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Influence of the Diketonato Ligand on the Cytotoxicities of [Ru(η^6-*p*-cymene)-(R_2acac)(PTA)]$^+$ Complexes (PTA = 1,3,5-triaza-7-phosphaadamantane)

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A series of compounds of general formula [Ru(η^6-*p*-cymene)(R_2acac)(PTA)][X] (R_2acac = Me_2acac, *t*Bu_2acac, Ph_2acac, Me_2acac-Cl; PTA = 1,3,5-triaza-7-phosphaadamantane; X = BPh_4, BF_4), and the precursor to the Me_2acac-Cl derivative [Ru(η^6-*p*-cymene)(Me_2acac-Cl)Cl], have been prepared and characterised spectroscopically. Five of the compounds have also been characterised in the solid state by X-ray crystallography. The tetrafluoroborate salts are water-soluble, quite resistant to hydrolysis, and have been evaluated for cytotoxicity against A549 lung carcinoma and A2780 human ovarian cancer cells. The compounds are cytotoxic towards the latter cell line, and relative activities are discussed in terms of hydrolysis (less important) and lipophilicity, which appears to exert the dominating influence.

Introduction

Since the discovery of cisplatin and its anticancer properties in 1965,[1,2] the use of metal complexes as potential agents in anticancer and antibiotic therapy has become a prospering field of research.[3] In particular, ruthenium complexes have gained increasing attraction during the last decade,[4] since ruthenium offers several interesting advantages in comparison with platinum: a broad range of oxidation states, i.e. Ru^{II}, Ru^{III} and Ru^{IV}, are accessible under physiological conditions, combined with a lower general toxicity of ruthenium compounds in comparison with platinum complexes. Two (azole)Ru^{III} complexes, NAMI-A (**1**)[5] and KP1019 (**2**)[6] (Figure 1), have successfully completed phase I clinical trials and will presumably enter phase II trials in the near future.

Recently, there has been growing interest in the anticancer properties of (η^6-arene)ruthenium(II) compounds with various additional ligands. Compounds of general formula [Ru(η^6-arene)(pta)Cl_2] (pta = 1,3,5-triaza-7-phosphaadamantane) have been developed in our group, the prototype being [Ru(η^6-*p*-cymene)(pta)Cl_2] (**3**) (RAPTA-C) (Figure 1).[7,8] In vitro, **3** shows pH-dependent DNA-damaging properties in such a way that DNA damage occurs in cells with pH < 7 (like in the tumour mass of poorly oxygenated cancer cells), while no effect is observed in normal cells with pH > 7.[7] Indeed, this selectivity was observed in comparative cell tests of several structurally diversified RAPTA derivatives with TS/A adenocarcinoma cancer cells and non-tumourigenic (healthy) HBL-100 mammary cells.[8a,8b] A series of (η^6-arene)ruthenium(II) compounds of general formula [Ru(η^6-arene)(imidazole)$_n$$Cl_{3-n}$][X]$_{n-1}$ have been synthesized and evaluated in the same comparative test system,[9] the most promising compound in terms of selectivity being the dicationic complex [Ru(η^6-benzene)(mimid)$_3$]-[BF_4]$_2$ (**4**) (mimid = *N*-methylimidazole) (Figure 1) with IC_{50} values of 249 μM (TS/A) vs. 740 μM (HBL-100), determined in MTT assays. The rather low cytotoxicities of complexes like **4** with simple imidazole ligands could be considerably improved by attaching structurally modified Pgp inhibitors to an (η^6-arene)ruthenium(II) centre through imidazole linkers.[10] Using this strategy the most promising derivative [Ru(η^6-*p*-cymene)(anthraimid)Cl_2] **5** {anthraimid = *N*-(anthracen-9-yl)imidazole} (Figure 1) showed cytotoxicities from 22 to 37 μM in four different cancer cell lines.[10] The cytotoxicities were significantly improved in comparison with the free ligand, and fluorescence microscopy revealed the enrichment of fluorescent material in the cell nucleus, indicating DNA to be a possible target. Sadler et al. have focussed extensively on monocharged complexes with chelating ethylenediamine-type ligands.[11] The complexes exhibit comparatively high cytotoxic properties, with [Ru(η^6-tetrahydroanthracene)(ethylenediamine)Cl][PF_6] (**6**) being of similar cytotoxicity as cisplatin in A2780 human ovarian cancer cells.[11b]

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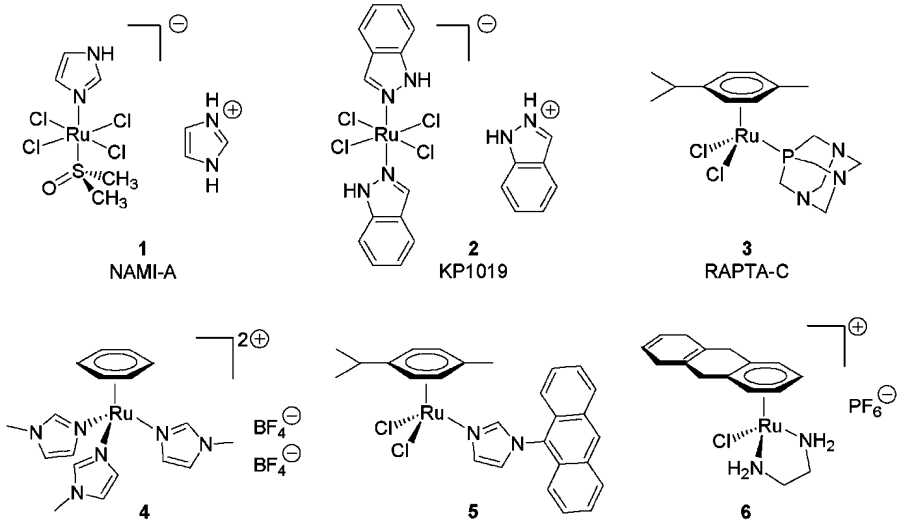
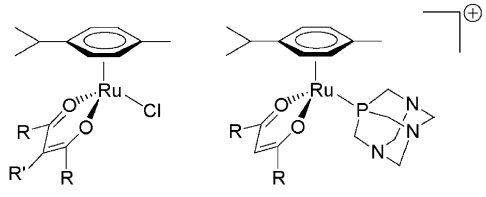


Figure 1. Structures of NAMI-A (**1**), KP1019 (**2**), RAPTA-C (**3**), [Ru(η^6-benzene)(mimid)$_3$][BF$_4$]$_2$ (**4**), [Ru(η^6-*p*-cymene)(anthraimid)Cl$_2$] (**5**) and [Ru(η^6-tetrahydroanthracene)(ethylenediamine)Cl][PF$_6$] (**6**).

In previous studies we have shown that complexes of type [Ru(η^6-*p*-cymene)(*O*,*O*′-dicarboxylato)(PTA)] (dicarboxylato = oxalato or 1,1-cyclobutanedicarboxylato), resist hydrolysis in aqueous medium; however, the complexes essentially showed no cytotoxic effect in several cancer cell lines.[12] In contrast, Sadler et al. reported the synthesis, ligand-exchange reactions and biological evaluation of neutral complexes [Ru(η^6-*p*-cymene)(R$_2$acac)Cl] (**7**–**9**) with different *O*,*O*′-chelating 1,3-diketone-based ligands R$_2$acac (Figure 2), thereby obtaining high cytotoxicities, comparable with the ethylenediamine-type complexes mentioned above.[13] In order to combine both aspects, we have synthesized a series of monocationic complexes [Ru(η^6-*p*-cymene)(R$_2$acac)(PTA)][X] (**11**–**13**) (X = BPh$_4$, BF$_4$) (Figure 2). In addition, a new derivative **10** with the 3-chloroacetylacetonato ligand and its corresponding PTA derivative **14**·BF$_4$ were prepared and investigated. We present here the spectroscopic and crystallographic aspects of the new compounds in combination with biological in vitro cytotoxicity assays and hydrolysis studies.



7: R = Me, R'=H
8: R = *t*Bu, R'=H
9: R = Ph, R'=H
10: R = Me, R' = Cl

11 · BF$_4$: R = Me, R'=H
11 · BPh$_4$: R = Me, R'=H
12 · BF$_4$: R = *t*Bu, R'=H
12 · BPh$_4$: R = *t*Bu, R'=H
13 · BF$_4$: R = Ph, R'=H
13 · BPh$_4$: R = Ph, R'=H
14 · BF$_4$: R = Me, R'=Cl

Figure 2. Structures of the neutral complexes **7**–**10** and the new monocationic PTA derivatives **11**–**14**.

Results and Discussion

In contrast to previously published procedures,[13,14] the neutral complexes **7**–**10** were prepared in a one-pot reaction by treating a solution of [Ru(η^6-*p*-cymene)Cl$_2$]$_2$ and the appropriate 1,3-diketone with an excess of Na$_2$CO$_3$ in acetone at room temp. for 3–3.5 h. Removal of the solvent, and extraction of the residue with CH$_2$Cl$_2$, followed by evaporation of the solvent or crystallisation by addition of Et$_2$O and/or petroleum ether, afforded complexes **7**–**10** in moderate to very good yields of 69–98%. Complexes **11**·BF$_4$–**14**·BF$_4$ were prepared by treatment of the corresponding precursors **7**–**10** with PTA and an excess of NaBF$_4$ in acetone. For derivatives **11**·BPh$_4$–**14**·BPh$_4$, an acetone/CH$_2$Cl$_2$ mixture was used as solvent, and only a slight excess of NaBPh$_4$ was applied. Occasional heating for both types of products was useful to shorten reaction times; however, continuous heating results in increased levels of by-product impurities. Compounds **11**–**14** were obtained as yellow/yellow-orange solids in reasonable yields ranging from 51 to 76%.

