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Rhodium, Iridium, and Ruthenium Half-Sandwich Picolinamide Complexes as Anticancer Agents

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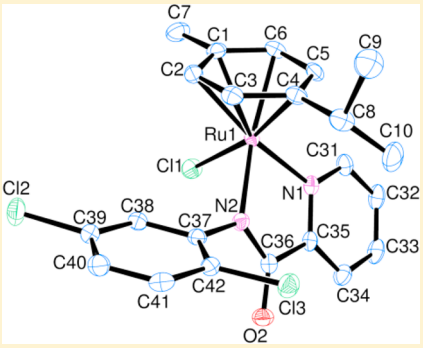
Supporting Information

ABSTRACT: Novel rhodium, iridium, and ruthenium half-sandwich complexes containing (*N*,*N*)-bound picolinamide ligands have been prepared for use as anticancer agents. The complexes show promising cytotoxicities, with the presence, position, and number of halides having a significant effect on the corresponding IC_{50} values. One ruthenium complex was found to be more cytotoxic than cisplatin on HT-29 and MCF-7 cells after 5 days and 1 h, respectively, and it remains active with MCF-7 cells even under hypoxic conditions, making it a promising candidate for *in vivo* studies.



INTRODUCTION

In recent years, organometallic ruthenium complexes have been well researched as anticancer agents.[1−15] Rhodium and iridium complexes, however, remain relatively unexplored.[14,16−29] We have previously reported an initial study demonstrating that half-sandwich ruthenium-arene picolinamide and quinaldamide complexes with an ancillary chloride ligand show promising activity as anticancer agents, whereby the quinaldamide complexes are more active than their picolinamide analogues.[15] In collaboration with Sadler, we have also shown that osmium congeners have shown potential as cytotoxic agents.[4] More recently, we reported a preliminary investigation into two iridium-Cp* chloride picolinamide complexes and their IC_{50} values for both HT-29 and MCF-7 cell lines.[14] Compounds investigated in these studies are shown in Figure 1. In our continued study to optimize the design and potency of organometallic anticancer agents, we have switched on the activity of ruthenium *para-cymene* and rhodium-/iridium-Cp* complexes through functionalization of the phenyl ring on the picolinamide ligands. It is known that cancerous cells are in a hypoxic environment whereby the median oxygen partial pressure is approximately 10 mmHg.[30] Many cytotoxic drugs are significantly less active when tested *in vitro* on cells in a hypoxic environment compared to normoxic conditions.[31] This is thought to be independent of the cell pathway of the drug and rather due to hypoxia-induced resistance. For this reason, the most active compound of the series under normoxic conditions has been tested on MCF-7 cells under hypoxic conditions.

RESULTS AND DISCUSSION

Synthesis of Compounds. Scheme 1 shows the synthesis of the group 8 and 9 complexes **1**−**12**. The group 9 picolinamide complexes, **1**−**8**, were prepared using various methods depending on their identity. The iridium Cp* complexes (shown in Scheme 1a), were prepared either according to method A in the cases of **1**, **6**, and **7** or Method B in the cases of **2**−**5**. Complex **8** was prepared according to Scheme 1**b**). The ruthenium-*para*-cymene picolinamide complexes, **9**−**12**, and quinaldamide complex, **13**, were prepared according to parts c and d in Scheme 1, respectively. In all cases, the picolinamide/quinaldamide ligand was deprotonated and bound through the nitrogen atoms to form a neutral 18 electron species. All complexes were characterized by ^{1}H NMR/$^{13}C\{^{1}H\}$ NMR spectroscopy, CHN analysis, and mass spectrometry. In addition, crystal structures were obtained for compounds **3**, **4**, and **9**−**13**.

X-ray Crystallographic Data. Figure 2 shows the molecular structures of compounds **3**, **4**, and **9**−**13**, with general X-ray data shown in Table 1 and selected bond lengths and angles shown in Table 2 and Table 3 respectively. The iridium picolinamide complexes **3** and **4** were crystallized using layer diffusion with a dichloromethane/hexane solvent system. The ruthenium picolinamide and quinaldamide complexes, **9** and **12** respectively, were crystallized from a methanolic solution, complexes **11** and **12** from a deuterated methanolic solution and complex **10** from an acetone solution. All of the compounds exhibit a pseudo octahedral geometry about the

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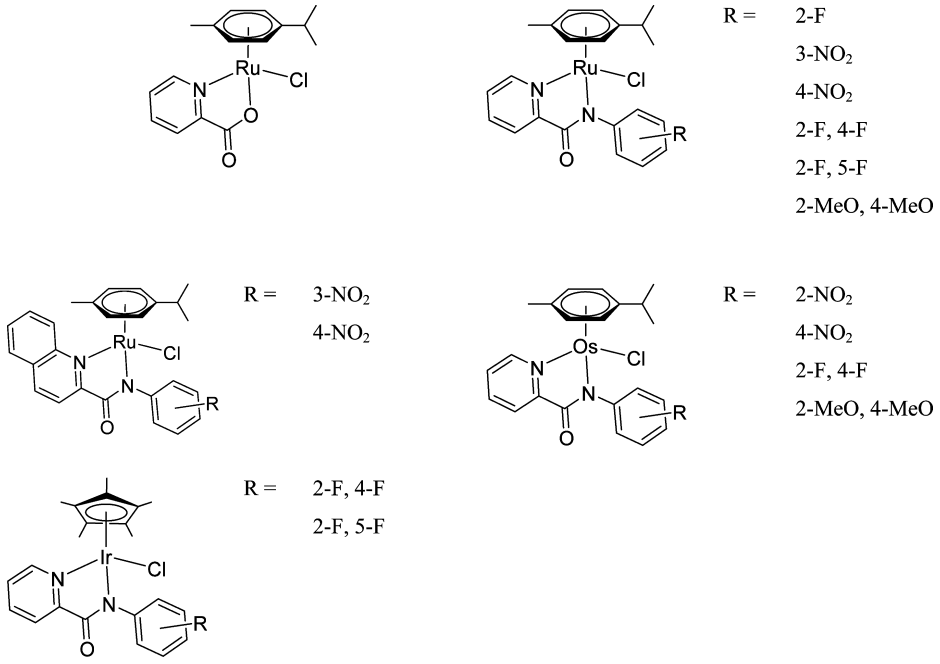

