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## Cytotoxic Hydrogen Bridged Ruthenium Quinaldamide Complexes Showing Induced Cancer Cell Death by Apoptosis

Rianne M. Lord,<sup>a\*</sup> Simon J. Allison,<sup>b</sup> Karen Rafferty,<sup>a</sup> Laura Ghandhi,<sup>a</sup> Christopher M. Pask<sup>a</sup> and Patrick C. McGowan<sup>a\*</sup>

This report presents the first known *p*-cymene ruthenium quinaldamide complexes which are stabilised by a hydrogen-bridging atom,  $[[\{(p\text{-cym})\text{Ru}^{\text{II}}\text{X}(N,N)\}\{\text{H}^+\}\{(N,N)\text{XRu}^{\text{II}}(p\text{-cym})\}][\text{PF}_6]]$  ( $N,N$  = functionalised quinaldamide and  $X = \text{Cl}$  or  $\text{Br}$ ). These complexes are formed by a reaction of  $[\text{p-cymRu}(\mu\text{-X})_2]_2$  with a functionalised quinaldamide ligand. When filtered over  $\text{NH}_4\text{PF}_6$ , and under aerobic conditions the equilibrium of  $\text{NH}_4\text{PF}_6 \rightleftharpoons \text{NH}_3 + \text{HPF}_6$  enables incorporation of  $\text{HPF}_6$  and the stabilisation of two monomeric ruthenium complexes by a bridging  $\text{H}^+$ , which are counter-balanced by a  $\text{PF}_6$  counterion. X-ray crystallographic analysis is presented for six new structures with  $\text{O}\cdots\text{O}$  distances of 2.430(3)–2.444(17) Å, which is significant for strong hydrogen bonds. Chemosensitivity studies against HCT116, A2780 and cisplatin-resistant A2780cis human cancer cells showed the ruthenium complexes with a bromide ancillary ligand to be more potent than those with a chloride ligand. The 4'-fluoro compounds show a reduction in potency for both chloride and bromide complexes against all cell lines, but an increase in selectivity towards cancer cells compared to non-cancer ARPE-19 cells, with a selectivity index > 1. Mechanistic studies showed a clear correlation between  $\text{IC}_{50}$  values and induction of cell death by apoptosis.

### Introduction

There are only a small number of reports on the synthesis and isolation of transition metal hydrogen-bridging complexes. Usually solvent molecules provide the  $\text{H}^+$  source and few researchers suggest the possibility of the reagent  $\text{NH}_4\text{PF}_6$  providing the source of  $\text{H}^+$ . Peacock *et al.* were amongst the first to isolate and characterise by X-ray crystallographic analysis, cobalt, manganese and chromium hydrogen-bridged structures,  $[\text{Co}^{\text{III}}(\text{L}\cdot\text{H}_3\text{L})\text{Co}^{\text{III}}][\text{PF}_6]_3$ ,<sup>1</sup>  $[\text{Mn}^{\text{II}}(\text{L}\cdot\text{H}_3\text{L})\text{Mn}^{\text{IV}}][\text{PF}_6]_3$ ,<sup>2</sup> and  $[\text{Cr}^{\text{III}}(\text{L}\cdot\text{H}_3\text{L})\text{Cr}^{\text{III}}][\text{PF}_6]_3$ ,<sup>3</sup> ( $\text{LH}_3 = N,N',N''\text{-tris}[(2\text{S})\text{-2-hydroxypropyl}]\text{-1,4,7-triazacyclononane}$ ) respectively. Some of these compounds have been studied using circular dichroism, magnetic susceptibility and cyclic voltammetry, in order to understand their spin states and oxidation states.<sup>2</sup> Ward *et al.* have also synthesised and characterised by X-ray crystallographic analysis nickel and copper hydrogen-bridged structures,  $[\text{Ni}^{\text{II}}(\text{L}\cdot\text{HL})_2][\text{PF}_6]_2$ ,<sup>4</sup> ( $\text{L} = 6\text{-}(2\text{-hydroxyphenyl})\text{-2,2'}$ -bipyridine) and  $[\text{Cu}^{\text{II}}(\text{L}^2)]\cdot(\text{HPF}_6)_{0.5}\cdot\text{H}_2\text{O}$ ,<sup>5</sup> ( $\text{L} = 6,6'\text{-bis}(2\text{-hydroxyphenyl})\text{-2,2'}$ -bipyridine) respectively. All these compounds have a shortened  $\text{O}\cdots\text{O}$  bond distance, averaging 2.34 Å, indicative of strong hydrogen-bonds. In all cases, the hydrogen atoms could not be located in the crystal structures; however their presence is needed in order to balance the  $\text{PF}_6$  counterions. Nothing has yet been reported on the possible applications of such compounds, therefore we report here the

application of hydrogen-bridged ruthenium complexes as possible anti-cancer agents.

In a search for less toxic and more potent alternatives to cisplatin, organometallic complexes have shown promising activity as anti-cancer agents.<sup>6–16</sup> Ruthenium-based complexes are some of the most promising, with reported selective potency *in vitro* and *in vivo*.<sup>17–22</sup> McGowan *et al.* have synthesised a range of ruthenium metal complexes for their uses as anticancer agents.<sup>23–26</sup> The work published on ruthenium quinaldamides showed that under inert atmosphere conditions, the filtering over  $\text{NH}_4\text{PF}_6$  yielded the ruthenium quinaldamide monomers.<sup>27</sup> The use of dry conditions avoids the hydrolysis of  $\text{NH}_4\text{PF}_6$  to  $\text{NH}_3$  and  $\text{HPF}_6$ . These monomeric complexes show low  $\text{IC}_{50}$  values against a range of cell lines and also form adducts with guanine nucleotides. Herein, we present the same synthetic strategy using aerobic conditions and show that the monomers are no longer stable under these conditions and the  $\text{HPF}_6$  present from the hydrolysis of  $\text{NH}_4\text{PF}_6$ , stabilises two ruthenium quinaldamide species,  $[[\{(p\text{-cym})\text{Ru}^{\text{II}}\text{X}(N,N)\}\{\text{H}^+\}\{(N,N)\text{XRu}^{\text{II}}(p\text{-cym})\}][\text{PF}_6]]$ , with incorporation of  $\text{HPF}_6$ . This motif has previously been reported for our ruthenium picolinamide complexes, in which an average  $\text{O}\cdots\text{O}$  bond distance of 2.43 Å was observed.<sup>17</sup> The X-ray crystallographic data was reported, however, chemosensitivity studies were not determined.