The ^{31}P NMR spectra of **11**–**14** each consist of one single peak in the region typical for (arene)(PTA)ruthenium(II) complexes (from δ = –28.08 ppm for **13**·BF$_4$ to δ = –30.60 ppm for **11**·BPh$_4$), indicating the presence of the desired products when compared with the chemical shift of δ = –30.16 for the related complex [Ru(η^6-*p*-cymene)-(*O*,*O*′-cyclobutanedicarboxylato)(PTA)].[12] ^{1}H NMR spectroscopy in CDCl$_3$ reveals differences for the resonances of the aromatic protons at the cymene system between the corresponding BF$_4$ and BPh$_4$ derivatives. While for all BPh$_4$ salts two distinct doublets are observed, the signals are much less separated in the corresponding BF$_4$ derivatives, in the case of **11**·BF$_4$ and **14**·BF$_4$ merging to give one signal. Furthermore, there is a strong shift of these signals to higher frequencies, approaching to some extent the resonance of free cymene, which is observed at δ = 7.13 ppm in

$CDCl_3$, indicating that the cymene ring system might be less strongly coordinated in the BF_4 salts than in the corresponding BPh_4 compounds. In addition, the ^{31}P NMR resonances are shifted to higher frequencies for BF_4 salts in comparison with the corresponding BPh_4 derivatives, the difference being most obvious for the couple **12**·BF_4/**12**·BPh_4 with $\Delta\delta$ = 1.62 ppm, indicating that the PTA ligand might compensate for the reduced bonding interaction of the arene system.

The ESI mass spectra of **11**–**14** in CH_3CN provide parent peaks corresponding to the parent cations [Ru(η^6-*p*-cymene)(R_2acac)(PTA)]$^+$; no fragmentation peaks or ligand-exchange products are observed. MS/MS analysis with 20–30% relative collision energy reveals the loss of the PTA ligand to be the first fragmentation reaction for all complexes.

Characterisation of 11·BF_4, 11·BPh_4, 12·BPh_4, 13·BF_4 and 14·BF_4 in the Solid State

Crystals suitable for X-ray analysis were obtained for **11**·BF_4, **11**·BPh_4, **12**·BPh_4, **13**·BF_4 and **14**·BF_4. Crystallisation conditions are described in the Experimental Section. Graphical representations for the cationic parts of complexes **11**·BPh_4, **12**·BPh_4, **13**·BF_4 and **14**·BF_4 are depicted in Figure 3. Selected bond lengths and angles are given in Table 1, and relevant crystallographic parameters are listed in Table 5.

All four complexes adopt the expected three-legged piano-stool geometry, with the corresponding β-diketonato ligand and the ruthenium centre forming a six-membered chelate. The O–Ru–O bond angles show little strain and are between 87.34(13)° and 88.63(7)°, comparable to those

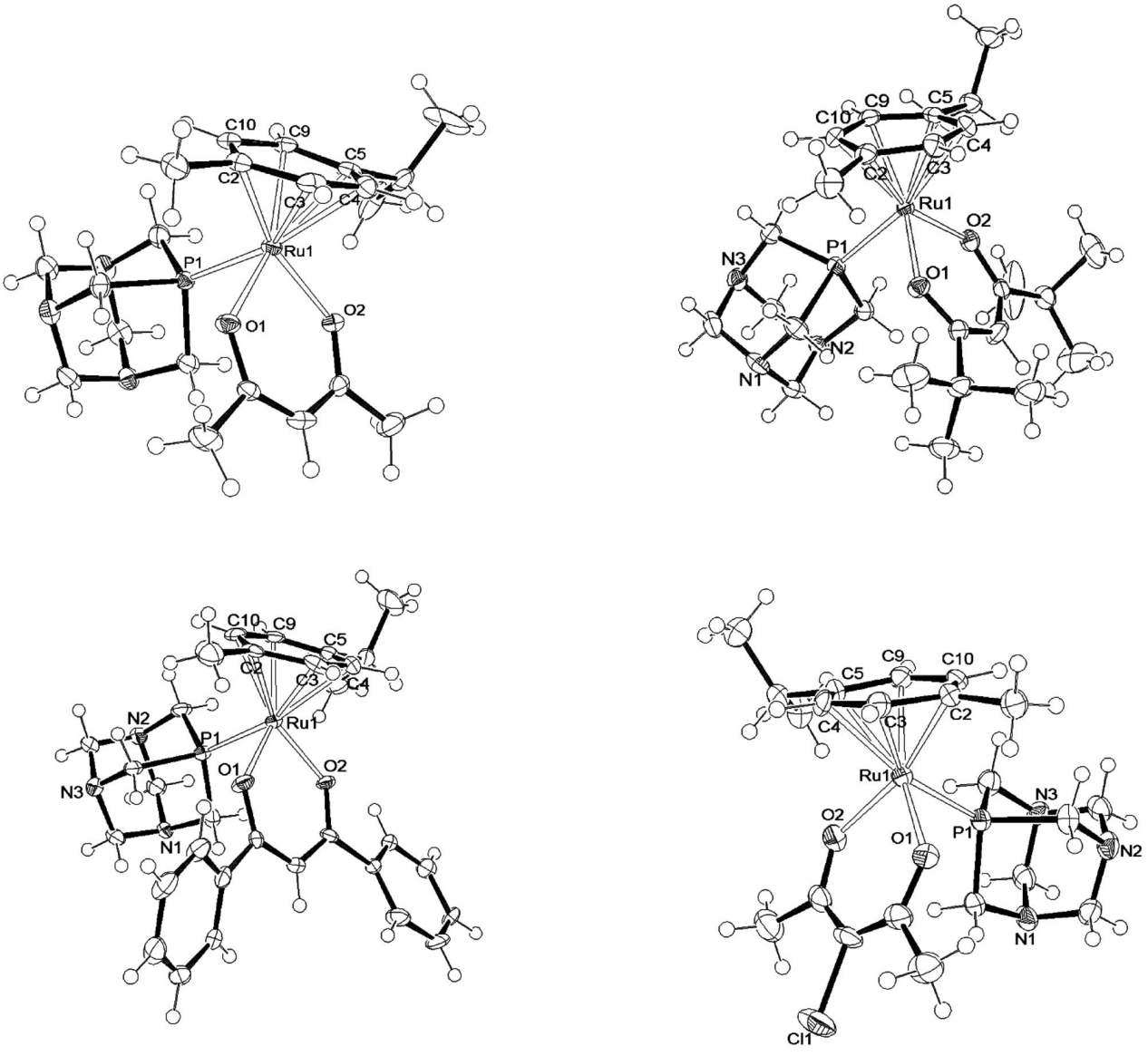


Figure 3. ORTEP plots of **11**·BPh_4 (top, left), **12**·BPh_4 (top, right), **13**·BF_4 (bottom, left) and **14**·BF_4 (bottom, right) drawn with 50% probability ellipsoids (BF_4 and BPh_4 anions omitted for clarity).

Table 1. Selected bond lengths [Å] and angles [°] for **11**·BF_4, **11**·BPh_4, **12**·BPh_4, **13**·BF_4 and **14**·BF_4.

	11·BF_4	**11**·BPh_4	**12**·BPh_4	**13**·BF_4	**14**·BF_4
Ru1–P1	2.322(2)	2.3164(11)	2.3279(7)	2.347(2)	2.3208(13)
Ru1–C2	2.224(6)	2.187(4)	2.200(2)	2.202(7)	2.204(5)
Ru1–C3	2.264(5)	2.243(4)	2.250(2)	2.275(7)	2.246(5)
Ru1–C4	2.277(5)	2.256(4)	2.257(3)	2.269(7)	2.252(4)
Ru1–C5	2.235(5)	2.202(6)	2.194(2)	2.202(6)	2.205 (4)
Ru1–C9	2.200(5)	2.201(4)	2.202(2)	2.188(6)	2.206 (4)
Ru1–C10	2.199(6)	2.187(4)	2.196(2)	2.202(6)	2.195(4)
Ru1–Ar(centroid)	1.717	1.695	1.703	1.710	1.703
Ru1–O1	2.077(4)	2.083(2)	2.071(2)	2.083(4)	2.073(3)
Ru1–O2	2.094(4)	2.091(3)	2.073(2)	2.086(4)	2.076(3)
O1–Ru1–O2	88.2(2)	88.58(10)	88.63(7)	88.7(2)	87.34(13)

reported for similar complexes of type [Ru(η^6-arene)(R_2acac)Cl] [88.40(9)°].[14] Ruthenium–oxygen bond lengths are in agreement with the literature and are not greatly affected by variation of the R_2acac substituent. Ru–arene [1.695–1.717 Å] and Ru–P distances [2.3164(11)–2.3279(7) Å] are close to those of [Ru(η^6-*p*-cymene)(*O*,*O*′-oxalato)(PTA)] [1.69 Å and 2.310(1) Å, respectively].[12] Interestingly, replacement of the BPh_4 counteranion by BF_4 in **11** results in an increase of the Ru–arene distance by 2.2 pm, although this distance is within the esds (see Table 2), but corroborates well with the ^{1}H NMR study described above. Indeed, several interactions are observed between the BF_4 fluorine atoms and the cymene hydrogen atoms H9 (aromatic system; H9–F3A 2.601 Å), H6 (isopropyl group; H6–F4A 2.449 Å), H8C (isopropyl group; H8C–F3A 2.595 Å) and H1B (methyl group; H1B–F4A 2.589 Å) (Figure 4).

Table 2. Decomposition of **11**·BF_4–**14**·BF_4; the integral ratios complex/hydrolysis product from ^{31}P NMR spectroscopy are depicted. Conditions: 2.0 mM solution of complex in 100 mM NaCl/D_2O containing 1% [D_6]DMSO, T = 37 °C.