Figure 1. Previously reported Ru, Ir, and Os picolinamide complexes.[4,14,15]

metal center, whereby the *para*-cymene/Cp* occupies three coordination sites and the angle between the centroid of the Cp*/*para*-cymene ring and the other coordinating atoms is between 125.9 and 135.1°. The angle between the coordinated nitrogens and the metal center is between 76.27 and 77.05°. This is due to the rigidity of the picolinamide ligand. The angle between the nitrogens and chloride is between 81.04 and 89.59°. The picolinamide ligands adopt nonplanar configurations, presumably to avoid a steric clash between the ring defined as C(37)−C(42) and the arene ring. The torsion angle between the picolinamide rings ranges from 37 to 73° with no distinct trend for the varied picolinamide substituents. The Ir-centroid distances for complexes **3** and **4**, within error, are the same length, with distances of 1.804 and 1.811 Å, respectively. In comparison, the Ru−centroid distances are shorter than the M−centroid distances for group 9 compounds and lie in the range of 1.683−1.693 Å.

Cytotoxicities. Table 4 highlights the IC_{50} values for compounds **1**−**13** on various cell lines. The cytotoxicities of the group 9 picolinamide complexes, **1**−**8**, were tested on A2780 cells over a 5 day exposure, along with cisplatin and their respective dimeric starting materials $[MCp^*Cl_2]_2$, where M = Ir, Rh, for reference. The cytotoxicities of the ruthenium compounds, **9**−**13**, were tested on both HT-29 and MCF-7 cells over a 5 day exposure along with a further 1 h exposure for the MCF-7 cells. The dimeric ruthenium starting material $[Ru(p\text{-cymene})Cl_2]_2$ has been previously tested on HT-29 and MCF-7 cell lines and been found to be inactive.[14]

For the group 9 compounds, **1**−**8**, the presence and position of the halide substituents on the picolinamide ligand has a significant effect on the complexes' anticancer activity for A2780 cells. The unsubstituted IrCp* complex, **1**, shows poor activity with an IC_{50} value of 66 μM, whereas the addition of a chloride group on the ortho and meta position of the arene ring of the picolinamide decreases the IC_{50} value to 25 and 33 μM, respectively ($p < 0.01$, relative to complex **1**). The dichloro substituted picolinamide complexes show even higher activity with IC_{50} values of 19 and 23 μM for compounds **4** and **5**, respectively ($p < 0.01$, relative to complex **1**). As shown in both the mono and dichloro substituted picolinamide complexes, a chloride on the ortho position of the arene ring gives a more active complex than one on the meta position. This trend is also observed with the di-fluoro-substituted picolinamide complexes, **6** and **7**, however they are less active than the chloro analogues. The rhodium complex **8** is slightly more active than its iridium analogue, **3**, with an IC_{50} value of 28 μM compared to 33 μM ($p < 0.01$).

The ruthenium picolinamide complexes, **9**−**12**, show a similar trend to their iridium-Cp* analogues whereby the cytotoxicities are in the order **12** > **11** ∼ **10** > **9** (where the phenyl ring substituents are 2,5-diCl, 2,4-diCl, 3-Cl, and 2-Cl, respectively) for all of the cell lines. The quinaldamide complex **13** has similar activity to the picolinamide complex **10**. Compound **12** is the most cytotoxic compound of the series, by an order of magnitude, which is comparable to previous work involving electron withdrawing substituents (NO_2) attached to the ligand,[15] for both cell lines after a 5 day exposure, particularly for HT-29 cells with higher activity than cisplatin (IC_{50} value of 6 μM compared to 10 μM). As expected, all compounds display lower activity toward MCF-7 cells after a 1 h exposure compared to 5 days, compound **12** is still the most active and, unlike the 5 day exposure of the same cell line, is more cytotoxic than cisplatin with an IC_{50} of 32 μM compared to 53 μM. This implies that compound **12** is a more potent drug than cisplatin. Because of this promising result, compound **12** was retested on MCF-7 cells in a hypoxic environment. The method for hypoxic testing was validated by testing a known hypoxia selective drug, tirapazamine (Table 5). Cisplatin exhibits a decrease in efficacy of between 2- and 8-fold, depending on cell line.

Compound **12** was tested for a 1 h exposure and maintained its activity with an IC_{50} of 34 μM. This suggests that unlike cisplatin and many other cytotoxic drugs, which are reported to have reduced cytotoxic activity in a hypoxic environment,[30] compound **12** retains its activity against hypoxic cells and is not adversely affected by hypoxia. Compound **12** has the potential

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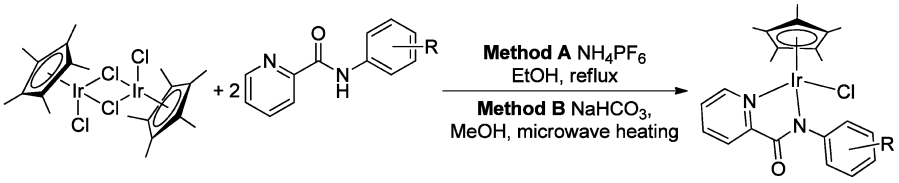
Scheme 1. Synthesis of (a) Iridium-Cp*, (b) Rhodium-Cp*, (c) Ruthenium-*para*-cymene Picolinamide Complexes, and (d) a Ruthenium-*para*-cymene Quinaldamide Complex

a)



