. Biochem.* **2012**, *117*, 171−188.

(14) Vock, C. A.; Renfrew, A. K.; Scopelliti, R.; Juillerat-Jeanneret, L.; Dyson, P. J. Influence of the Diketonato Ligand on the Cytotoxicities of $[Ru(\eta^6\text{-}p\text{-cymene})(R_2acac)(PTA)]^+$ Complexes (PTA = 1,3,5-Triaza-7-Phosphaadamantane). *Eur. J. Inorg. Chem.* **2008**, *2008*, 1661−1671.

(15) Singh, S. K.; Pandey, D. S. Multifaceted Half-Sandwich Arene−ruthenium Complexes: Interactions with Biomolecules, Photoactivation, and Multinuclearity Approach. *RSC Adv.* **2014**, *4*, 1819−1840.

(16) Nazarov, A. A.; Hartinger, C. G.; Dyson, P. J. Opening the Lid on Piano-Stool Complexes: An Account of ruthenium(II)- Arene Complexes with Medicinal Applications. *J. Organomet. Chem.* **2014**, *751*, 251−260.

(17) Ang, W. H.; Casini, A.; Sava, G.; Dyson, P. J. Organometallic Ruthenium-Based Antitumor Compounds with Novel Modes of Action. *J. Organomet. Chem.* **2011**, *696*, 989−998.

(18) Murray, B. S.; Babak, M. V.; Hartinger, C. G.; Dyson, P. J. The Development of RAPTA Compounds for the Treatment of Tumors. *Coord. Chem. Rev.* **2016**, *306*, 86−114.

(19) Allardyce, C. S.; Dyson, P. J.; Ellis, D. J.; Heath, S. L. $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2(pta)]$ (pta = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]-decane): A Water Soluble Compound That Exhibits pH Dependent DNA Binding Providing Selectivity for Diseased Cells. *Chem. Commun.* **2001**, *2*, 1396−1397.

(20) Weiss, A.; Berndsen, R. H.; Dubois, M.; Müller, C.; Schibli, R.; Griffioen, A. W.; Dyson, P. J.; Nowak-Sliwinska, P. In Vivo Anti-Tumor Activity of the Organometallic ruthenium(II)-Arene Complex $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2(pta)]$ (RAPTA-C) in Human Ovarian and Colorectal Carcinomas. *Chem. Sci.* **2014**, *5*, 4742−4748.

(21) Nowak-Sliwinska, P.; van Beijnum, J. R.; Casini, A.; Nazarov, A. A.; Wagnières, G.; van den Bergh, H.; Dyson, P. J.; Griffioen, A. W. Organometallic Ruthenium(II) Arene Compounds with Antiangiogenic Activity. *J. Med. Chem.* **2011**, *54*, 3895−3902.

(22) Weiss, A.; Bonvin, D.; Berndsen, R. H.; Scherrer, E.; Wong, T. J.; Dyson, P. J.; Griffioen, A. W.; Nowak-Sliwinska, P. Angiostatic Treatment prior to Chemo- or Photodynamic Therapy Improves Anti-Tumor Efficacy. *Sci. Rep.* **2015**, *5*, 8990.

(23) Gossens, C.; Dorcier, A.; Dyson, P. J.; Rothlisberger, U. pKa Estimation of Ruthenium(II)−Arene PTA Complexes and Their Hydrolysis Products via a DFT/Continuum Electrostatics Approach. *Organometallics* **2007**, *26*, 3969−3975.

(24) Groessl, M.; Hartinger, C. G.; Dyson, P. J.; Keppler, B. K. CZE-ICP-MS as a Tool for Studying the Hydrolysis of Ruthenium Anticancer Drug Candidates and Their Reactivity towards the DNA Model Compound dGMP. *J. Inorg. Biochem.* **2008**, *102*, 1060−1065.