Time [h]	Complex			
	11·BF_4	**12**·BF_4	**13**·BF_4	**14**·BF_4
0	100:0	100:0	100:0	100:0
25	97.8:2.2	100:0	100:0	73.8:26.2
53	93.5:6.5	100:0	96.4:3.6	49.8:50.2
77	90.5:9.5	100:0	95.5:4.5	37.0:63.0
99	83.4:16.6	100:0	90.8:9.2	25.1:74.9
125	77.2:22.8	95.3:4.7	87.4:12.6	19.1:80.9
168	65.0:35.0	89.5:10.5	80.3:19.7	10.8:89.2

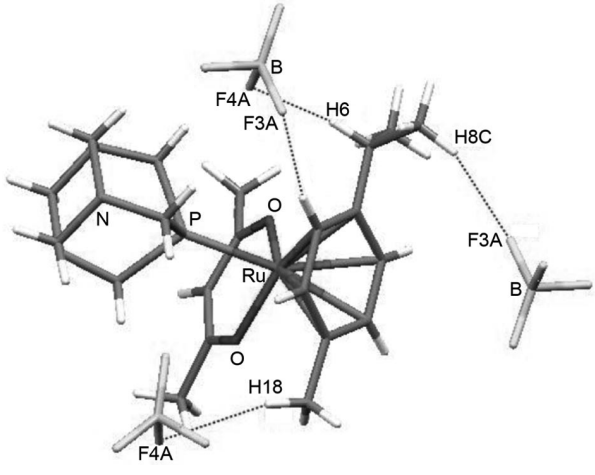


Figure 4. Interactions between the cymene moiety and BF_4 counterions in complex **11**·BF_4.

Hydrolysis Study for Complexes 11·BF_4–14·BF_4

To determine the stability of **11**·BF_4–**14**·BF_4, a hydrolysis study was carried out under pseudo-pharmacological conditions. The hydrolytic decomposition of the compounds was studied in 5 mM NaCl solution (being a model for the low intracellular NaCl concentration in cells) and in 100 mM NaCl solution (approximating the higher NaCl levels in blood plasma). Solutions of the complexes (c = 2.0 mM) in aqueous NaCl (c = 5 mM or 100 mM in D_2O containing 1% of [D_6]DMSO) were prepared and maintained at 37 °C for 7 d. The decomposition of the complexes was monitored by ^{31}P NMR spectroscopy (Figure 5). During the measurements in 100 mM aqueous NaCl solution, generally just one major product was observed, presumably corresponding to [Ru(η^6-*p*-cymene)(PTA)Cl_2],[15] which allowed the approximation of decomposition by integration of the resonances of unchanged complex and hydrolysis product in the ^{31}P NMR spectra (Table 2). In 5 mM aqueous NaCl solution, the decomposition pattern for all complexes with exception of **12**·BF_4 (which did not hydrolyze at all) turned out to be more complicated; several hydrolysis products were observed, probably including [Ru(η^6-*p*-cymene)(PTA)(H_2O)Cl]$^+$,[15] which prevented the extent of hydrolysis being quantified.

Increased rates of reaction were observed in 100 mM aqueous NaCl solution for all compounds, with the stability of the complexes increasing in the order **14**·BF_4 << **11**·BF_4 < **13**·BF_4 < **12**·BF_4. The most stable complex, **12**·BF_4, bears the sterically demanding *t*Bu_2acac β-diketonato ligand. In 5 mM NaCl solution, no changes were observed even after 7 d, and in 100 mM NaCl solution 125 h were required before any changes were observed. **13**·BF_4 is slightly less stable, with small amounts of hydrolysis product in 5 mM aqueous NaCl detected after 7 d and approximately 20% decomposition in 100 mM NaCl solution after the same time. **11**·BF_4 reacted comparatively rapidly in 100 mM aqueous NaCl; however, approximately 65% of the complex remained unchanged in solution after 7 d. In comparison, **14**·BF_4 with an electron-withdrawing chloro substituent at the acetylacetonato ligand, is much less stable. In 100 mM aqueous NaCl solution, approximately 50% of the complex had transformed after 53 h, and only 11% of unchanged complex remained after 7 d. In 5 mM NaCl solution, the reaction was slightly slower, but a much more complicated pattern of decomposition products was observed, indicated by ca. six peaks in the ^{31}P NMR spectrum after 7 d. ^{1}H NMR spectra measured in parallel show the presence of detectable amounts of free *p*-cymene, indicating the loss of the η^6-coordinated aromatic ligand being involved in the hydrolysis process.

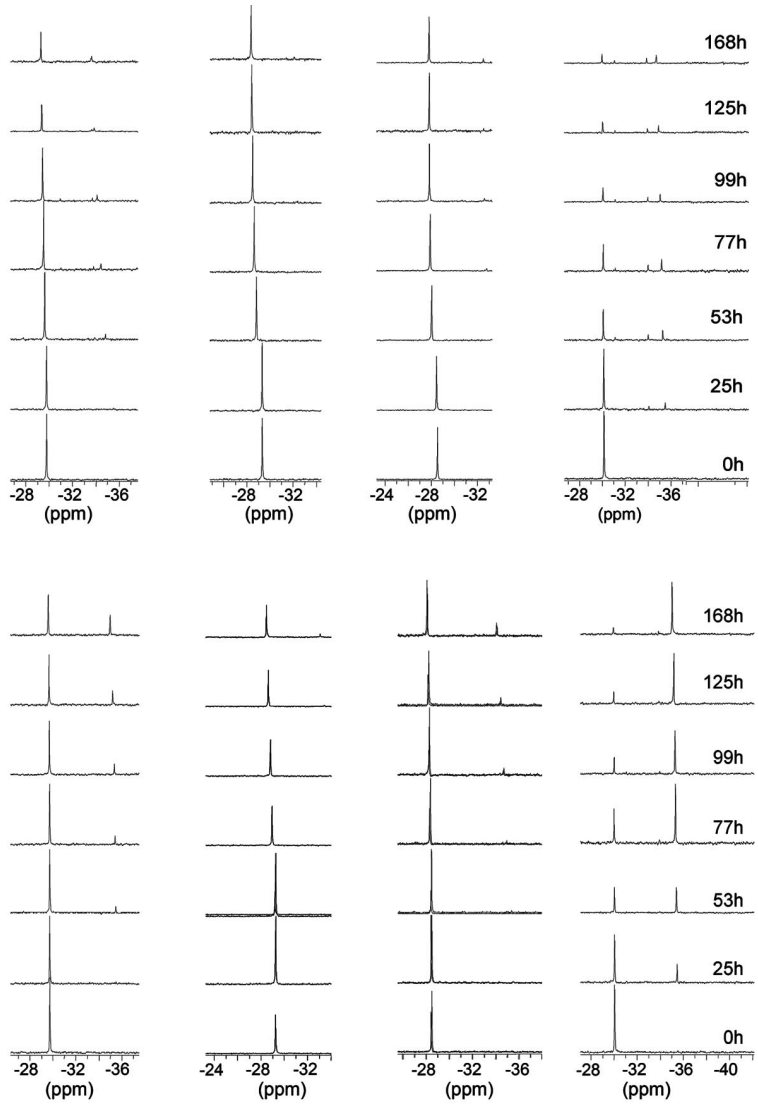


Figure 5. Kinetic hydrolysis experiment at 37 °C: 2.0 mM solution of complex **11**·BF_4–**14**·BF_4 in (top) 5.0 mM NaCl/D_2O (1% [D_6]DMSO) and (bottom) 100 mM NaCl/D_2O (1% [D_6]DMSO).

In vitro Evaluation

Complexes **10** and **11**·BF_4–**14**·BF_4 were evaluated in a comparative in vitro MTT cell viability assay[16] with two cancer cell lines, viz. A549 lung carcinoma and A2780 human ovarian cancer cells. The IC_{50} values for compounds **10** and **11**·BF_4–**14**·BF_4 are listed in Table 3. The IC_{50} values for complexes **7**–**9** in A2780 cells have been previously reported and found to be 19 μM (**7**), 14 μM (**8**) and 11 μM (**9**), respectively.[13]

The PTA complexes **11**·BF_4–**14**·BF_4 exhibited strong cytotoxicities in A2780 cells, each of them being even slightly more cytotoxic than the corresponding parent chloro complexes **7**–**10**. In comparison, the cytotoxicity of the complexes towards the A549 lung cancer cell line was significantly lower, with **11**·BF_4 being completely inactive. The new neutral complex **10** exhibited slightly lower cytotoxic properties in A2780 cells than derivatives **7**–**9** (see above). However, in A549 cells a comparatively high cytotoxicity was observed, with **10** being more cytotoxic than **11**·BF_4–**13**·BF_4 and of similar cytotoxicity to the PTA derivative **14**·BF_4.

Table 3. Results of the MTT-assays: IC_{50} values for compounds **10**, **11a**–**13a** and **14** in comparison with the literature values for **7**–**9**.

Compound	IC_{50} [μM] A549	A2780
10	51	30
11·BF_4	> 2000	15
12·BF_4	97	13
13·BF_4	57	7
14·BF_4	50	14

To evaluate the influence of lipophilicity of the complexes on cytotoxicity, the log *P* values (*P* = partition coefficient between *n*-octanol and H_2O) of the free R_2acac ligands were calculated. Since the experimental and theoretical determination of log *P* values for metal complexes is

rather difficult, especially here where various reactions occur in aqueous solution, we assumed that for the homologous series of complexes [Ru(η^6-*p*-cymene)(R_2acac)(PTA)][BF_4], the change in lipophilicity should correlate to the different R_2acac ligands. Therefore, the different lipophilicities of the complexes may be estimated by calculating the corresponding values for the free ligands. The log *P* values for the free β-diketones (R_2acac) in non-enolized form are listed in Table 4.