1 R = H

2 R = 2'-Cl

3 R = 3'-Cl

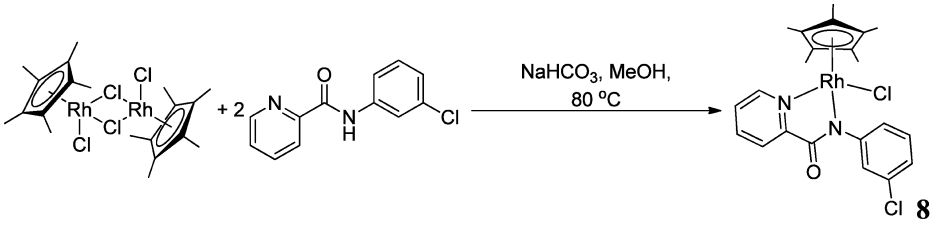
4 R =2',4'-dichloro

5 R = 2',5'-dichloro

6 R = 2',4'-difluoro

7 R = 2',5'-difluoro

b)



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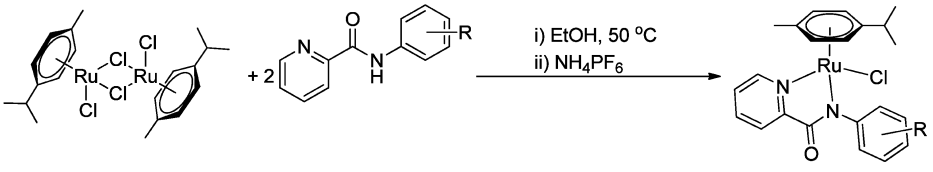
c)



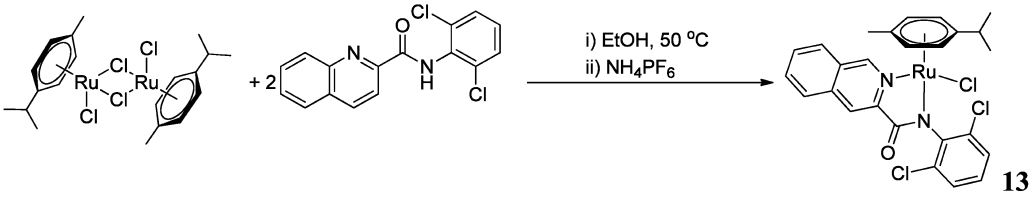
9 R = 2'-Cl

10 R = 3'-Cl

11 R =2',4'-dichloro

12 R = 2',5'-dichloro

d)



13

to eradicate both the aerobic and hypoxic fraction of tumor cells and it is therefore a promising candidate for *in vivo* applications.

In order to investigate the mode of action of these complexes, the inhibition of thioredoxin reductase 1 (Trx-R) activity by compounds **1**−**12** was investigated (Figure 3). Trx-R has previously been identified as a target for ruthenium drugs.[32−34]

The group 9 picolinamide complexes, **1**−**8**, were found to be potent inhibitors of Trx-R, with IC_{50} values ranging from 54.3 to 180.3 nM. In contrast, the Ru complexes **9**−**12** were found to be almost completely inactive against Trx-R, with IC_{50} values in excess of 10 μM. This is in contrast to previous reports of Ru complexes inhibiting Trx-R activity. This therefore introduces a potential mechanism of action for compounds **1**−**8**. In contrast, Trx-R appears to not be responsible for the cytotoxic behavior of compounds **9**−**12**. Further studies are required to fully explore whether Trx-R inhibition plays a significant role in the cytotoxic behavior of **1**−**8** and to further investigate the mechanism of action of **9**−**12**.

Future work will evaluate these compounds against cells derived from normal tissues. The major issue is that the culture of normal cells is challenging and it is not possible to replicate conditions *in vivo*, bearing in mind that cells live in a complex partnership with other cells and the extracellular matrix. We accept that the therapeutic index is vitally important, but we believe that studies to address potential toxicity to normal

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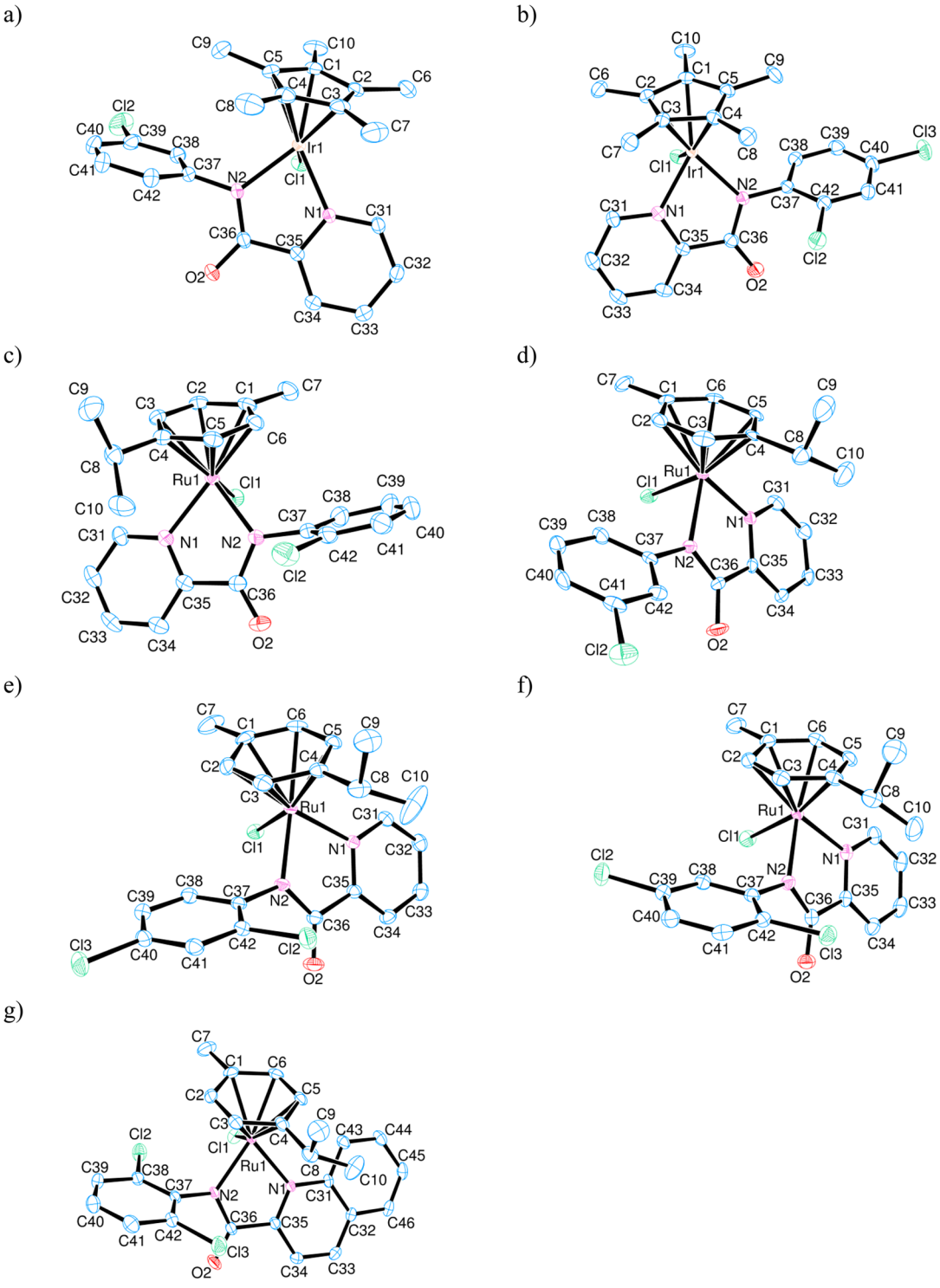