(25) Noffke, A. L.; Habtemariam, A.; Pizarro, A. M.; Sadler, P. J. Designing Organometallic Compounds for Catalysis and Therapy. *Chem. Commun.* **2012**, *48*, 5219−5246.

(26) Gonsalvi, L.; Guerriero, A.; Hapiot, F.; Krogstad, D. A.; Monflier, E.; Reginato, G.; Peruzzini, M. Lower- and Upper-Rim-Modified Derivatives of 1,3,5-Triaza-7-Phosphaadamantane: Coordination Chemistry and Applications in Catalytic Reactions in Water. *Pure Appl. Chem.* **2012**, *85*, 385−396.

(27) Krogstad, D. A.; Guerriero, A.; Ienco, A.; Manca, G.; Peruzzini, M.; Reginato, G.; Gonsalvi, L. Imidazolyl-PTA Derivatives as Water-Soluble (P,N) Ligands for Ruthenium-Catalyzed Hydrogenations. *Organometallics* **2011**, *30*, 6292−6302.

(28) Six, N.; Guerriero, A.; Landy, D.; Peruzzini, M.; Gonsalvi, L.; Hapiot, F.; Monflier, E. Supramolecularly Controlled Surface Activity of an Amphiphilic Ligand. Application to Aqueous Biphasic Hydroformylation of Higher Olefins. *Catal. Sci. Technol.* **2011**, *1*, 1347−1353.

(29) Casini, A.; Edafe, F.; Erlandsson, M.; Gonsalvi, L.; Ciancetta, A.; Re, N.; Ienco, A.; Messori, L.; Peruzzini, M.; Dyson, P. J. Rationalization of the Inhibition Activity of Structurally Related Organometallic Compounds against the Drug Target Cathepsin B by DFT. *Dalton Trans.* **2010**, *39*, 5556−5563.

(30) Renfrew, A. K.; Phillips, A. D.; Egger, A. E.; Hartinger, C. G.; Bosquain, S. S.; Nazarov, A. A.; Keppler, B. K.; Gonsalvi, L.; Peruzzini, M.; Dyson, P. J. Influence of Structural Variation on the Anticancer Activity of RAPTA-Type Complexes: Ptn versus Pta. *Organometallics* **2009**, *28*, 1165−1172.

(31) Erlandsson, M.; Gonsalvi, L.; Ienco, A.; Peruzzini, M. Diastereomerically Enriched Analogues of the Water-Soluble Phosphine PTA. Synthesis of phenyl(1,3,5-triaza-7-phosphatricyclo-$[3.3.1.1^{3,7}]$dec-6- yl)methanol (PZA) and the Sulfide PZA(S) and X-Ray Crystal Structures of the Oxide PZA(O) and $[Cp^*IrCl_2(PZA)]$. *Inorg. Chem.* **2008**, *47*, 8−10.

(32) Dorcier, A.; Ang, W. H.; Bolano, S.; Gonsalvi, L.; Juillerat-Jeannerat, L.; Laurenczy, G.; Peruzzini, M.; Phillips, A. D.; Zanobini, F.; Dyson, P. J. In Vitro Evaluation of Rhodium and Osmium RAPTA Analogues: The Case for Organometallic Anticancer Drugs Not Based on Ruthenium. *Organometallics* **2006**, *25*, 4090−4096.

(33) Akbayeva, D. N.; Gonsalvi, L.; Oberhauser, W.; Peruzzini, M.; Vizza, F.; Brüggeller, P.; Romerosa, A.; Sava, G.; Bergamo, A. Synthesis, Catalytic Properties and Biological Activity of New Water