Table 4. Calculated log *P* values for the free β-diketones; values were determined for the non-enolized β-diketone form.[17]

Free ligand	log *P* (calculated)
Me_2acacH	0.339 ± 0.369
tBu_2acacH	2.796 ± 0.396
Ph_2acacH	3.043 ± 0.303
Me_2acac-ClH	1.637 ± 0.468

For both the A2780 and the A549 cell line, the observed cytotoxicity data correlate well with the lipophilicity parameters. As an exception, complex **14·BF$_4$** exhibited a much higher cytotoxicity in A549 cells than expected from the corresponding log *P* value of the free ligand Me_2acac-ClH. The similarity of the IC_{50} values obtained in A2780 cells indicates that lipophilicity might not be of significant importance for the mechanism of action in this cell line. In contrast, the differences in the less sensitive A549 lung cancer cell line are more pronounced, with **14**·BF_4 being more than 40 times more cytotoxic than **11**·BF_4.

In general, hydrolysis of metal-based drugs is frequently assumed to be necessary for their cytotoxic action in order to generate reactive intermediates for binding to DNA, proteins or other biomolecules. However, there is no clear correlation between the hydrolysis behaviour and the cytotoxic properties for the complexes **11**·BF_4–**14**·BF_4. Compound **14**·BF_4 is the least stable derivative against hydrolysis, and indeed it is the most cytotoxic derivative in A549 cells. However, it does not show superior properties in A2780 cells compared to **11**·BF_4–**13**·BF_4. The most stable derivative **12**·BF_4 shows weaker cytotoxicities in both cell lines, although it is still more (and towards A549 cells much more) cytotoxic than the comparatively reactive species **11**·BF_4. The most cytotoxic compound in A2780 cells, **13**·BF_4, shows similar hydrolytic stability to **12**·BF_4 and is probably not hydrolyzed during the timeframe of the MTT experiments. Based on these observations, it can be assumed that hydrolysis does not play a significant role in the mechanism of action for compounds **11**·BF_4–**14**·BF_4, and that differences in cytotoxicity are more likely explained from their lipophilicities. However, it has to be mentioned that strong cytotoxicities have been also observed for free ligands of type R_2acacH, some of which have shown selective effects towards certain cancer cell lines.[18] The cytotoxicity of the (dissociated) ligand has to be taken into consideration especially for the rapidly hydrolyzing derivatives **11**·BF_4 and **14**·BF_4, although the coordinated ligands may also interact with the same intracellular targets.

The family of RAPTA complexes [Ru(η^6-arene)Cl_2(PTA)] previously synthesized in our group[8] tend to be hydrophilic and show fast and complicated hydrolysis behaviour, and in general their observed cytotoxicities are low. In comparison, the new derivatives presented here show high cytotoxicities with no or only minor hydrolysis likely during the MTT assay time scale (with exception of compound **14**·BF_4). Therefore, it can be assumed that hydrolysis, in order to generate more labile species that can bind to DNA or proteins, may not be necessary to obtain high cytotoxicities, although it is likely that nucleophiles in the cell would accelerate hydrolysis (as was observed herein with higher concentrations of chloride). It is possible that the complexes may induce their effects by targeting receptors inside the cell. Alternatively, the ability of (arene)ruthenium(II) compounds to undergo substitution reactions by a "ring-slippage" mechanism[19] could result in direct reaction with potential biomolecular targets without necessitating the need for prior activation by hydrolysis. In other words, loss of the dicarboxylate ligand could occur after reaction with the target inside the cell.[20]

Conclusions

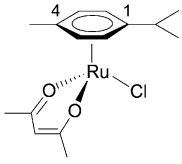
We have synthesized and characterised a series of new complexes [Ru(η^6-*p*-cymene)(R_2acac)(PTA)][X] (**11**–**14**) (X = BPh_4, BF_4). The water-soluble BF_4 salts have been evaluated in MTT assays and found to be highly cytotoxic in A2780 human ovarian cancer cells and to have pronounced cytotoxicities also in A549 human lung cancer cells, which are known to be insensitive against many applied chemotherapeutical agents. The hydrolysis behaviour was studied under conditions similar to the physiological environment in blood plasma and cells. The compounds were found to exhibit reasonably to very good stability against hydrolysis for days, the most reactive complex being [Ru(η^6-*p*-cymene)(Me_2acac-Cl)(PTA)][BF_4] (**14**·BF_4), and the least reactive being [Ru(η^6-*p*-cymene)(*t*Bu_2acac-Cl)(PTA)][X] (**12**·BF_4). Due to the high cytotoxicities in combination with stability against hydrolysis and with respect to the cytotoxic behaviour of certain metal-free β-diketone derivatives, we assume the mechanism of action to be different from "classical" DNA or protein targeting known for organometallic drugs. A receptor-based mechanism of action is considered to be possible, at least in the first instance, as a direct reaction without proceeding via a hydrolysis intermediate, although hydrolysis cannot be ruled out within a cancer cell.

Experimental Section

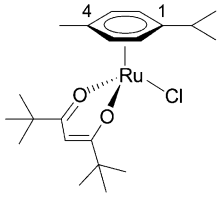
Synthesis and Chemical Characterization: [$RuCl_2(\eta^6$-*p*-cymene)]$_2$ was synthesized according to a literature protocol.[21] All other reagents and solvents were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 400 MHz spectrometer at room temperature in $CDCl_3$. NMR spectra were referenced to internal solvents as follows: δ($CHCl_3$, ^{1}H) = 7.26 and δ($CDCl_3$, ^{13}C) = 77.00.[22] Electrospray ionization mass spectra (ESI-MS) and MS/MS fragmentation data were recorded with a Thermofinigan LCQ Deca XP Plus quadrupole ion trap instrument in positive mode in

CH_3CN according to a literature procedure.[23] Elemental analyses were provided by the analytical service of the EPFL.

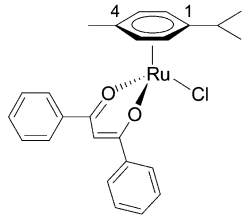
[Ru(η⁶-*p*-cymene)(Me₂acac)Cl] (7): To a suspension of Na_2CO_3 (864 mg, 8.15 mmol, 5.00 equiv.) in acetone (50 mL), acetylacetone (0.840 mL, 817 mg, 8.16 mmol, 5.01 equiv.) and [Ru(η⁶-*p*-cymene)Cl_2]$_2$ (1.00 g, 1.63 mmol) were added, and the resulting mixture was stirred at room temperature for 3 h and then filtered. The residue was washed with CH_2Cl_2 (4× 10 mL), and the combined filtrates were concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), and the solution was filtered again. After washing the filter with CH_2Cl_2 (4× 10 mL), the combined filtrates were reduced in vacuo to a volume of ca. 10 mL. Et_2O (5 mL) and an excess of petroleum ether (ca. 100 mL) were added, and the mixture was stored at –25 °C for 30 min to accomplish precipitation. The precipitate was filtered, washed with petroleum ether (2× 10 mL) and dried in vacuo, affording the title compound as orange needles (837 mg, 2.26 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 [d, J = 6.9 Hz, 6 H, 1-CH(CH_3)$_2$], 1.98 [s, 6 H, 2× CH_3 (Me_2acac)], 2.26 (s, 3 H, 4-CH_3), 2.86 [sept, J = 6.9 Hz, 1 H, 1-CH(CH$_3$)$_2$], 5.14 [s, 1 H, COCHCO (Me_2acac)], 5.19 (d, J = 5.9 Hz, 2 H, 2-H, 6-H), 5.44 (d, J = 5.9 Hz, 2 H, 3-H, 5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.07 (4-CH$_3$), 22.25 [1-CH(CH$_3$)$_2$], 27.25 [2× CH$_3$ (Me_2acac)], 30.70 [1-CH(CH$_3$)$_2$], 78.80 (C-2, C-6), 82.41 (C-3, C-5), 97.55 (C-4), 98.74 [COCHCO (Me_2acac)], 99.53 (C-1), 186.4 [2× CO (Me_2acac)] ppm.



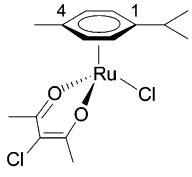
[Ru(η⁶-*p*-cymene)(*t*Bu₂acac)Cl] (8): To a suspension of Na_2CO_3 (605 mg, 5.71 mmol, 5.01 equiv.) in acetone (35 mL), 2,2,6,6-tetramethylheptane-3,5-dione (1.15 mL, 1.03 g, 5.59 mmol, 4.99 equiv.) and [Ru(η⁶-*p*-cymene)Cl_2]$_2$ (700 mg, 1.14 mmol) were added, and the resulting mixture was stirred at room temperature for 3.5 h. The solvent was evaporated in vacuo. The residue was extracted with CH_2Cl_2 (4× 20 mL). The extracts were filtered and the solvents evaporated in vacuo to a volume of ca. 10 mL. Et_2O (20 mL) and petroleum ether (ca. 100 mL) were added. The turbid solution was concentrated in vacuo to a volume of ca. 40 mL, and additional petroleum ether (ca. 100 mL) was added. Reduction of the solvent volume in vacuo to ca. 20 mL and storing at –25 °C for 1 h led to the precipitation of an orange-red crystalline solid, which was filtered, washed with petroleum ether (3× 10 mL) and dried in vacuo (822 mg, 1.81 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 [s, 18 H, 2× C(CH_3)$_3$ (tBu$_2$acac)], 1.35 [d, J = 6.9 Hz, 6 H, 1-CH(CH_3)$_2$], 2.23 (s, 3 H, 4-CH_3), 2.89 [sept, J = 6.9 Hz, 1 H, 1-CH(CH$_3$)$_2$], 5.13 (d, J = 5.8 Hz, 2 H, 2-H, 6-H), 5.39 [s, 1 H, COCHCO (tBu$_2$acac)], 5.40 (d, J = 5.8 Hz, 2 H, 3-H, 5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.74 (4-CH$_3$), 22.37 [1-CH(CH$_3$)$_2$], 28.47 [2× C(CH$_3$)$_3$ (tBu$_2$acac)], 30.73 [1-CH(CH$_3$)$_2$], 40.72 [2× C(CH$_3$)$_3$ (tBu$_2$acac)], 78.95 (C-2, C-6), 83.11 (C-3, C-5), 88.96 [COCHCO (tBu$_2$acac)], 91.26 (C-4), 99.03 (C-1), 196.0 [2× CO (tBu$_2$acac)] ppm.