<sup>a</sup> School of Chemistry, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, p.c.mcgowan@leeds.ac.uk

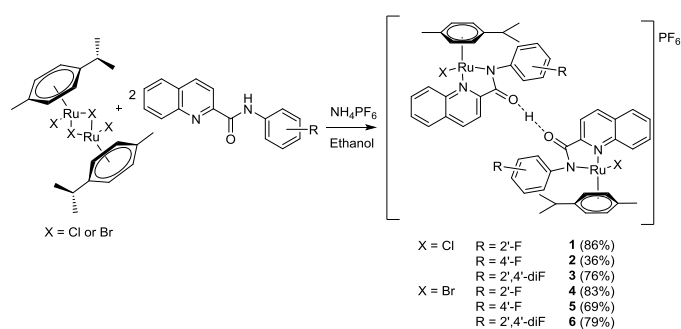
<sup>b</sup> Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Huddersfield, HD1 3DH

† Electronic Supplementary Information (ESI) available: Experimental procedures for compounds, cell line experimental, apoptosis studies and crystal structure determination details. The cifs for complexes 1–6 were deposited to the CCDC with codes 1472239–1472244.

Herein, chemosensitivity studies have been carried out against HCT116 (human colon carcinoma), A2780 (human ovarian carcinoma) and A2780cis (cisplatin resistant A2780) cancer cell lines, and against non-cancer ARPE-19 (human retinal epithelium) cells. Studies investigated whether the complexes might induce apoptosis (programmed cell death), a cell death mechanism that is commonly suppressed in cancers. This was measured in the HCT116 cancer cells by loss of mitochondrial membrane potential which is an early marker of apoptosis. Cell images by phase contrast microscopy at various time-points after compound addition suggested induction of cell death rather than growth arrest. Apoptotic analyses revealed a clear correlation between chemosensitivity and levels of apoptosis, whereby the most active compound induces the highest percentage of apoptosis.

## Results and discussion

Using a modification of the previously established literature method by Bennett *et al.*,<sup>28, 29</sup> the ruthenium(II) *p*-cymene halide complexes were synthesised by dissolving Ru<sup>III</sup>X<sub>3</sub>.xH<sub>2</sub>O (X = Cl or Br) and  $\alpha$ -terpinene in ethanol, then heating to reflux for 16 hours. The resulting dark red powder was filtered and washed with ice cold ethanol to yield the desired starting ruthenium *p*-cymene dimer. Upon addition of two equivalents of a substituted quinaldamide in ethanol and filtering over NH<sub>4</sub>PF<sub>6</sub>, the reaction mixture formed a pale orange precipitate and yielded complexes **1-6** as analytically pure products (Scheme 1). Single orange-red crystals suitable for X-ray crystallographic analysis were obtained for complexes **1-6**. They crystallised in either a triclinic *P* 1 (**1-3**, **5-6**) or monoclinic *C*2/*c* (**4**) space group. All of the angles around the metal centre show the geometry expected for *pseudo* octahedral compounds which is common for half-sandwich “piano-stool” structures (Tables 1). The angles between the metal and bidentate ligands are in the range 75.4(2)–87.5(3)°, with the remaining three coordination sites occupied by the *p*-cymene ligand, with the angles observed for their centroids to the halide or bidentate ligand ranging between 126.81–134.78°. Molecular structures for complexes **1-6** are shown in