Figure 2. Molecular structures of compounds (a) **3**, (b) **4**, (c) **9**, (d) **10**, (e) **11**, (f) **12**, and (g) **13**. Hydrogen atoms and solvent molecules are omitted for clarity. Displacement ellipsoids are at the 50% probability level.

tissues are best conducted in the *in vivo* setting later on in the drug discovery program.

■ CONCLUSIONS

Various Ru-*para*-cymene and Rh-/Ir-Cp* complexes have been prepared containing (*N*,*N*)-binding picolinamide ligands and their cytotoxicities on either HT-29, MCF-7, or A2780 cells have been tested. The Ir-Cp* chloride unfunctionalized picolinamide complex, **1**, shows modest activity that, upon addition of a chloride, improves by 2-fold. The dihalide substituted picolinamide complexes are even more potent with the 2,4-dichloro substituent showing the highest activity with an IC_{50} value of 18.6 μM. The Rh-Cp* 3-chloro picolinamide complex, **8**, is slightly more active than its iridium analogue **5**. Ruthenium-*para*-cymene analogues **10**-**13** display promising cytotoxicities on HT-29 and MCF-7 cells whereby the most active compound, **12**, is more active than cisplatin for HT-29 cells and MCF-7 cells after a 5 day and 1 h exposure,

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Table 1. Summary of the Crystallographic Data for Complexes 3, 4, and 9−13

	3	4	9	10	11	12	13
formula	$C_{23}H_{25}Cl_4IrN_2O$	$C_{22}H_{24}Cl_3IrN_2O_2$	$C_{44}H_{50}Cl_4N_4O_5Ru_2$	$C_{22}H_{22}Cl_2N_2ORu$	$C_{22}H_{21}Cl_3N_2ORu$	$C_{23}H_{25}Cl_3N_2O_2Ru$	$C_{26}H_{23}Cl_3N_2ORu$
formula wt	679.45	646.98	1058.82	502.39	536.83	568.87	586.88
cryst syst	monoclinic	monoclinic	monoclinic	orthorhombic	triclinic	orthorhombic	monoclinic
space group	$P2_1/n$	$P2_1/n$	$P2_1/n$	$Pca2_1$	$P\bar{1}$	$P2_12_12_1$	$P2_1/c$
a (Å)	7.7924(10)	9.7097(9)	17.8200(4)	16.1177(10)	8.3556(7)	8.5250(6)	8.4336(2)
b (Å)	22.664(3)	14.6340(15)	10.5378(2)	8.5924(5)	8.3782(8)	13.3830(12)	14.5042(3)
c (Å)	14.6133(19)	16.3669(15)	24.2106(6)	29.2109(19)	16.2423(15)	20.7498(17)	19.5495(6)
α (deg)	90	90	90.00	90.00	104.245(5)	90.00	90.00
β (deg)	97.996(6)	96.546(4)	102.2500(10)	90.00	91.676(4)	90.00	91.2760(10)
γ (deg)	90	90	90.00	90.00	99.021(4)	90.00	90.00
V (Å^3)	2555.7(6)	2310.4(4)	4442.84(17)	4045.4(4)	1085.71(17)	2367.3(3)	2390.75(11)
Z, molecules/cell	4	4	4	8	2	4	4
density (Mg/m^3)	1.766	1.86	1.583	1.650	1.642	1.596	1.631
absorp coeff (mm^{-1})	5.66	6.147	0.970	1.055	1.107	1.024	1.014
λ[Mo−K$_\alpha$] (Å)				0.71073			
T (°C)				150(2)			
no. of reflns collected	90089	63960	41538	19466	52845	59908	48568
no. of independent reflns	10785	6880	10185	8230	6471	5810	5471
no. of obsd reflns	8163	5864	8799	7732	6057	5517	4940
R1	0.0235	0.022	0.0284	0.0314	0.0194	0.0213	0.0213
wR2	0.0346	0.0444	0.0785	0.0800	0.0504	0.0450	0.0553
GOF	1.096	1.067	1.053	1.069	1.058	1.041	1.091