[Ru(η⁶-*p*-cymene)(Ph₂acac)Cl] (9): To a suspension of Na_2CO_3 (600 mg, 5.66 mmol, 4.96 equiv.) in acetone (50 mL), [Ru(η⁶-*p*-cymene)Cl_2]$_2$ (700 mg, 1.14 mmol) and dibenzoylmethane (513 mg, 2.29 mmol, 2.01 equiv.) were added, and the resulting mixture was stirred at room temperature for 3 h, followed by evaporation of the solvent in vacuo. The residue was taken up in CH_2Cl_2 (20 mL), and the mixture was filtered through a short pad of Celite. The residue was washed with CH_2Cl_2 (4× 10 mL). Concentration of the combined filtrates in vacuo yielded an orange-red powder (1.10 g, 2.23 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 [d, J = 6.9 Hz, 6 H, 1-CH(CH_3)$_2$], 2.34 (s, 3 H, 4-CH_3), 3.03 [sept, J = 6.9 Hz, 1 H, 1-CH(CH$_3$)$_2$], 5.32 (d, J = 5.9 Hz, 2 H, 2-H, 6-H), 5.59 (d, J = 5.9 Hz, 2 H, 3-H, 5-H), 6.45 [s, 1 H, COCHCO (Ph_2acac)], 7.39 [t, J = 7.3 Hz, 4 H, 4× *meta*-H (Ph_2acac)], 7.45 [t, J = 7.3 Hz, 2 H, 2× *para*-H (Ph_2acac)], 7.91 [d, J = 7.3 Hz, 4 H, 4× *ortho*-H (Ph_2acac)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.01 (4-CH$_3$), 22.40 [1-CH(CH$_3$)$_2$], 30.82 [1-CH(CH$_3$)$_2$], 79.34 (C-2, C-6), 83.12 (C-3, C-5), 93.33 [COCHCO (Ph_2acac)], 97.39 (C-4), 99.73 (C-1), 127.3 [4× *ortho*-C (Ph_2acac)], 128.1 [4× *meta*-C (Ph_2acac)], 130.9 [2× *para*-C (Ph_2acac)], 139.0 [2× *ipso*-C (Ph_2acac)], 181.5 [2× CO (Ph_2acac)] ppm.

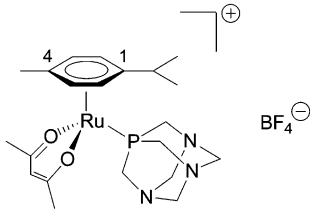


[Ru(η⁶-*p*-cymene)(Me₂acac-Cl)Cl] (10): To a suspension of Na_2CO_3 (605 mg, 5.71 mmol, 5.01 equiv.) in acetone (35 mL), 3-chloroacetylacetone (680 μL, 5.66 mmol, 4.96 equiv.) and [Ru(η⁶-*p*-cymene)Cl_2]$_2$ (700 mg, 1.14 mmol) were added, and the resulting mixture was stirred at room temperature for 3 h, then the solvent was removed in vacuo. The residue was extracted with CH_2Cl_2 (6× 10 mL). The extracts were filtered and reduced in vacuo to a volume of ca. 10 mL. Petroleum ether (80 mL) was added, and the mixture was stored at –25 °C for 20 min. The formed precipitate was filtered, washed with petroleum ether (3× 10 mL) and dried in vacuo, affording a dark yellow to yellow-brown solid (733 mg, 1.81 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 [d, J = 6.9 Hz, 6 H, 1-CH(CH_3)$_2$], 2.24 (s, 3 H, 4-CH_3), 2.25 [s, 6 H, 2× CH_3 (Me_2acac-Cl)], 2.88 [sept, J = 6.9 Hz, 1 H, 1-CH(CH$_3$)$_2$], 5.21 (d, J = 5.9 Hz, 2 H, 2-H, 6-H), 5.47 (d, J = 5.9 Hz, 2 H, 3-H, 5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.94 (4-CH$_3$), 22.26 [1-CH(CH$_3$)$_2$], 28.09 [2× CH$_3$ (Me_2acac-Cl)], 30.77 [1-CH(CH$_3$)$_2$], 79.13 (C-2, C-6), 82.43 (C-3, C-5), 97.31 (C-4), 99.87 (C-1), 106.4 [COCClCO (Me_2acac-Cl)], 184.7 [2× CO (Me_2acac-Cl)] ppm.

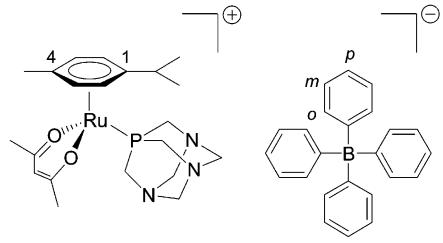


[Ru(η⁶-*p*-cymene)(Me₂acac)(PTA)][BF_4] (11·BF_4): To a solution of **7** (100 mg, 0.270 mmol) in acetone (10 mL) and CH_2Cl_2 (10 mL), PTA (45.0 mg, 0.286 mmol, 1.06 equiv.) and $NaBF_4$ (60.0 mg, 0.546 mmol, 2.02 equiv.) were added at room temperature. The mixture was heated to reflux temperature with a heating gun and then stirred at room temperature for 15 min. The heating/ambient temperature cycle was repeated three more times (total reaction

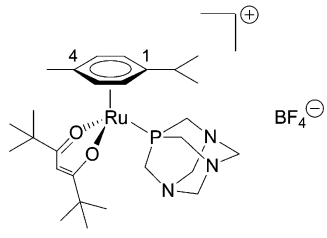
time: 1 h). The solvent was removed in vacuo. The residue was extracted with CH_2Cl_2 (4× 10 mL). The extracts were filtered and the solvents evaporated in vacuo. The residue was taken up in CH_2Cl_2 (5 mL) and ethyl acetate (40 mL). The resulting solution was concentrated in vacuo to ca. 10 mL, and an orange-yellow precipitate began to form. Precipitation was accomplished by storing the mixture at –25 °C for 1 h. Petroleum ether (50 mL) was added, and the solid was filtered, washed with petroleum ether (2× 10 mL) and dried in vacuo, affording a dark yellow crystalline solid (79.6 mg, 0.138 mmol, 51%). Crystals suitable for X-ray analysis were obtained by layering a $CHCl_3$ solution of **11·BF$_4$** with Et_2O and storing at room temperature for several days. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 [d, J = 6.9 Hz, 6 H, 1-CH(CH_3)$_2$], 1.94 (s, 3 H, 4-CH_3), 1.97 [s, 6 H, 2× CH_3 (Me_2acac)], 2.50 [sept, J = 6.9 Hz, 1 H, 1-CH(CH$_3$)$_2$], 4.17 [s, 6 H, 3× PCH_2N (PTA)], 4.50 [br. d, J_{AB} = 13.3 Hz, 3 H, 3× NCH_AH$_B$N (PTA)], 4.60 [br. d, J_{AB} = 13.3 Hz, 3 H, 3× NCH$_A$$H_B$N (PTA)], 5.39 [s, 1 H, COCHCO (Me_2acac)], 5.83 (d, J = 1.1 Hz, 4 H, 2-H, 3-H, 5-H, 6-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.78 (4-CH_3), 21.99 [1-CH(CH_3)$_2$], 27.05 [2× CH_3 (Me_2acac)], 30.64 [1-CH(CH$_3$)$_2$], 50.95 [d, J_{CP} = 13.3 Hz, 3× PCH_2N (PTA)], 72.90 [d, J_{CP} = 7.4 Hz, 3× NCH_2N (PTA)], 87.86 (d, J_{CP} = 4.0 Hz, C-2, C-6), 88.73 (d, J_{CP} = 4.3 Hz, C-3, C-5), 97.98 (C-4), 101.5 [COCHCO (Me_2acac)], 104.2 (C-1), 189.4 [2× CO (Me_2acac)] ppm. ^{31}P{^{1}H} NMR (126 MHz, $CDCl_3$): δ = –29.26 ppm. ESI-MS (CH_3CN): m/z (%) = 492.1 (100) [Ru(cymene)(Me_2acac)(PTA)]$^+$. ESI-MS (CH_3CN, MS/MS, 30% relative collision energy): m/z (%) = 492.1 (8) [Ru(cymene)(Me_2acac)(PTA)]$^+$, 335.0 (100) [Ru(cymene)(Me_2acac)]$^+$. $C_{21}H_{33}BF_4N_3O_2PRu·0.5H_2O$ (587.4): calcd. C 42.94, H 5.83, N 7.15; found C 42.78, H 5.66, N 7.32.