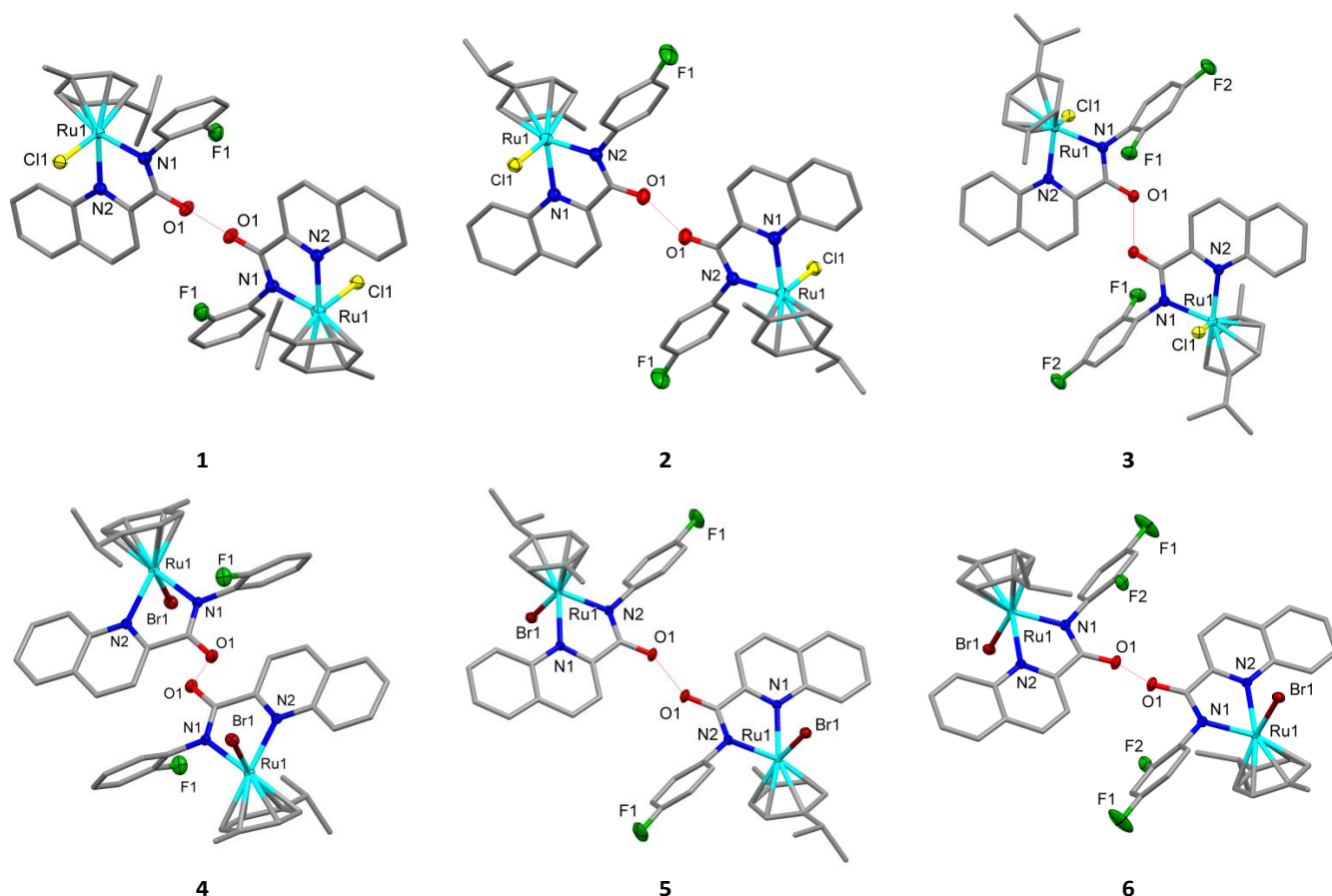


**Scheme 1** Synthetic route for the synthesis of ruthenium quinaldamide complexes **1-6** via addition of a functionalised quinaldamide ligand to [*p*-cymRuX(μ-X)]<sub>2</sub>.

**Figure 1**, with displacement ellipsoids placed at the 50% probability level and hydrogen atoms and PF<sub>6</sub> anions omitted for clarity. The proton bridging between the two carbonyl oxygens provides the +1 charge, which is counter-balanced by the PF<sub>6</sub> anion, and both metal centres are in their +2 oxidation state. The two such monomer units [*p*-cymRu<sup>II</sup>(*N,N*)X] are held together by one intermolecular hydrogen bond which links O(1) and O(1'). The short O...O distances of 2.439(3)–2.444(17) Å (Table 2), which are only slightly longer than double of a typical O-H distance, are at the lower limit for a pair of hydrogen-bonded oxygen atoms, indicative of strong hydrogen bonds. This was also reported for nickel complexes synthesised by Ward *et al.*, in which they observed O...O distances of 2.37–2.39 Å.<sup>4, 30, 31</sup> However, weak asymmetric O-H...O hydrogen bonds more typically have O...O distance > 2.7 Å.<sup>32</sup> As shown in the previously reported structures by Ward *et al.*,<sup>4</sup> the hydrogen-bridging complexes are further stabilized by intermolecular interactions. The packing diagrams for complexes **1-6** are presented in Figures S1-2, and show that these ruthenium quinaldamide complexes have several intramolecular and intermolecular interactions (Table S1a-f), which could also contribute to the stability of the dimers. All the complexes have their aromatic quinaldamide rings brought into close proximity, with relatively short π-π stacking interactions of 3.753–3.919 Å. X-ray crystallographic data is also presented in the supplementary information (Table S2).

**Table 1** Selected bond lengths (Å) and bond angles (°) for complexes **1-6**, with s.u.s in parenthesis

Bond Length (Å)	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
Ru(1)-N(1)	2.100(2)/2.035(2)	2.130(2)	2.0800(18)	2.079(2)	2.130(3)	2.076(3)
Ru(1)-N(2)	2.1222(19)/2.113(2)	2.076(2)	2.1368(18)	2.136(2)	2.085(3)	2.123(3)
Ru(1)-X(1)	2.3854(6)/2.4093(9)	2.3969(9)	2.3962(6)	2.5438(5)	2.5328(5)	2.5402(5)
Ru(1)-Cg(4)	1.6735(10)/1.6954(12)	1.6803(12)	1.6814(9)	1.7006(14)	1.6930(18)	1.6953(17)
Bond Angles (°)	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
N(1)-Ru(1)-N(2)	75.42(8)/76.99(8)	76.10(8)	76.00(7)	76.32(9)	76.13(11)	76.52(11)
N(1)-Ru(1)-X(1)	86.47(2)/87.29(6)	86.15(6)	87.76(5)	86.94(6)	85.89(8)	87.03(8)
N(2)-Ru(1)-X(1)	83.65(6)/83.26(6)	87.61(7)	86.32(5)	84.45(6)	87.50(8)	84.03(8)
N(1)-Ru(1)-Cg(4)	126.83(7)/129.68(8)	132.47(8)	128.18(6)	128.78(7)	132.41(10)	128.46(11)
N(2)-Ru(1)-Cg(4)	134.73(7)/133.88(7)	128.01(8)	132.57(6)	134.15(7)	128.37(10)	133.79(10)
X(1)-Ru(1)-Cg(4)	130.53(4)/127.74(5)	128.83(5)	128.45(4)	128.12(5)	128.79(6)	128.73(7)



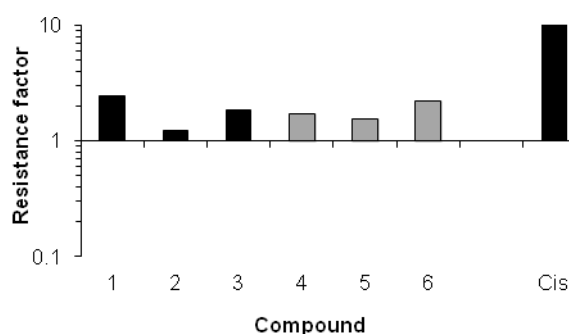
**Figure 1** Molecular structures for compounds 1-6. Hydrogen atoms and  $\text{PF}_6^-$  anions are omitted for clarity and displacement ellipsoids are shown only for heteroatoms, at the 50% probability level.