Table 2. Selected Bond Lengths (Å) for Compounds 3,4, and 9−13, where M = Ru or Ir

compd	M(1)−Cl(1)	M(1)−N(1)	M(1)−N(2)	M(1)−C$_g$
3	2.4305(6)	2.1061(16)	2.1151(16)	1.8040(10)
4	2.4475(7)	2.115(2)	2.124(2)	1.8110(12)
9	2.4306(6)	2.1000(19)	2.074(2)	1.6836(9)
10	2.4028(12)	2.074(3)	2.102(3)	1.6832(18)
11	2.4258(4)	2.1124(11)	2.0891(11)	1.6930(6)
12	2.4480(6)	2.1052(17)	2.0956(16)	1.6896(8)
13	2.4152(5)	2.1352(14)	2.1007(14)	1.6819(7)

respectively, as well as being active under hypoxic conditions for the latter. This makes compound **12** a promising candidate for further studies. Mechanistic studies have been undertaken that have shown that Trx-R inhibition may be a potential mechanism of action for compounds **1**−**8**. In contrast, compounds **9**−**12** have been shown to be inactive against Trx-R inhibition, indicating a different mode of action.

EXPERIMENTAL DETAILS

The picolinamide ligands[35] were prepared according to the literature method. All other reagents are commercially available and were used as received. ^{1}H- and ^{13}C NMR spectra were recorded on Bruker DPX 300 spectrometer. Microanalyses were obtained by Mr. Ian Blakeley at the University of Leeds Microanalytical Service. X-ray data was collected by Stephanie Lucas or Andrew Hebden. A suitable single crystal was selected and immersed in an inert oil. The crystal was then mounted onto a glass capillary and attached to a goniometer head on a Bruker X8 Apex diffractor using graphite monochromated Mo−Kα radiation (λ = 0.71073 Å) and 1.0° ϕ-rotation frames. The crystal was then cooled to 150K by an Oxford cryostream low-temperature device.[36] The full data set was recorded and the images processed using DENZO and SCALEPACK programs.[37] The structures were solved by Stephanie Lucas or Christopher Pask. Structure solution by direct methods was achieved through the use of SHELXS86,[38] SIR92[39] or SIR97[40] programs, and the structural model defined by full matrix least-squares on F^2 using SHELX97.[38] Molecular graphics were plotted using ORTEP. Editing of crystallographic information files (CIFs) and construction of tables of bond lengths and angles was achieved using WC[41] and PLATON.[42] Hydrogen atoms were placed using idealized 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.

Cell Line Testing. The *in vitro* tests were performed on HT-29 (human colon adenocarcinoma), A2780 (human ovarian carcinoma) and MCF-7 (human breast adenocarcinoma) cell lines. Cells were incubated in 96-well plates at a concentration of 2 × 10^4 cells/mL. Two-hundred microliters of growth media (RPMI 1640 supplemented with 10% fetal calf serum, sodium pyruvate (1 mM), and L-glutamine

Table 3. Selected bond Angles (deg) for Compounds 3, 4, and 9−13, where M = Ru or Ir

compd	Cl(1)−M(1)−N(1)	Cl(1)−M(1)−N(2)	N(1)−M(1)−N(2)	C$_g$−M(1)-Cl(1)	C$_g$−M(1)-N(1)	C$_g$−M(1)-N(2)
3	84.62(4)	86.25(5)	76.27(6)	126.74(3)	132.09(5)	132.75(5)
4	83.26(6)	85.75(7)	76.28(8)	125.93(4)	132.99(7)	133.95(7)
9	84.31(5)	86.12(5)	76.50(8)	127.53(3)	133.71(6)	130.45(6)
10	84.40(10)	87.73(10)	76.67(13)	127.14(7)	131.88(11)	131.35(12)
11	83.12(3)	85.46(3)	76.78(4)	127.73(2)	133.86(4)	131.18(4)
12	84.11(5)	85.74(5)	76.81(7)	128.39(3)	132.19(5)	131.22(5)
13	81.04(4)	89.59(4)	77.05(5)	128.04(3)	135.09(4)	128.15(5)

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Table 4. IC_{50} Values for Complexes 1−8 on A2780 Cells (with cisplatin and their respective starting dimers: $[IrCp^*Cl_2]_2$ and $[RhCp^*Cl_2]_2$) and Complexes 9−13 on HT-29 and MCF-7 Cells

compd	A2780 $IC_{50}/\mu M$[a]	compd	HT-29 $IC_{50}/\mu M$[a]	MCF-7 $IC_{50}/\mu M$[a]	MCF-7 $IC_{50}/\mu M$[b]
cisplatin	0.93 ± 0.04[c]/1.4 ± 0.3[d]/ 1.5 ± 0.1[e] /0.97 ± 0.07[f]	cisplatin	10 ± 3	3 ± 1	53 ± 8
$[IrCp^*Cl_2]_2$[c]	30.9 ± 0.4	**9**	33 ± 7	35 ± 14	184 ± 2
$[RhCp^*Cl_2]_2$[c]	95 ± 2	**10**	13 ± 3	11.2 ± 0.7	-
1[d]	66 ± 2	**11**	16 ± 3	11.5 ± 0.9	64 ± 17
2[d]	25 ± 3	**12**	5.9 ± 0.8	5 ± 1	32 ± 15
3[d]	33 ± 1	**12** (0.5% O_2)			34 ± 5
4[d]	18.6 ± 0.4	**13**	11.5 ± 0.7	13 ± 3	
5[d]	23 ± 1				
6[e]	19.7 ± 0.6				
7[e]	27 ± 2				
8[d]	28.8 ± 0.5				

[a]The drugs were incubated for 5 days. [b]The drugs were incubated for 1 h. [c]Refer to different sets of A2780 cells, with different IC_{50} values for cisplatin. [d]Refer to different sets of A2780 cells, with different IC_{50} values for cisplatin. [e]Refer to different sets of A2780 cells, with different IC_{50} values for cisplatin. [f]Refer to different sets of A2780 cells, with different IC_{50} values for cisplatin.