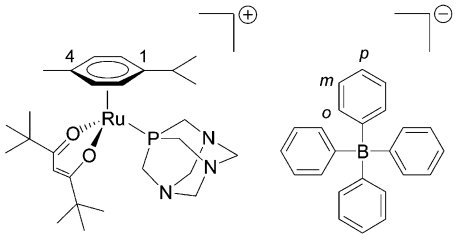
[Ru(η^6-*p*-cymene)(Me_2acac)(PTA)][BPh$_4$] (11·BPh$_4$): To a solution of **7** (100 mg, 0.270 mmol) in acetone (10 mL) and CH_2Cl_2 (10 mL), PTA (45.0 mg, 0.286 mmol, 1.06 equiv.) and $NaBPh_4$ (97.0 mg, 0.283 mmol, 1.05 equiv.) were added, and the mixture was heated to reflux temperature with a heating gun and then stirred at room temperature for 15 min. The heating/ambient temperature cycle was repeated two more times (total reaction time: 45 min). The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 (4× 10 mL). The extracts were filtered and reduced in vacuo to a volume of ca. 10 mL. Addition of Et_2O (50 mL) and stirring at room temperature for several minutes led to the formation of a precipitate, which was filtered off, washed with Et_2O (2× 10 mL) and dried in vacuo, affording a light yellow powder (164 mg, 0.202 mmol, 75%). Crystals suitable for X-ray analysis were obtained by layering a $CHCl_3$ solution of **11·**BPh$_4$ with Et_2O and storing at 4 °C for 36 h. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 [d, J = 6.9 Hz, 6 H, 1-CH(CH_3)$_2$], 1.61 (s, 3 H, 4-CH_3), 1.93 [s, 6 H, 2× CH_3 (Me_2acac)], 2.27 [sept, J = 6.9 Hz, 1 H, 1-CH(CH$_3$)$_2$], 3.77 [s, 6 H, 3× PCH_2N (PTA)], 4.33 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH_AH$_B$N (PTA)], 4.47 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH$_A$$H_B$N (PTA)], 4.87 (d, J = 5.9 Hz, 2 H, 2-H, 6-H), 5.06 (d, J = 5.9 Hz, 2 H, 3-H, 5-H), 5.34 [s, 1 H, COCHCO (Me_2acac)], 6.93 [t, J = 7.2 Hz, 4 H, 4× *para*-H (BPh$_4$)], 7.07 [t, J = 7.2 Hz, 8 H, 8× *meta*-H (BPh$_4$)], 7.45 [br. m$_c$, 8 H, 8× *ortho*-H (BPh$_4$)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.94 (4-CH_3), 21.90 [1-CH(CH_3)$_2$], 27.03 [2× CH_3 (Me_2acac)], 30.60 [1-CH(CH$_3$)$_2$], 51.40 [d, J_{CP} = 13.2 Hz, 3× PCH_2N (PTA)], 72.95 [d, J_{CP} = 7.2 Hz, 3× NCH_2N (PTA)], 87.55 (d, J_{CP} = 4.0 Hz, C-2, C-6), 88.09 (d, J_{CP} = 4.3 Hz, C-3, C-5), 98.17 (C-4), 101.5 [COCHCO (Me_2acac)], 104.5 (C-1), 121.9 [4× *para*-C (BPh$_4$)], 125.7 [q, J_{CB} = 2.8 Hz, 8× *meta*-C (BPh$_4$)], 136.3 [q, J_{CB} = 1.4 Hz, 8× *ortho*-C (BPh$_4$)], 164.1 [q, J_{CB} = 49.4 Hz, 4× *ipso*-C (BPh$_4$)], 189.3 [2× CO (Me_2acac)] ppm. ^{31}P{^{1}H} NMR (126 MHz, $CDCl_3$): δ = –30.60 ppm. ESI-MS (CH_3CN): m/z (%) = 491.9 (100) [Ru(cymene)(Me_2acac)(PTA)]$^+$. ESI-MS (CH_3CN, MS/MS, 20% relative collision energy): m/z (%) = 491.9 (29) [Ru(cymene)(Me_2acac)(PTA)]$^+$, 335.0 (100) [Ru(cymene)(Me_2acac)]$^+$. $C_{45}H_{53}BN_3O_2PRu·1.5H_2O$ (837.8): calcd. C 64.51, H 6.74, N 5.02; found C 64.54, H 6.36, N 4.91.



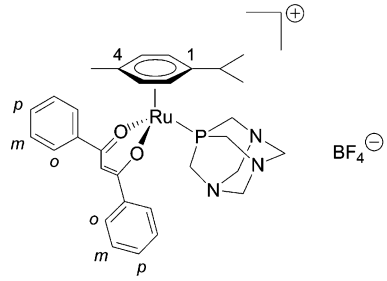
[Ru(η^6-*p*-cymene)(*t*Bu$_2$acac)(PTA)][BF$_4$] (12·BF$_4$): To a solution of **8** (100 mg, 0.220 mmol) in acetone (15 mL), PTA (36.0 mg, 0.229 mmol, 1.04 equiv.) and $NaBF_4$ (120 mg, 1.09 mmol, 4.97 equiv.) were added at room temperature. The mixture was stirred at room temperature for 2 h, and the solvent was removed in vacuo. The residue was extracted with CH_2Cl_2 (5× 10 mL). The extracts were filtered through a pad of Celite and reduced in vacuo to a volume of ca. 10 mL. Addition of Et_2O (80 mL) and pentane (60 mL) and subsequent cooling to –25 °C for 20 min led to the formation of a precipitate, which was filtered, washed with Et_2O (2× 10 mL) and dried in vacuo, affording a yellow solid (111 mg, 0.168 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 [s, 18 H, 2× C(CH_3)$_3$ (*t*Bu$_2$acac)], 1.23 [d, J = 6.9 Hz, 6 H, 1-CH-(CH_3)$_2$], 1.96 (s, 3 H, 4-CH_3), 2.48 [sept, J = 6.9 Hz, 1 H, 1-CH(CH$_3$)$_2$], 4.16 [s, 6 H, 3× PCH_2N (PTA)], 4.49 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH_AH$_B$N (PTA)], 4.58 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH$_A$$H_B$N (PTA)], 5.72 [s, 1 H, COCHCO (*t*Bu$_2$acac)], 5.80 (d, J = 5.8 Hz, 2 H, 2-H, 6-H), 5.89 (d, J = 5.8 Hz, 2 H, 3-H, 5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.96 (4-CH_3), 21.94 [1-CH(CH_3)$_2$], 28.47 [2× C(CH_3)$_3$ (*t*Bu$_2$acac)], 30.55 [1-CH-(CH$_3$)$_2$], 41.79 [2× C(CH$_3$)$_3$ (*t*Bu$_2$acac)], 50.80 [d, J_{CP} = 13.4 Hz, 3× PCH_2N (PTA)], 72.95 [d, J_{CP} = 7.4 Hz, 3× NCH_2N (PTA)], 88.10 (d, J_{CP} = 3.4 Hz, C-2, C-6), 89.71 (d, J_{CP} = 3.7 Hz, C-3, C-5), 92.43 [COCHCO (*t*Bu$_2$acac)], 96.38 (C-4), 103.8 (C-1), 199.1 [2× CO (*t*Bu$_2$acac)] ppm. ^{31}P{^{1}H} NMR (126 MHz, $CDCl_3$): δ = –29.91 ppm. ESI-MS (CH_3CN): m/z (%) = 576.1 (100) [Ru(cymene)(*t*Bu$_2$acac)(PTA)]$^+$. ESI-MS (CH_3CN, MS/MS, 30% relative collision energy): m/z (%) = 419.0 (100) [Ru(cymene)(*t*Bu$_2$acac)]$^+$. $C_{27}H_{45}BF_4N_3O_2PRu$ (662.52): calcd. C 48.95, H 6.85, N 6.34; found C 48.57, H 6.76, N 6.34.