**Table 2** Hydrogen bonding donor-acceptor distances (Å) for complexes 1-6

Compound	O(1)···O(1') (Å)
1	2.425(3)
2	2.420(4)
3	2.442(3)
4	2.439(3)
5	2.444(17)
6	2.448(15)

### Chemosensitivity Studies

Chemosensitivity studies were undertaken using the MTT assay and  $\text{IC}_{50}$  values were determined against HCT116 (human colon carcinoma), A2780 (human ovarian carcinoma) and A2780cis (cisplatin resistant A2780 cells) cell lines, exposed to each of compounds 1-6 or cisplatin (Table 3). Against all three cancer cell lines the Ru-Br complexes were consistently more active than the Ru-Cl analogues. The 4-fluoro compounds 2 and 5 are the least active when compared to the other fluoro compounds, however, changing from Ru-Cl (compound 2,  $39.2 \pm 0.8 \mu\text{M}$ ) to Ru-Br (compound 5,  $8.7 \pm 0.4 \mu\text{M}$ ) there is a > 4-fold increase in cytotoxicity. The results show that the 2',4'-difluoro compounds 3 and 6 are the most active, and when comparing Ru-Cl (compound 3,  $5.9 \pm 0.2 \mu\text{M}$ ) and Ru-Br (compound 6,  $3.9 \pm 0.3 \mu\text{M}$ ) there is a 1.5-fold increase in cytotoxicity. They are an increase in cytotoxicity when compared



**Figure 2** The resistance factor for the compounds as indicated. This is defined as the  $\text{IC}_{50}$  in A2780cis divided by  $\text{IC}_{50}$  in A2780 cells. An RF of 1 indicates equal potency against both cell lines. An RF > 1 indicates that the A2780cis is more resistant than A2780. An RF < 1 indicates that the A2780cis is more sensitive than the A2780 cells.

to the 2'-fluoro compounds 1 and 4, but to a similar degree in both cancer and non-cancer cells. Most of the compounds were more active against A2780 cells than A2780cis cells, but the level of resistance is much less than for that of cisplatin (Figure 2 and Table S3, SI). Compound 2 is the least potent but showed similar activity towards A2780 and A2780cis cancer cells, and was more active against all three cancer cell lines when compared to non-cancer ARPE-19 cells. The results show that potency is dependent on position of the fluoro.

**Table 3** IC<sub>50</sub> values (μM) for cisplatin and compounds 1-6 against HCT116, A2780, A2780cis and ARPE-19 cell lines

Compound	IC <sub>50</sub> values (μM) ± Standard Deviation			
	HCT116	A2780	A2780cis	ARPE-19
Cisplatin	N.D.	1.00 ± 0.16	10.6 ± 0.9	6 ± 1 <sup>26</sup>
1	6.7 ± 0.5	4.8 ± 0.6	11.7 ± 0.6	4.3 ± 0.3
2	39.2 ± 0.8	17.56 ± 1	22 ± 1	> 50
3	5.9 ± 0.2	4.0 ± 0.5	7.4 ± 0.5	3.7 ± 0.8
4	4.02 ± 0.11	3.2 ± 0.4	5.46 ± 0.17	3.06 ± 0.09
5	8.7 ± 0.4	9 ± 3	14 ± 2	10.4 ± 3.3
6	3.9 ± 0.3	3.0 ± 0.4	6.5 ± 0.9	2.9 ± 0.2

substituent and increasing the number of electron withdrawing substituents increased the potency by > 6-fold.

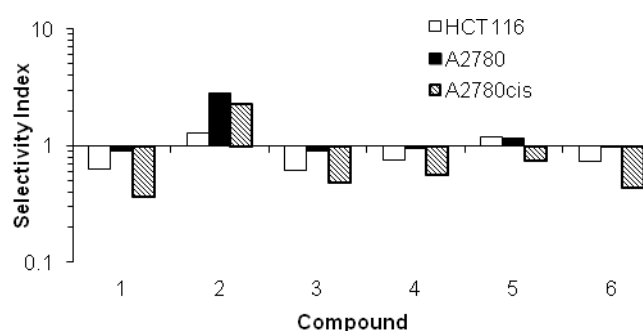
### Selectivity for Cancer Cells

One of the major limitations of existing anti-cancer drugs is their poor selectivity towards cancer cells, restricting the drugs' dosage. As well as causing harmful side effects for the patient, this dose-limiting toxicity impacts upon treatment effectiveness. Comparing the response of tumour cell lines to non-cancer ARPE-19 cells provides a preliminary indication of selectivity. Whilst compounds **1**, **3**, **4** and **6** show no selectivity towards cancer cells (ratio of IC<sub>50</sub> values in ARPE-19 cells to cancer cells ≤ 1), compounds **2** and **5** showed evidence of selectivity to certain cancer cells (**Figure 3** and **Table S4, S1**). Compound **2** in particular demonstrated selectivity against all the cancer cell lines tested with selectivity ranging from 2.85 to 1.27 fold increased chemosensitivity towards cancer cells compared to ARPE-19 non-cancer cells (HCT116: 1.27; A2780: 2.85; A2780cis: 2.29; **Figure 3** and **Table S3, S1**). However, compound **2** is the least active compound against all cancer cell lines tested.

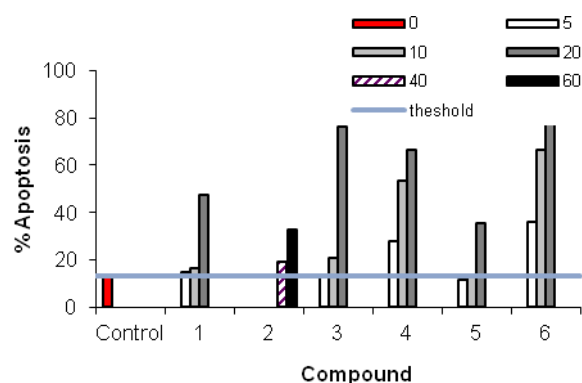
### Induction of Cancer Cell Death by Apoptosis

IC<sub>50</sub> values determined by chemosensitivity studies using the MTT assay indicates the concentration of drug required for a 50% reduction in cell number. This provides invaluable information about the activity of the drug against the cell line but does not distinguish between effects on cell proliferation and effects on cell survival. The observed activity of these compounds towards the cell lines could be caused by induction of cell growth arrest or the compounds may cause cell death. Cell images under phase contrast microscopy at various time-points after compound addition suggested induction of cell death as suggested by an increase in the proportion of non-adhered cells rather than growth arrest. Using flow cytometry and staining for loss of mitochondrial membrane potential the percentage of apoptotic cells were quantified following incubation of HCT116 cells with 0–60 μM of compounds **1-6** for 72 hours (**Figure 4** and **Table S4, S1**).