Table 5. IC_{50} Results of 12 and the Positive Control Tiripazamine on MCF7 Cell Lines at 21% and 0.5% O_2

	MCF7	
compd	21% O_2	0.5% O_2
Tirapazamine	1102.8 ± 387.5	183.2 ± 49.5
12	32.3 ± 14.8	34.8 ± 5.2

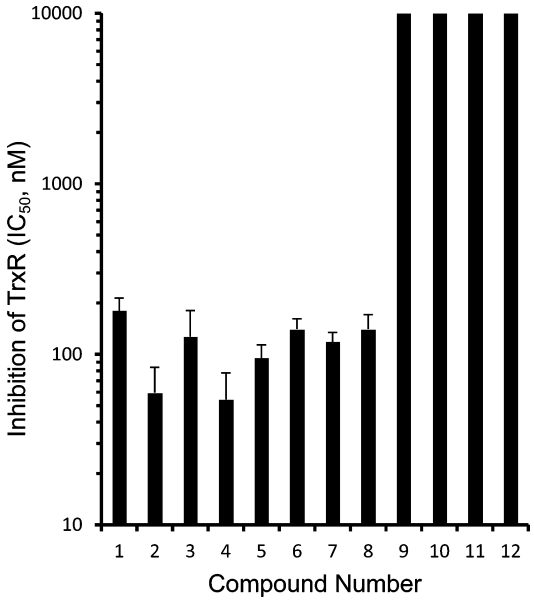

Figure 3. Inhibition of mammalian Trx-R by compounds **1**−**12**. Each value presented is the mean IC_{50} ± standard deviation for three independent experiments. For compounds **9**−**12**, the IC_{50} was >10 μM, which was the highest concentration used in these experiments.

(2 mM)) was added to each well and the plates were incubated for 24 h at 37 °C in an atmosphere of 5% CO_2 prior to drug exposure. Compounds **1**−**12**, $[IrCp^*Cl_2]_2$, $[RhCp^*Cl_2]_2$ and cisplatin were all dissolved in DMSO at a concentration of 25 mM and diluted further with medium to obtain drug solutions ranging from 250 to 0.49 μM. The final DMSO concentration was 0.1% (v/v), which is nontoxic to cells. Drug solutions were applied to cells and incubated for either one hour or five days at 37 °C in an atmosphere of 5% CO_2. For 1 h exposures, cells were washed three times with Hanks Balanced Salt Solution and then incubated for 5 days in growth medium before carrying out the MTT assay. Studies conducted under hypoxic conditions (0.1% oxygen) were performed in a Whitley H35 Hypoxystation (Don Whitley Scientific, UK) using the same protocol as described above. Following drug exposure, 20 μL of MTT (5 mg mL^{-1}) was added to each well and incubated for three hours at 37 °C in an atmosphere of 5% CO_2. The solutions were then removed and 150 μL of DMSO was added to each well to dissolve the purple formazan crystals. A Thermo Scientific Multiskan EX microplate photometer was used to measure the absorbance at 540 nm. Lanes containing medium only and cells in medium (no drug) were used as blanks for the spectrophotometer and 100% cell survival respectively. Cell survival was determined as the absorbance of treated cells divided by the absorbance of controls and expressed as a percentage. The IC_{50} values were determined from plots of % survival against drug concentration. Each experiment was repeated three times and a mean value obtained. A 2-tailed *t* test was performed for each triplicate of IC_{50} values to identify statistical differences between corresponding complexes.

Statistical Analysis. Statistical significance of difference was determined using the Student's *t*-test. $P < 0.01$ was considered to be statistically significant at the 1% level.

Inhibition of Thioredoxin Reductase 1 (Trx-R). The inhibition of Trx-R activity was determined using the substrate 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) as described elsewhere.[43,44] Compounds **1**−**12** were incubated with 0.232 Units of recombinant rat Trx-R (Sigma Aldrich, UK) in a final volume of 500 μL of potassium phosphate buffer (0.1 M, pH 7.0) containing EDTA (1 mM), 0.1 mg/mL bovine serum albumin and NADPH (0.2 mM). Samples were incubated at room temperature for one minute followed by the addition of 500 μL of potassium phosphate buffer (0.1 M, pH 7.0) containing EDTA (1 mM), 0.1 mg/mL bovine serum albumin, NADPH (0.2 mM) and DTNB (100 μM). The increase in absorbance at 412 nm was determined using a Cary UV/vis spectrophotometer over the first minute of the reaction. Inhibition of Trx-R activity in test compound treated samples was calculated as a percentage of enzyme activity of that of DMSO (0.1% v/v) vehicle treated controls.

*Synthesis of IrCp*Cl($C_{12}H_9N_2O$), 1.* Pyridine-2-carboxylic acid phenylamide (0.05 g, 0.26 mmol) was added to a stirred suspension of $[Ir\{\eta^5\text{-}C_5(CH_3)_5\}Cl_2]_2$ (0.10 g, 0.13 mmol) in ethanol (30 mL) at 80 °C. After 15 min, ammonium hexafluorophosphate (0.10 g, 0.61 mmol) was added and the mixture was stirred at 80 °C for 20 h. The solvent was evaporated and the residue dissolved in dichloromethane (50 mL), washed with water (2 × 20 mL), brine (20 mL), dried over sodium sulfate, and evaporated to form an orange solid. The crude product was recrystallized using vapor diffusion (dichloromethane/pentane solvent system) to give **1** as orange crystals (0.06 g, 0.11 mmol, 46%). ES-MS (CH_2Cl_2, *m*/*z*): 525.2 [M-Cl]. Anal. Found: C, 46.5; H, 4.5; N, 4.8; Cl, 6.7%. Anal. Calcd (with 0.05 molecules of dichloromethane): C, 46.9; H, 4.3; N, 5.0; Cl, 6.9%. ^1H NMR (300 MHz, $CDCl_3$, 300 K) 8.57 (br. d, ^3J (^1H−^1H) = 5.4 Hz, 1H, pyridyl CH ortho to N), 8.17 (br. d, ^3J (^1H−^1H) = 8.0 Hz, 1H, pyridyl CH