[Ru(η⁶-*p*-cymene)(*t*Bu₂acac)(PTA)][BPh₄] (12·BPh₄): To a solution of **8** (100 mg, 0.220 mmol) in acetone (10 mL) and CH_2Cl_2 (10 mL), PTA (36.0 mg, 0.229 mmol, 1.04 equiv.) and $NaBPh_4$ (79.0 mg, 0.231 mmol, 1.05 equiv.) were added at room temperature. The mixture was heated to reflux temperature with a heating gun and then stirred at room temperature for 15 min. The heating/ambient temperature cycle was repeated three more times (total reaction time: 1 h). The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 (4× 10 mL). The extracts were filtered and reduced in vacuo to a volume of ca. 10 mL. Formation of a yellow crystalline precipitate was induced by addition of Et_2O (50 mL), followed by concentration to ca. 20 mL, addition of petroleum ether (50 mL), followed by concentration to ca. 20 mL and addition of petroleum ether (50 mL). The solid was filtered, washed with petroleum ether (2× 10 mL) and dried in vacuo, affording a yellow-orange crystalline solid (144 mg, 0.161 mmol, 73%). Crystals suitable for X-ray analysis were obtained by layering a $CHCl_3$ solution of **12**·BPh_4 with Et_2O and storing at 4 °C for 5 d. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 [s, 18 H, 2× C(CH_3)$_3$ (*t*Bu$_2$acac)], 1.13 [d, *J* = 7.1 Hz, 6 H, 1-CH(CH_3)$_2$], 1.60 (s, 3 H, 4-CH_3), 2.29 [sept, *J* = 7.1 Hz, 1 H, 1-CH(CH$_3$)$_2$], 3.74 [s, 6 H, 3× PCH_2N (PTA)], 4.30 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH_AH$_B$N (PTA)], 4.47 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH$_A$$H_B$N (PTA)], 4.89 (d, *J* = 6.9 Hz, 2 H, 2-H, 6-H), 5.03 (d, *J* = 6.9 Hz, 2 H, 3-H, 5-H), 5.68 [s, 1 H, COCHCO (*t*Bu$_2$acac)], 6.95 [t, *J* = 7.2 Hz, 4 H, 4× *para*-H (BPh$_4$)], 7.08 [t, *J* = 7.2 Hz, 8 H, 8× *meta*-H (BPh$_4$)], 7.45 [br. m$_c$, 8 H, 8× *ortho*-H (BPh$_4$)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.07 (4-*C*H$_3$), 21.91 [1-CH(*C*H$_3$)$_2$], 28.46 [2× C(*C*H$_3$)$_3$ (*t*Bu$_2$acac)], 30.45 [1-*C*H(CH$_3$)$_2$], 41.80 [2× *C*(CH$_3$)$_3$ (*t*Bu$_2$acac)], 51.24 [d, J_{CP} = 13.0 Hz, 3× P*C*H$_2$N (PTA)], 72.97 [d, J_{CP} = 6.9 Hz, 3× N*C*H$_2$N (PTA)], 87.88 (d, J_{CP} = 3.4 Hz, C-2, C-6), 89.01 (d, J_{CP} = 4.0 Hz, C-3, C-5), 92.43 [CO*C*HCO (*t*Bu$_2$acac)], 96.90 (C-4), 103.7 (C-1), 122.0 [4× *para*-C (BPh$_4$)], 125.7 [8× *meta*-C (BPh$_4$)], 136.3 [8× *ortho*-C (BPh$_4$)], 164.1 [q, J_{CB} = 49.3 Hz, 4× *ipso*-C (BPh$_4$)], 199.0 [2× *C*O (*t*Bu$_2$acac)] ppm. ^{31}P{^{1}H} NMR (126 MHz, $CDCl_3$): δ = –29.84 ppm. ESI-MS (CH_3CN): *m*/*z* (%) = 575.9 (100) [Ru(cymene)(*t*Bu$_2$acac)(PTA)]$^+$. ESI-MS (CH_3CN, MS/MS, 20% relative collision energy): *m*/*z* (%) = 576.0 (65) [Ru(cymene)(*t*Bu$_2$acac)(PTA)]$^+$, 419.2 (100) [Ru(cymene)(*t*Bu$_2$acac)]$^+$. $C_{51}H_{65}BN_3O_2PRu$ (894.95): calcd. C 68.45, H 7.32, N 4.70; found C 68.47, H 7.32, N 4.73.

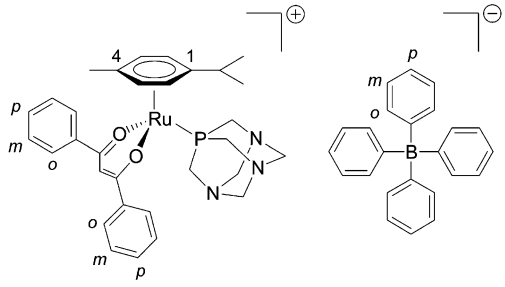


[Ru(η⁶-*p*-cymene)(Ph₂acac)(PTA)][BF₄] (13·BF₄): To a solution of **9** (90.5 mg, 0.183 mmol) in acetone (15 mL), PTA (30.8 mg, 0.196 mmol, 1.07 equiv.) and $NaBF_4$ (200 mg, 1.82 mmol, 9.95 equiv.) were added at room temperature. The mixture was heated to reflux temperature with a heating gun, then stirred at room temperature for 30 min, heated to reflux temperature again and stirred afterwards at room temperature for 3 h (total reaction time: 3.5 h). The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 (5× 10 mL). The extracts were filtered. Petroleum ether (50 mL) was added to the filtrate, and the solvent was evaporated in vacuo to afford an oily residue, which was taken up in CH_2Cl_2 (5 mL). Precipitation was induced by slow addition of petroleum ether (60 mL) and accomplished by storing the mixture at room temperature for 20 min. The solid was filtered off, washed with petroleum ether (3× 10 mL) and dried in vacuo, affording a dark yellow crystalline solid (81.0 mg, 0.115 mmol, 63%). Crystals suitable for X-ray analysis were obtained by layering a $CHCl_3$ solution of **13**·BF_4 with ethyl acetate and storing at 4 °C for 4 d. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 [d, *J* = 6.9 Hz, 6 H, 1-CH(CH_3)$_2$], 2.10 (s, 3 H, 4-CH_3), 2.65 [sept, *J* = 6.9 Hz, 1 H, 1-CH(CH$_3$)$_2$], 4.26 [s, 6 H, 3× PCH_2N (PTA)], 4.45 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH_AH$_B$N (PTA)], 4.56 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH$_A$$H_B$N (PTA)], 5.94 (d, *J* = 5.9 Hz, 2 H, 2-H, 6-H), 6.01 (d, *J* = 5.9 Hz, 2 H, 3-H, 5-H), 6.77 [s, 1 H, COCHCO (Ph$_2$acac)], 7.49 [t, *J* = 7.5 Hz, 4 H, 4× *meta*-H (Ph$_2$acac)], 7.58 [t, *J* = 7.5 Hz, 2 H, 2× *para*-H (Ph$_2$acac)], 7.84 [d, *J* = 7.5 Hz, 4 H, 4× *ortho*-H (Ph$_2$acac)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.12 (4-*C*H$_3$), 22.16 [1-CH(*C*H$_3$)$_2$], 30.67 [1-*C*H(CH$_3$)$_2$], 51.16 [d, J_{CP} = 13.1 Hz, 3× P*C*H$_2$N (PTA)], 72.80 [d, J_{CP} = 7.4 Hz, 3× N*C*H$_2$N (PTA)], 88.43 (d, J_{CP} = 3.9 Hz, C-2, C-6), 89.41 (d, J_{CP} = 4.4 Hz, C-3, C-5), 95.13 [CO*C*HCO (Ph$_2$acac)], 98.31 (C-4), 104.0 (C-1), 126.9 [4× *ortho*-C (Ph$_2$acac)], 128.9 [4× *meta*-C (Ph$_2$acac)], 132.3 [2× *para*-C (Ph$_2$acac)], 137.0 [2× *ipso*-C (Ph$_2$acac)], 183.3 [2× *C*O (Ph$_2$acac)] ppm. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = –28.08 ppm. ESI-MS (CH_3CN): *m*/*z* (%) = 616.1 (100) [Ru(cymene)(Ph$_2$acac)(PTA)]$^+$. ESI-MS (CH_3CN, MS/MS, 30% relative collision energy): *m*/*z* (%) = 616.1 (100) [Ru(cymene)(Ph$_2$acac)(PTA)]$^+$, 459.0 (27) [Ru(cymene)(Ph$_2$acac)]$^+$. $C_{31}H_{37}BF_4N_3O_2PRu·H_2O$ (720.5): calcd. C 51.68, H 5.46, N 5.83; found C 51.56, H 5.18, N 6.15.

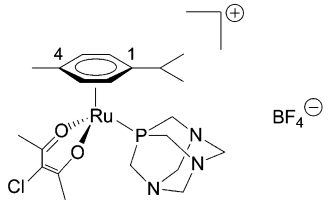


[Ru(η⁶-*p*-cymene)(Ph₂acac)(PTA)][BPh₄] (13·BPh₄): To a solution of **9** (100 mg, 0.202 mmol) in acetone (10 mL) and CH_2Cl_2 (10 mL), PTA (34.0 mg, 0.216 mmol, 1.07 equiv.) and $NaBPh_4$ (70.0 mg, 0.205 mmol, 1.01 equiv.) were added at room temperature. The mixture was heated to reflux temperature and then stirred at room temperature for 15 min. The heating/ambient temperature cycle was repeated three more times, and afterwards the mixture was stirred at room temperature for additional 75 min (total reaction time: 2.25 h). The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 (4× 10 mL). The extracts were filtered, petroleum ether (40 mL) was added, and precipitation was induced by gradually decreasing the CH_2Cl_2 content in several cycles of partial solvent evaporation and re-addition of petroleum ether. Precipitation was accomplished by storing the mixture at –25 °C for 15 min. The solid was filtered, washed with petroleum ether (3× 15 mL) and dried in vacuo, affording a yellow powder (139 mg, 0.149 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 [d, *J* = 6.9 Hz, 6 H, 1-CH(CH_3)$_2$], 1.73 (s, 3 H, 4-CH_3), 2.42 [sept, *J* = 6.9 Hz, 1 H, 1-CH(CH$_3$)$_2$], 3.82 [s, 6 H, 3× PCH_2N (PTA)], 4.28 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH_AH$_B$N (PTA)], 4.42 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH$_A$$H_B$N (PTA)], 5.01 (d, *J* = 5.8 Hz, 2 H, 2-H, 6-H), 5.18 (d, *J* = 5.8 Hz, 2 H, 3-H, 5-H), 6.72 [s, 1 H, COCHCO (Ph$_2$acac)], 6.93 [t, *J* = 7.2 Hz, 4 H, 4× *para*-H (BPh$_4$)], 7.08 [t, *J* = 7.2 Hz, 8 H, 8× *meta*-H (BPh$_4$)], 7.43–7.52 [m, 12 H,