The 2',4'-difluoro compounds **3** and **6**, which were the most active compounds in the MTT chemosensitivity studies, also induced significant levels of apoptotic cell death against HCT116 cancer cell lines (**Figure 4** and **Table S5, S1**) in a dose-responsive manner. A 72 hour exposure of HCT116 cells to 20



**Figure 3** Show the selectivity index defined as the IC<sub>50</sub> in ARPE-19 divided by IC<sub>50</sub> relevant cancerous cells. An SR = 1 indicates equitoxic potency against tumour and normal cells. An SR > 1 indicates preferential selectivity for tumour cells compared to normal cells. An RF < 1 indicates poor selectivity (greater cytotoxicity towards ARPE cells compared to normal cells)



**Figure 4** % of apoptosis for control and compounds 1-6 against HCT116 cells at concentrations ranging from 0-60 μM.

μM of compound **3** resulted in ~76% of cells in early stages of apoptosis and compound **6** which was the most active against the MTT assay showed significant apoptosis, with 84% apoptotic cells. In contrast, compounds **2** and **5** were the least active compounds against the MTT assay and show the least amount of apoptotic cells. Compound **2** is the least active of this series of compounds, and a higher concentration of 60 μM of the compound had to be used to induce apoptosis, resulting in only 33% apoptotic cells. Whereas the more active compound **5** induces apoptosis at a concentration of 20 μM and gave 35% apoptotic cells. These observations indicate a clear correlation between IC<sub>50</sub> value and levels of apoptosis induced.

## Conclusions

We report the successful synthesis of ruthenium hydrogen-bridged complexes from the reaction of  $[p\text{-cymRuX}_2]_2$  ( $X = \text{Cl}$  or  $\text{Br}$ ) with a functionalised quinaldamide ligand. The reaction conditions differ from our previously synthesised ruthenium quinaldamide complexes, as here we utilise aerobic conditions and show the hydrolysis of the  $\text{NH}_4\text{PF}_6$  reagent yields the stabilisation of these unusual  $\text{H}^+$  bridged complexes, counter-balanced by a  $\text{PF}_6$  anion. These compounds have been tested against HCT116, A2780 and A2780cis cancer cells, and results show the 2',4'-difluoro compounds **3** ( $X = \text{Cl}$ ) and **6** ( $X = \text{Br}$ ) are the most potent against all cell lines. The di-substituted compounds are more potent than the mono-substituted, showing the number and position of the fluoro group is important to the potency. Across all cell lines, the 4-fluoro compounds **2** and **5** are the least active, with >6-fold decrease in potency observed against HCT116 cancer cells. The most significant results when comparing the different ancillary ligands are that the chloride compounds **1-3** are general less active than the bromide complexes **4-6**, with up >4-fold increase in  $\text{IC}_{50}$  values observed against HCT116 cells. Induction of cell death by apoptosis was investigated and this showed a clear correlation between  $\text{IC}_{50}$  values and levels of apoptosis induced. However, the results also indicate the importance to consider selectivity and ability to overcome drug resistance as well as potency with compound appearing the most promising by these important criteria.

## Experimental

### Materials

All chemicals were supplied by Sigma-Aldrich Chemical Co., Acros Organics, Strem Chemical Co. and BOC gases. Functionalised quinaldamide ligands were prepared by adaptations of literature methods.<sup>33</sup> Deuterated NMR solvents were supplied by Sigma-Aldrich Chemical Co. or Acros Organics.

### Analysis

All NMR spectra were recorded on a Bruker DPX 300 or a Bruker DPX 500 spectrometer. Microanalyses were recorded at the University of Leeds Microanalytical Service. Mass Spectra were recorded on a Micromass ZMD spectrometer with electrospray ionisation and photoiodide array analyser at the University of Leeds Mass Spectrometry Service.

### X-ray Crystallography

A suitable single crystal was selected and immersed in an inert oil. The crystal was then mounted on a glass capillary or nylon loop and attached to a goniometer head on Nonius KappaCCD area detector diffractometer using graphite monochromated  $\text{Mo-K}\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) and a Bruker X8 Apex diffractometer. The crystal was cooled and data measured at 148-150K by an Oxford Cryostream low temperature device.<sup>34</sup> The full data sets were recorded and the images processed

using DENZO and SCALEPACK programs.<sup>35</sup> Structure solution by direct methods was achieved through the use of SHELXS programs,<sup>36</sup> and the structural model refined by full matrix least squares on  $F^2$  using SHELX97. Unless otherwise stated, hydrogen atoms were placed using idealised geometric positions (with free rotation for methyl groups), allowed to move in a "riding model" along with the atoms to which they were attached, and refined isotropically. Molecular graphics were plotted using OLEX2<sup>37</sup> and Mercury.<sup>38</sup> Editing of CIFs and construction of tables of bond lengths and angles were achieved using WC<sup>39</sup> and PLATON.<sup>30</sup>

### Chemosensitivity Studies

*In vitro* chemosensitivity tests were performed at the University of Huddersfield, against HCT116 (human colon carcinoma), A2780 (human ovarian carcinoma) and A2780cis (cisplatin resistant A2780 cells) cancer cell lines, and against ARPE-19 (human retinal epithelial non-cancer) cells. ARPE-19 cells were obtained from the American Type Culture Collection. Cancer cell lines were routinely maintained as monolayer cultures in appropriate medium (RPMI 1640 supplemented with 10% foetal calf serum, sodium pyruvate (1 mM) and L-glutamine (2 mM) ARPE-19 cells were cultured in DMEM-F12 medium containing 10% foetal calf serum. For chemosensitivity studies, cells were incubated in 96-well plates at a concentration of  $2 \times 10^3$  cells per well and the plates were incubated for 24 hours at 37 °C in an atmosphere of 5%  $\text{CO}_2$  prior to drug exposure. Compounds or cisplatin were each dissolved in dimethylsulfoxide to provide stock solutions that were diluted to provide a range of final concentrations. Drug solutions were added to cells (the final DMSO concentrations was less than 0.1% (v/v) in all cases) and incubated for 5 days at 37°C in an atmosphere of 5%  $\text{CO}_2$ . 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) ( $20 \mu\text{L}$ ,  $5 \text{ mg mL}^{-1}$ ) was added to each well and incubated for 4 hours at 37°C in an atmosphere of 5%  $\text{CO}_2$ . All solutions were then removed by pipetting and 150  $\mu\text{L}$  of dimethylsulfoxide added to each well in order to dissolve the purple formazan crystals absorbance of each well at 540 nm measured by spectrophotometer. Lanes containing medium only and 100% cells were used as blanks for the spectrophotometer and 100% cell survival respectively. Cell survival was determined as the true absorbance of treated cells divided by the true absorbance of controls and expressed as a percentage. The  $\text{IC}_{50}$  values were determined from dose response curves of % survival against drug concentration. Each experiment was repeated three times and a mean value obtained and stated as  $\text{IC}_{50} (\mu\text{M}) \pm \text{SD}$ .