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meta to N, ortho to amide), 7.92 (vtd (ddd), ^3J (^{1}H−^{1}H) = 7.7 Hz, ^3J (^{1}H−^{1}H) = 7.7 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, 1H, pyridyl CH para to N), 7.65 (br. dd, ^3J (^{1}H−^{1}H) = 8.3 Hz, ^4J (^{1}H−^{1}H) = 1.1 Hz, 2H, 2 × phenyl CH ortho to amide), 7.49 (ddd, ^3J (^{1}H−^{1}H) = 7.5 Hz, ^3J (^{1}H−^{1}H) = 5.6 Hz, ^4J (^{1}H−^{1}H) = 1.7 Hz, 1H, pyridyl CH para to amide), 7.32 (m, 2H, 2 × phenyl CH meta to amide), 7.09 (t, ^3J (^{1}H−^{1}H) = 7.3 Hz,) 1H, phenyl CH para to amide), 1.41 (s, 15H, 5 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_3, 300 K) 168.4 (NCO), 155.8 (CCON) 149.5 (CH ortho to N on pyridyl ring), 148.1 (CNCO), 138.5 (CH para to N on pyridyl ring), 128.1 (CH meta to NCOR), 127.3 (CH para to CO on pyridyl ring) 126.9 (CH ortho to NCOR), 126.5 (CH ortho to CON on pyridyl ring), 124.3 (CH para to NCO), 86.5 ($\underline{C}CH_3$), 8.4 ($C\underline{C}H_3$).

*Synthesis of IrCp*Cl($C_{12}H_8ClN_2O$), 2.* Pyridine-2-carboxylic acid (2-chloro-phenyl) amide (0.06 g, 0.26 mmol) was added to a stirred suspension of [Ir{η^5-$C_5(CH_3)_5$}Cl_2]$_2$ (0.10 g, 0.13 mmol) and sodium bicarbonate (0.02 g, 0.26 mmol) in methanol (3 mL) in a 10 mL capacity microwave tube. The tube was then sealed and microwave heating was applied at 150 °C for 10 min. After effervescence from the solution had subsided, the tube was opened and left to cool. The resulting suspension was filtered, washed with diethyl ether, and dried *in vacuo* to yield orange crystals of **2** (0.10 g, 0.17 mmol, 65%). ES-MS (CH_2Cl_2, *m/z*): 559.1 [M-Cl]. Anal. Found: C, 44.2; H, 4.1; N, 4.6; Cl, 11.5%. Anal. Calcd: C, 44.4; H, 3.9; N, 4.7; Cl, 11.9%. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) 8.58 (ddd, ^3J (^{1}H−^{1}H) = 5.5 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, ^5J (^{1}H−^{1}H) = 0.7 Hz, 1H, pyridyl CH ortho to N), 8.21 (ddd, ^3J (^{1}H−^{1}H) = 7.9 Hz, ^4J (^{1}H−^{1}H) = 1.7 Hz, ^5J (^{1}H−^{1}H) = 0.7 Hz, 1H, pyridyl CH meta to N, ortho to amide), 7.93 (vtd (ddd), ^3J (^{1}H−^{1}H) = 8.1 Hz, ^3J (^{1}H−^{1}H) = 7.8 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, 1H, pyridyl CH para to N), 7.84 (dd, ^3J (^{1}H−^{1}H) = 7.9 Hz, ^4J (^{1}H−^{1}H) = 1.7 Hz, 1H, phenyl CH ortho to amide), 7.49 (vt (dd), ^3J (^{1}H−^{1}H) = 6.6 Hz, ^3J (^{1}H−^{1}H) = 5.6 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, 1H, pyridyl CH para to amide), 7.40 (dd, ^3J (^{1}H−^{1}H) = 7.9 Hz, ^4J (^{1}H−^{1}H) = 1.6 Hz, 1H, phenyl CH ortho to Cl), 7.23 (masked vtd (ddd), ^3J (^{1}H−^{1}H) = 8.1 Hz, ^3J (^{1}H−^{1}H) = 7.6 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, 1H, phenyl CH para to Cl), 7.09 (ddd, ^3J (^{1}H−^{1}H) = 8.1 Hz, ^3J (^{1}H−^{1}H) = 7.8 Hz, ^4J (^{1}H−^{1}H) = 1.7 Hz,, 1H, phenyl CH para to amide), 1.47 (s, 15H, 5 × CH_3). ^{13}C{^{1}H} NMR (125 MHz, CD_2Cl_2, 300 K) 168.5 (NCO), 155.2 (CCON), 150.4 (CH ortho to N on pyridyl ring), 147.2 (CNCO), 139.2 (C para to N on pyridyl ring), 132.8 (CCl), 129.5 (CH ortho to Cl and meta to NCO), 128.7 (CH ortho to NCO and meta to Cl), 128.0 (CH para to CO and meta to N on pyridyl ring), 127.9 (CH para to Cl), 126.9 (CH ortho to CO and meta to N on pyridyl ring), 126.3 (CH para to NCO), 87.5 ($\underline{C}CH_3$), 9.0 ($C\underline{C}H_3$).