4× *meta*-H (Ph_2acac), 8× *ortho*-H (BPh_4)], 7.59 [t, J = 7.2 Hz, 2 H, 2× *para*-H (Ph_2acac)], 7.78 [d, J = 7.7 Hz, 4 H, 4× *ortho*-H (Ph_2acac)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.30 (4-CH_3), 22.06 [1-CH(CH_3)$_2$], 30.57 [1-CH(CH_3)$_2$], 51.66 [d, J_{CP} = 13.0 Hz, 3× PCH_2N (PTA)], 72.89 [d, J_{CP} = 7.2 Hz, 3× NCH_2N (PTA)], 88.11 (d, J_{CP} = 3.7 Hz, C-2, C-6), 88.78 (d, J_{CP} = 4.4 Hz, C-3, C-5), 95.14 [CH (Ph_2acac)], 98.39 (C-4), 104.1 (C-1), 122.0 [4× *para*-C (BPh_4)], 125.8 [q, J_{CB} = 2.6 Hz, 8× *meta*-C (BPh_4)], 126.8 [4× *ortho*-C (Ph_2acac)], 129.0 [4× *meta*-C (Ph_2acac)], 132.5 [2× *para*-C (Ph_2acac)], 136.3 [q, J_{CB} = 1.4 Hz, 8× *ortho*-C (BPh_4)], 136.9 [2× *ipso*-C (Ph_2acac)], 164.1 [q, J_{CB} = 49.3 Hz, 4× *ipso*-C (BPh_4)], 183.2 [2× CO (Ph_2acac)] ppm. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = –29.70 ppm. ESI-MS (CH_3CN): *m/z* (%) = 615.9 (100) [Ru(cymene)(Ph_2acac)(PTA)]$^+$. ESI-MS (CH_3CN, MS/MS, 20% relative collision energy): *m/z* (%) = 615.9 (75) [Ru(cymene)(Ph_2acac)-(PTA)]$^+$, 458.9 (100) [Ru(cymene)(Ph_2acac)]$^+$. $C_{55}H_{57}BN_3O_2PRu\cdot 0.25CH_2Cl_2\cdot 1.5H_2O$ (983.2): calcd. C 67.50, H 6.20, N 4.27; found C 67.36, H 5.76, N 4.26.



[Ru(η^6-*p*-cymene)(Me_2acac-Cl)(PTA)][BF_4] (14·BF_4): To a solution of **10** (150 mg, 0.371 mmol) in acetone (30 mL), PTA (59.0 mg, 0.375 mmol, 1.01 equiv.) and $NaBF_4$ (205 mg, 1.87 mmol, 5.03 equiv.) were added, and the mixture was stirred at room temperature for 3 h. The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 (5× 10 mL). The extracts were filtered through a pad of Celite and reduced in vacuo to ca. 15 mL. Addition of Et_2O (100 mL) and hexanes (30 mL) led to the formation of a precipitate, which was filtered, washed with Et_2O (3× 10 mL) and dried in vacuo, affording a yellow powder (149 mg, 0.243 mmol, 66%). Crystals suitable for X-ray analysis were obtained by layering a CH_2Cl_2 solution of **14**·BF_4 with Et_2O and storing at room temperature for 24 h. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 [d, J = 6.9 Hz, 6 H, 1-CH(CH_3)$_2$], 1.95 (s, 3 H, 4-CH_3), 2.27 [s, 6 H, 2× CH_3 (Me_2acac-Cl)], 2.50 [sept, J = 6.9 Hz, 1 H, 1-CH(CH_3)$_2$], 4.18 [s, 6 H, 3× PCH_2N (PTA)], 4.51 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH_AH_BN (PTA)], 4.62 [d, J_{AB} = 13.3 Hz, 3 H, 3× NCH_AH_BN (PTA)], 5.88 (d, J = 1.1 Hz, 4 H, 2-H, 3-H, 5-H, 6-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.86 (4-CH_3), 21.99 [1-CH(CH_3)$_2$], 28.08 [2× CH_3 (Me_2acac-Cl)], 30.76 [1-CH(CH_3)$_2$], 50.88 [d, J_{CP} = 13.4 Hz, 3× PCH_2N (PTA)], 72.83 [d, J_{CP} = 7.5 Hz, 3× NCH_2N (PTA)], 88.10 (d, J_{CP} = 3.8 Hz, C-2, C-6), 89.00 (d, J_{CP} = 4.4 Hz, C-3, C-5), 97.83 (C-4), 103.9 (C-1), 108.8 [COCClCO (Me_2acac-Cl)], 187.8 [2× CO (Me_2acac-Cl)] ppm. ^{31}P{^{1}H} NMR (126 MHz, $CDCl_3$): δ = –30.05 ppm. ESI-MS (CH_3CN): *m/z* (%) = 525.8 (100) [Ru(cymene)(Me_2acac-Cl)-(PTA)]$^+$. ESI-MS (CH_3CN, MS/MS, 20% relative collision energy): *m/z* (%) = 525.9 (20) [Ru(cymene)(Me_2acac-Cl)(PTA)]$^+$, 368.9 (100) [Ru(cymene)(Me_2acac-Cl)]$^+$. $C_{21}H_{32}BClF_4N_3O_2PRu\cdot 0.5H_2O$ (621.8): calcd. C 40.56, H 5.35, N 6.76; found C 40.49, H 5.25, N 6.76.



Crystallography: Crystal structure determinations of **11**·BF_4, **11**·BPh_4, **12**·BPh_4, **13**·BF_4 and **14**·BF_4 were performed with a KUMA CCD area detector (graphite-monochromated Mo-K_α radiation) at 140 K (Table 5). Multiscan absorption corrections were applied

Table 5. Crystallographic parameters for **11**·BF_4, **11**·BPh_4, **12**·BPh_4, **13**·BF_4 and **14**·BF_4.

	11·BF_4	**11**·BPh_4	**12**·BPh_4	**13**·BF_4	**14**·BF_4
Empirical formula	$C_{21}H_{33}BF_4N_3O_2PRu$	$C_{45}H_{53}BN_3O_2PRu$	$C_{51}H_{65}BN_3O_2PRu$	$C_{31}H_{37}BF_4N_3O_2PRu$	$C_{21}H_{32}BClF_4N_3O_2PRu$
Formula mass	578.35	810.75	894.91	702.50	612.80
Colour, habit	yellow, prismatic	yellow, prismatic	yellow, prismatic	yellow, prismatic	yellow, prismatic
Crystal system	monoclininc	triclinic	monoclinic	monoclinic	triclinic
Space group	$P2_1/n$	$P\bar{1}$	$P2_1/n$	$P2_1/n$	$P\bar{1}$
a [Å]	11.865(2)	10.1560(4)	16.2440(11)	22.7719(10)	8.519(3)
b [Å]	14.783(3)	11.5070(8)	15.3450(11)	11.840(2)	9.636(2)
c [Å]	14.088(2)	17.4540(12)	19.196(2)	23.606(8)	15.307(3)
a [°]	90	90.646(6)	90	90	85.24(2)
β [°]	103.63(2)	92.492(5)	103.181(6)	98.246(10)	84.16(2)
γ [°]	90	90.357(5)	90	90	85.01(2)
V [Å^3]	2401.4(7)	2037.6(2)	4658.8(6)	6280(2)	1241.8(5)
Z	4	2	4	8	4
Crystal size [mm]	0.30×0.28×0.23	0.34×0.22×0.20	0.38×0.30×0.27	0.205×0.084×0.055	0.30×0.20×0.17
$d_{calcd.}$ [g cm^{-1}]	1.600	1.321	1.276	1.486	1.639
μ [mm^{-1}]	0.774	0.46	0.41	0.607	0.858
No. of reflections	15178	13888	30143	75297	10371
R(int)	0.0564	0.0378	0.0528	0.1875	0.0626
No. of observed reflections	4327	5064	9927	9503	4205
R_1 (observed reflections)	0.0596	0.0409	0.0401	0.0642	0.0502
wR_2 (all)	0.1572	0.1010	0.1056	0.1104	0.1257
Restraints	36	0	0	0	0
Parameters	339	484	541	781	312
Goodness-of-fit on F^2	1.106	1.078	0.966	1.081	1.013

using PLATON.[24] The structures were solved by direct methods using SHELXS 97[25] and refined by least-squares methods on F^2 using SHELXL 97. All non-hydrogen atoms were refined anisotropically and hydrogen atoms placed in geometrically calculated positions. In **11**·BPh_4, the C8 *p*-cymene methyl group is disordered over two positions and the occupancy of the two sites refined to 0.54:0.46. The disordered BF_4 counterion in **14**·BF_4 was refined to two sites of occupancy 0.70:0.30. CCDC-668990 (**11**·BF_4), -668988 (**11**·BPh_4), -668989 (**12**·BPh_4), -668992 (**13**·BF_4), and -668991 (**14**·BF_4) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Biological Evaluation: Cell mitochondrial functions were determined by the MTT test essentially as described previously.[16] Inhibition of cell growth was determined in triple parallel experiments. Cells were routinely grown in the appropriate medium (DMEM HG 10% FCS for A549 human lung cancer cells; RPMI 10% FCS for A2780 human ovarian cancer cells). Solutions of the substances for application were routinely prepared by diluting a freshly prepared stock solution of the corresponding compound in DMSO with the appropriate medium for the cell line (see above) containing 5% of FCS. The maximum DMSO concentration in the cells was 1% v/v. Cells were exposed to the compounds at T = 37 °C in an atmosphere containing 5% of CO_2 for 72 h. MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Sigma, Switzerland] dissolved in PBS (phosphate-buffered saline) (5 mg/mL) was added (10 μL per 250 μL of medium) to all wells, and the plates were incubated at 37 °C for 2 h; the medium was removed, and the precipitated formazan was dissolved in a mixture of aqueous HCl and *i*PrOH (4 mL of 2 N HCl + 100 mL of *i*PrOH). The UV absorption was measured at 540 nm using a multiwell plate reader (iEMS Reader MF; Labsystems, Waltham, MA). Cell viability was calculated by dividing the (corrected) UV absorption of the wells exposed to the test substance by the (corrected) absorption of control cells not exposed to the substances.

Acknowledgments

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