### Induction of Cancer Cell Death by Apoptosis

HCT116 cells were incubated in T-25 flasks and diluted to concentrations of  $2.5 \times 10^4$  cells/flask ( $0.5 \times 10^4$  cells/ mL) using complete RPMI 1640 medium. These were incubated for 24 hours at 37°C in an atmosphere of 5.0%  $\text{CO}_2$ . Complexes were dissolved in dimethylsulfoxide and then further diluted with RPMI 1640 to obtained concentrations ranging from 0-60  $\mu\text{M}$ . The cells were then incubated with the varying concentrations

of complex for 72 hours, media/drug solutions were removed and flasks were washed with PBS (5 mL), adding all collected supernatants to a centrifuge tube. Trypsin (1 mL/flask) was added to each flask and then incubated for 5 minutes until a single cell suspension was obtained. The trypsin was then neutralised with medium (5 mL) and the whole contents of the flask transferred to the same centrifuge tube. The tube was centrifuged at 1000 rcf for 3-5 minutes, the supernatant removed and the pellet re-suspended in PBS (1 mL). The 1 mL suspension was transferred to an Eppendorf tube and centrifuged at 1500 rpm for 5 minutes. The supernatant was removed and the pellet stained with JC-1 in order to stain for loss of mitochondrial membrane potential and apoptosis. This was performed as per the manufacturer's protocol (Chemometec) and cell samples were analysed using an NC3000 flow cytometer (Chemometec).

### Characterisation

**Compound 1. Yield:** 72 mg, 0.06 mmol, 86 %. **ES-MS (+) (MeOH):** m/z 501.1 [RuC<sub>26</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>F]<sup>+</sup>, 581.02 [RuC<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>Br]<sup>+</sup>. **Anal. Calc.:** C 49.8, H 4.2, N 4.7%. **Anal. Found:** C 49.5, H 4.0, N 4.3%. **<sup>1</sup>H NMR:** (CD<sub>3</sub>OD, 500 MHz, 298 K) δ 8.92 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.8 Hz, quin), 8.60 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.4 Hz, quin), 8.15-8.04 (m, 3H, quin), 7.89 (td, 2H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 7.9 Hz, <sup>4</sup>J(<sup>1</sup>H-<sup>19</sup>F) = 0.8 Hz, ar), 7.33-7.30 (m, 2H, ar), 7.23-7.20 (m, 1H, ar), 5.72 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.1 Hz, *p*-cym), 5.58 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.9 Hz, *p*-cym), 5.41 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.1 Hz, *p*-cym), 4.81 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.9 Hz, *p*-cym), 2.30-2.27 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.14 (s, 3H, CH<sub>3</sub>), 0.93 (d, 3H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 0.80 (d, 3H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR:** (CD<sub>3</sub>OD, 125 MHz, 298 K) δ 168.6 (Q, C-O), 158.2 (d, Q, C-F, <sup>1</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 267.9 Hz), 150.0 (Q), 141.2 (CH, quin), 140.0 (Q), 132.6 (CH, quin), 131.7 (CH, quin), 131.6 (CH, quin), 130.1 (CH, quin), 129.3 (Q), 128.8 (d, CH, <sup>3</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 7.5 Hz, ar), 128.2 (CH, ar) 125.6 (CH, ar), 122.5 (CH, quin), 116.9 (d, CH, <sup>2</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 21.4 Hz, ar), 105.4 (Q), 101.7 (Q), 101.4 (Q), 86.7 (CH, *p*-cym), 86.4 (CH, *p*-cym), 85.5 (CH, *p*-cym), 85.3 (CH, *p*-cym), 32.4 (CH(CH<sub>3</sub>)<sub>2</sub>), 22.2 (CH(CH<sub>3</sub>)<sub>2</sub>), 22.0 (CH(CH<sub>3</sub>)<sub>2</sub>), 19.6 (CH<sub>3</sub>).

**Compound 2. Yield:** 39 mg, 0.03 mmol, 36%. **ES-MS (+) (MeOH):** m/z 501.1 [RuC<sub>26</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>F]<sup>+</sup>. **Anal. Calc.:** C 50.3, H 4.9, N 4.4%. **Anal. Found:** C 49.2, H 4.7, N 4.7%. **<sup>1</sup>H NMR:** (CD<sub>3</sub>OD, 500 MHz, 298 K) δ 8.94 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.9 Hz, quin), 8.61 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.4 Hz, quin), 8.14-8.11 (m, 2H, quin), 8.05 (td, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, <sup>4</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 1.6 Hz, quin), 7.87-7.79 (m, 3H, quin+ar), 7.16 (td, 2H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 7.9 Hz, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.1 Hz), 5.71 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.9 Hz, *p*-cym), 5.53 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.9 Hz, *p*-cym), 5.41 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.9 Hz, *p*-cym), 4.75 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.9 Hz, *p*-cym), 2.31-2.22 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.22 (s, 3H, CH<sub>3</sub>), 0.98 (d, 3H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 0.85 (d, 3H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>). **<sup>13</sup>C{<sup>1</sup>H} NMR:** (CD<sub>3</sub>OD, 125 MHz, 298 K) δ 169.1 (Q, C-O), 162.0 (d, Q, C-F, <sup>1</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 241.3 Hz), 158.3 (Q), 150.4 (Q), 149.3 (Q), 141.6 (CH, quin), 133.0 (CH, quin), 132.0 (CH, quin), 131.6 (CH, quin), 130.5 (Q), 130.1 (CH, quin), 129.4 (d, 2 x CH, <sup>3</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 7.5 Hz, ar), 123.0 (CH, quin), 116.5 (d, 2 x CH, <sup>2</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 22.6

Hz, ar), 105.1 (Q), 102.7 (Q), 87.2 (CH, *p*-cym), 87.0 (CH, *p*-cym), 86.3 (CH, *p*-cym), 85.8 (CH, *p*-cym), 32.8 (CH(CH<sub>3</sub>)<sub>2</sub>), 22.6 (CH(CH<sub>3</sub>)<sub>2</sub>), 22.5 (CH(CH<sub>3</sub>)<sub>2</sub>), 20.1 (CH<sub>3</sub>).