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Soluble Ruthenium Cyclopentadienyl PTA Complexes $[(C_5R_5)RuCl(PTA)_2]$ (R = H, Me; PTA = 1,3,5-triaza-7-phosphaadamantane). *Chem. Commun.* **2003**, 264−265.
(34) Britvin, S. N.; Lotnyk, A. Water-Soluble Phosphine Capable of Dissolving Elemental Gold: The Missing Link between 1,3,5-triaza-7-phosphaadamantane (PTA) and Verkade's Ephemeral Ligand. *J. Am. Chem. Soc.* **2015**, *137*, 5526−5535.
(35) Bravo, J.; Bolaño, S.; Gonsalvi, L.; Peruzzini, M. Coordination Chemistry of 1,3,5-triaza-7-phosphaadamantane (PTA) and Derivatives. Part II. The Quest for Tailored Ligands, Complexes and Related Applications. *Coord. Chem. Rev.* **2010**, *254*, 555−607.
(36) Phillips, A. D.; Gonsalvi, L.; Romerosa, A.; Vizza, F.; Peruzzini, M. Coordination Chemistry of 1,3,5-triaza-7-phosphaadamantane (PTA). *Coord. Chem. Rev.* **2004**, *248*, 955−993.
(37) Britvin, S. N.; Rumyantsev, A. M.; Zobnina, A. E.; Padkina, M. V. Between Adamantane and Atrane: Intrabridgehead Interactions in the Cage-Like Phosphane Related to a Novel Tris(homoadamantane) Ring System. *Chem. - Eur. J.* **2016**, *22*, 14227−14235.
(38) Fisher, K. J.; Alyea, E. C.; Shahnazarian, N. A $^{31}$P NMR Study of the Water Soluble Derivatives of 1,3,5-triaza-7-phosphaadamantane (PTA). *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *48*, 37−40.
(39) Darensbourg, D. J.; Robertson, J. B.; Larkins, D. L.; Reibenspies, J. H. Water-Soluble Organometallic Compounds. 7.[1] Further Studies of 1,3,5-Triaza-7-Phosphaadamantane Derivatives of Group 10 Metals, Including Metal Carbonyls and Hydrides. *Inorg. Chem.* **1999**, *38*, 2473−2481.
(40) Daigle, D. J.; Decuir, T. J.; Robertson, J. B.; Darensbourg, D. J. 1,3,5-triaza-7-phosphatricyclo[3.3.1.1$^{3,7}$]Decane and Derivatives. *Inorg. Synth* **1998**, *32*, 40−45.
(41) Dyson, P. J.; Ellis, D. J.; Laurenczy, G. Minor Modifications to the Ligands Surrounding a Ruthenium Complex Lead to Major Differences in the Way in Which They Catalyse the Hydrogenation of Arenes. *Adv. Synth. Catal.* **2003**, *345*, 211−215.
(42) Bolaño, S.; Gonsalvi, L.; Zanobini, F.; Vizza, F.; Bertolasi, V.; Romerosa, A.; Peruzzini, M. Water Soluble Ruthenium Cyclopentadienyl and Aminocyclopentadienyl PTA Complexes as Catalysts for Selective Hydrogenation of $\alpha,\beta$-Unsaturated Substrates (PTA = 1,3,5-triaza-7-phosphaadamantane). *J. Mol. Catal. A: Chem.* **2004**, *224*, 61−70.
(43) Dale, J.; Ryde-Petterson, G.; Strand, U.; Jalonen, H.; Lüning, B.; Swahn, C.-G. Exploratory Calculations of Medium and Large Rings. Part 1. Conformational Minima of Cycloalkanes. *Acta Chem. Scand.* **1973**, *27*, 1115−1129.
(44) Scolaro, C.; Bergamo, A.; Brescacin, L.; Delfino, R.; Cocchietto, M.; Laurenczy, G.; Geldbach, T. J.; Sava, G.; Dyson, P. J. In Vitro and in Vivo Evaluation of Ruthenium(II)−Arene PTA Complexes. *J. Med. Chem.* **2005**, *48*, 4161−4171.
(45) Kilpin, K. J.; Clavel, C. M.; Edafe, F.; Dyson, P. J. Naphthalimide-Tagged Ruthenium-Arene Anticancer Complexes: Combining Coordination with Intercalation. *Organometallics* **2012**, *31*, 7031−7039.



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