**Compound 3. Yield:** 65 mg, 0.05 mmol, 76%. **ES-MS (+) (MeOH):** m/z 519.1 [RuC<sub>26</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>F]<sup>+</sup>. **Anal. Calc.:** C 48.4, H 4.0, N 4.3%. **Anal. Found:** C 48.9, H 3.8, N 4.4%. **<sup>1</sup>H NMR:** (CD<sub>3</sub>OD, 500 MHz, 298 K) δ 8.92 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.8 Hz, quin), 8.61 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.4 Hz, quin), 8.14 (dd, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.2 Hz, <sup>4</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 1.5 Hz, quin), 8.10 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.4 Hz, quin), 8.05 (td, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 7.2 Hz, <sup>4</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 1.5 Hz, quin), 7.94-7.84 (m, 2H, quin+ar), 7.15 (td, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.9 Hz, <sup>3</sup>J(<sup>1</sup>H-<sup>19</sup>F) = 2.6 Hz, ar), 6.99 (td, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.0 Hz, <sup>4</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 1.4 Hz, ar), 5.72 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.1 Hz, *p*-cym), 5.58 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.9 Hz, *p*-cym), 5.43 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.1 Hz, *p*-cym), 4.80 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.9 Hz, *p*-cym), 2.30-2.25 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.22 (s, 3H, CH<sub>3</sub>), 0.93 (d, 3H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 0.81 (d, 3H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>). **<sup>13</sup>C{<sup>1</sup>H} NMR:** (CD<sub>3</sub>OD, 125 MHz, 298 K) δ 169.0 (Q, C-O), 161.9 (d, 2 x Q, C-F, <sup>1</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 233.9 Hz) 157.1 (Q), 150.0 (Q), 141.3 (CH, quin), 132.6 (2 x CH, quin), 131.8 (CH, quin), 131.2 (CH, quin), 130.1 (d, CH, <sup>3</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 18.9 Hz, ar), 122.5 (CH, quin), 112.3 (d, CH, <sup>2</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 25.2 Hz, ar), 105.0 (d, CH, <sup>2</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 61.6 Hz, ar), 104.3 (Q), 101.7 (Q), 88.7 (CH, *p*-cym), 86.0 (CH, *p*-cym), 85.6 (CH, *p*-cym), 85.2 (CH, *p*-cym), 32.5 (CH(CH<sub>3</sub>)<sub>2</sub>), 22.2 (CH(CH<sub>3</sub>)<sub>2</sub>), 22.0 (CH(CH<sub>3</sub>)<sub>2</sub>), 19.6 (CH<sub>3</sub>).

**Compound 4. Yield:** 82 mg, 0.06 mmol, 83%. **ES-MS (+) (MeOH):** m/z 501.091 [RuC<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>F]<sup>+</sup>. **Anal. Calc.:** C 47.8, H 3.8, N 4.3%. **Anal. Found:** C 47.3, H 3.9, N 4.6%. **<sup>1</sup>H NMR:** (CD<sub>3</sub>OD, 500 MHz, 298 K) δ 8.92 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.8 Hz, quin), 8.60 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.4 Hz, quin), 8.15-8.04 (m, 3H, quin), 7.89 (td, 2H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 7.9 Hz, <sup>5</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 0.8 Hz, quin+ar), 7.33-7.30 (m, 2H, ar), 7.23-7.20 (m, 1H, ar), 5.74 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.0 Hz, *p*-cym), 5.60 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.0 Hz, *p*-cym), 5.49 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.3 Hz, *p*-cym), 4.83 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.3 Hz, *p*-cym), 2.33-2.24 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.06 (s, 3H, CH<sub>3</sub>), 0.97 (d, 3H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 0.82 (d, 3H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, CH(CH<sub>3</sub>)<sub>2</sub>). **<sup>13</sup>C{<sup>1</sup>H} NMR:** (CD<sub>3</sub>OD, 125 MHz, 298 K) δ 168.7 (Q, C-O), 158.4 (d, Q, C-F, <sup>1</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 249.0 Hz), 152.2 (Q), 149.7 (Q), 141.5 (CH, quin), 140.0 (Q), 132.9 (CH, quin), 131.8 (CH, quin), 130.6 (CH, quin), 130.1 (CH, quin), 128.8 (d, CH, <sup>3</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 7.5 Hz, ar), 128.2 (CH, ar), 125.7 (CH, ar), 122.4 (CH, quin), 116.9 (d, CH, <sup>2</sup>J(<sup>13</sup>C-<sup>19</sup>F) = 21.3 Hz, ar), 104.4 (Q), 102.7 (Q), 102.0 (Q), 86.8 (CH, *p*-cym), 86.0 (CH, *p*-cym), 85.7 (CH, *p*-cym), 85.4 (CH, *p*-cym), 32.3 (CH(CH<sub>3</sub>)<sub>2</sub>) 22.2 (CH(CH<sub>3</sub>)<sub>2</sub>), 22.0 (CH(CH<sub>3</sub>)<sub>2</sub>), 18.9 (CH<sub>3</sub>).

**Compound 5. Yield:** 77 mg, 0.06 mmol, 69%. **ES-MS (+) (MeOH):** m/z 501.1 [RuC<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>F]<sup>+</sup>. **Anal. Calc.:** C 47.5, H 3.8, N 4.3%. **Anal. Found:** C 47.2, H 3.7, N 5.2%. **<sup>1</sup>H NMR:** (CD<sub>3</sub>OD, 500 MHz, 298 K) δ 8.93 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.8 Hz, quin), 8.62 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 8.3 Hz, quin), 8.13 (t, 2H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, quin), 8.07 (td, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, <sup>4</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 1.4 Hz, quin), 7.86 (td, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.9 Hz, <sup>4</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 1.4 Hz, quin), 7.77-7.74 (m, 2H, ar), 7.17 (t, 2H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.8 Hz, ar), 5.71 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 6.1 Hz, *p*-cym), 5.52 (d, 1H, <sup>3</sup>J(<sup>1</sup>H-<sup>1</sup>H) = 5.9 Hz, *p*-

cym), 5.45 (d, 1H,  $^3J(^1\text{H}-^1\text{H}) = 6.1$  Hz, *p*-cym), 4.78 (d, 1H,  $^3J(^1\text{H}-^1\text{H}) = 5.9$  Hz, *p*-cym), 2.25-2.22 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.13 (s, 3H,  $\text{CH}_3$ ), 0.98 (d, 3H,  $^3J(^1\text{H}-^1\text{H}) = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.84 (d, 3H,  $^3J(^1\text{H}-^1\text{H}) = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz, 298 K)  $\delta$  168.8 (Q,  $\text{C}-\text{O}$ ), 161.4 (d, Q,  $\text{C}-\text{F}$ ,  $^1J(^{13}\text{C}-^{19}\text{F}) = 238.9$  Hz), 158.2 (Q), 149.7 (Q), 148.8 (Q) 141.4 ( $\text{CH}$ , quin), 132.8 ( $\text{CH}$ , quin), 131.7 ( $\text{CH}$ , quin), 131.2 ( $\text{CH}$ , quin), 130.5 (Q), 130.1 ( $\text{CH}$ , quin), 128.8 (d, 2 x  $\text{CH}$ ,  $^3J(^{13}\text{C}-^{19}\text{F}) = 7.5$  Hz, ar), 122.5 ( $\text{CH}$ , quin), 116.1 (d, 2 x  $\text{CH}$ ,  $^2J(^{13}\text{C}-^{19}\text{F}) = 22.7$  Hz, ar), 103.6 (Q), 102.9 (Q), 87.0 ( $\text{CH}$ , *p*-cym), 86.7 ( $\text{CH}$ , *p*-cym), 85.5 ( $\text{CH}$ , *p*-cym), 85.4 ( $\text{CH}$ , *p*-cym), 32.3 ( $\text{CH}(\text{CH}_3)_2$ ), 22.2 ( $\text{CH}(\text{CH}_3)_2$ ), 22.0 ( $\text{CH}(\text{CH}_3)_2$ ), 18.9 ( $\text{CH}_3$ ).

**Compound 6.** Yield: 84 mg, 0.06 mmol, 79%. ES-MS (+) (MeOH): *m/z* 519.1 [ $\text{RuC}_{26}\text{H}_{24}\text{N}_2\text{OF}_2$ ] $^+$ . Anal. Calc.: C 45.3, H 4.6, N 3.9%. Anal. Found: C 45.0, H 4.8, N 4.4%.  $^1\text{H}$  NMR: ( $\text{CD}_3\text{OD}$ , 500 MHz, 298 K)  $\delta$  8.92 (d, 1H,  $^3J(^1\text{H}-^1\text{H}) = 8.8$  Hz, quin), 8.61 (d, 1H,  $^3J(^1\text{H}-^1\text{H}) = 8.4$  Hz, quin), 8.14 (dd, 1H,  $^3J(^1\text{H}-^1\text{H}) = 8.2$  Hz,  $^4J(^1\text{H}-^1\text{H}) = 1.5$  Hz, quin), 8.10 (d, 1H,  $^3J(^1\text{H}-^1\text{H}) = 8.4$  Hz), 8.05 (td, 1H,  $^3J(^1\text{H}-^1\text{H}) = 7.2$  Hz,  $^4J(^1\text{H}-^{13}\text{C}) = 1.5$  Hz, quin), 7.97-7.84 (m, 2H, quin+ar). 7.15 (td, 1H,  $^3J(^1\text{H}-^1\text{H}) = 8.9$  Hz,  $^3J(^1\text{H}-^{19}\text{F}) = 2.6$  Hz, ar), 6.99 (td, 1H,  $^3J(^1\text{H}-^1\text{H}) = 8.0$  Hz,  $^4J(^1\text{H}-^{13}\text{C}) = 1.4$  Hz, ar), 5.72 (d, 1H,  $^3J(^1\text{H}-^1\text{H}) = 6.1$  Hz, *p*-cym), 5.58 (d, 1H,  $^3J(^1\text{H}-^1\text{H}) = 5.9$  Hz, *p*-cym), 5.43 (d, 1H,  $^3J(^1\text{H}-^1\text{H}) = 6.1$  Hz, *p*-cym), 4.80 (d, 1H,  $^3J(^1\text{H}-^1\text{H}) = 5.9$  Hz, *p*-cym), 2.30-2.25 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ , *p*-cym), 2.07 (s, 3H,  $\text{CH}_3$ ), 0.93 (d, 3H,  $^3J(^1\text{H}-^1\text{H}) = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.81 (d, 3H,  $^3J(^1\text{H}-^1\text{H}) = 6.9$  Hz,  $\text{CH}(\text{CH}_3)_2$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR: ( $\text{CD}_3\text{OD}$ , 125 MHz, 298 K)  $\delta$  169.0 (Q,  $\text{C}-\text{O}$ ), 162.8 (d, Q,  $\text{C}-\text{F}$ ,  $^1J(^{13}\text{C}-^{19}\text{F}) = 244.0$  Hz), 160.9 (d, Q,  $\text{C}-\text{F}$ ,  $^1J(^{13}\text{C}-^{19}\text{F}) = 244.0$  Hz), 157.1 (Q), 150.0 (Q), 141.3 ( $\text{CH}$ , quin), 134.7 (Q), 132.6 (2 x  $\text{CH}$ , quin), 131.8 ( $\text{CH}$ , quin), 131.2 ( $\text{CH}$ , quin), 130.0 (d,  $\text{CH}$ ,  $^3J(^{13}\text{C}-^{19}\text{F}) = 18.9$  Hz, ar), 128.0 (Q), 122.5 ( $\text{CH}$ , quin), 112.3 (d,  $\text{CH}$ ,  $^2J(^{13}\text{C}-^{19}\text{F}) = 25.2$  Hz, ar), 105.0 (d,  $\text{CH}$ ,  $^2J(^{13}\text{C}-^{19}\text{F}) = 61.6$  Hz, ar), 101.7 (Q), 101.4 (Q), 88.7 ( $\text{CH}$ , *p*-cym), 86.0 ( $\text{CH}$ , *p*-cym), 85.6 ( $\text{CH}$ , *p*-cym), 85.2 ( $\text{CH}$ , *p*-cym), 32.2 ( $\text{CH}(\text{CH}_3)_2$ ), 22.2 ( $\text{CH}(\text{CH}_3)_2$ ), 22.0 ( $\text{CH}(\text{CH}_3)_2$ ), 19.6 ( $\text{CH}_3$ ).

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