*Synthesis of IrCp*Cl($C_{12}H_8ClN_2O$), 3.* Pyridine-2-carboxylic acid (3-chloro-phenyl) amide (0.06 g, 0.26 mmol) was added to a stirred suspension of [Ir{η^5-$C_5(CH_3)_5$}Cl_2]$_2$ (0.10 g, 0.13 mmol) and sodium bicarbonate (0.02 g, 0.26 mmol) in methanol (3 mL) in a 10 mL capacity microwave tube. The tube was then sealed and microwave heating was applied at 150 °C for 10 min. After effervescence from the solution had subsided, the tube was opened and left to cool. The resulting suspension was filtered, washed with hexane, and dried *in vacuo* to yield orange crystals of **3** (0.11 g, 0.19 mmol, 71%). ES-MS (CH_2Cl_2, *m/z*): 559.1 [M-Cl]. Anal. Found: C, 44.1; H, 4.3; N, 4.3; Cl, 11.5%. Anal. Calcd: C, 44.4; H, 3.9; N, 4.7; Cl, 11.9%. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) 8.58 (ddd, *J* = Hz, 1H, CH of pyridyl ortho to N), 8.16 (ddd, 1H, CH of pyridyl meta to N, ortho to CON), 7.94 (vtd (ddd), 1H, CH of pyridyl para to N), 7.73 (vt (dd), 1H, CH ortho to NCO and Cl), 7.61 (ddd, 1H, CH of phenyl para to NCO), 7.50 (ddd, 1H, CH of pyridyl meta to N, para to CON), 7.24 (vt (dd), 1H, CH of phenyl meta to NCO and Cl), 7.08 (ddd, 1H, CH para to Cl), 1.43 (s, 15H, 5 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_2$, 300 K) 168.4 (NCO), 155.4 (CCON), 149.6 (CH ortho to N on pyridyl ring), 149.4 (CNCO), 138.7 (C para to N on pyridyl ring), 133.5 (CCl), 129.0 (CH meta to Cl and NCO), 127.5 (CH para to CO and meta to N on pyridyl ring), 127.3 (CH ortho to NCO and Cl), 126.6 (CH ortho to CO and meta to N on pyridyl ring), 125.3 (CH ortho to Cl and meta to NCO), 124.3 (CH para to Cl), 86.7 ($\underline{C}CH_3$), 8.5 ($C\underline{C}H_3$).

*Synthesis of IrCp*Cl($C_{12}H_7Cl_2N_2O$), 4.* Pyridine-2-carboxylic acid (2,4-dichloro-phenyl) amide (0.07 g, 0.26 mmol) was added to a stirred suspension of [Ir{η^5-$C_5(CH_3)_5$}Cl_2]$_2$ (0.10 g, 0.13 mmol) and sodium bicarbonate (0.02 g, 0.26 mmol) in methanol (3 mL) in a 10 mL capacity microwave tube. The tube was then sealed and microwave heating was applied at 150 °C for 10 min. After effervescence from the solution had subsided, the tube was opened and left to cool. The resulting suspension was filtered, washed with ether, and dried *in vacuo* to yield orange crystals of **4** (0.11 g, 0.17 mmol, 67%). ES-MS (CH_2Cl_2, *m/z*): 593.1 [M-Cl]. Anal. Found: C, 41.6; H, 3.9; N, 4.1; Cl, 16.0% Anal. Calcd (with 0.8 molecules of water): C, 41.1; H, 3.7; N, 4.4; Cl, 16.5%. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) 8.61 (br. d, ^3J (^{1}H−^{1}H) = 5.7 Hz, 1H, pyridyl CH ortho to N), 8.24 (br. d, ^3J (^{1}H−^{1}H) = 8.1 Hz, pyridyl CH meta to N, ortho to amide), 7.98 (vtd, ^3J (^{1}H−^{1}H) = 7.6 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, 1H, pyridyl CH para to N), 7.86 (br. d, ^3J (^{1}H−^{1}H) = 8.6 Hz, 1H, phenyl CH ortho to amide, meta to both Cl), 7.54 (ddd, ^3J (^{1}H−^{1}H) = 7.5 Hz, ^3J (^{1}H−^{1}H) = 5.7 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz,, 1H, pyridyl CH para to amide), 7.47 (d, ^4J (^{1}H−^{1}H) = 2.4 Hz, 1H, phenyl CH ortho to both Cl), 7.25 (dd, ^3J (^{1}H−^{1}H) = 8.6 Hz, ^4J (^{1}H−^{1}H) = 2.4 Hz, 1H, phenyl CH meta to amide, ortho and para to Cl), 1.49 (s, 15H, 5 × CH_3). ^{13}C{^{1}H} NMR (125 MHz, CD_2Cl_2, 300 K) 168.6 (NCO), 154.9 (CCON), 150.5 (CH ortho to N on pyridyl ring), 146.1 (CNCO), 139.3 (C para to N on pyridyl ring), 133.6 (CCl ortho to NCO), 130.7 (CCl para to NCO) 129.7 (CH ortho to NCO and meta to both Cl), 129.2 (CH meta to NCO and ortho to both Cls), 128.2 (CH para to CO and meta to N on pyridyl ring), 127.0 (CH ortho to CO and meta to N on pyridyl ring), 87.6 (5 × $\underline{C}CH_3$), 9.1 (5 × $C\underline{C}H_3$).

*Synthesis of IrCp*Cl($C_{12}H_7Cl_2N_2O$), 5.* Pyridine-2-carboxylic acid (2,5-dichloro-phenyl) amide (0.07 g, 0.26 mmol) was added to a stirred suspension of [Ir{η^5-$C_5(CH_3)_5$}Cl_2]$_2$ (0.10 g, 0.13 mmol) and sodium bicarbonate (0.02 g, 0.26 mmol) in methanol (3 mL) in a 10 mL capacity microwave tube. The tube was then sealed and microwave heating was applied at 150 °C for 10 min. After effervescence from the solution had subsided, the tube was opened and left to cool. The resulting suspension was filtered, washed with ether, and dried *in vacuo* to yield **5** as a yellow powder (0.13 g, 0.21 mmol, 82%). ES-MS (CH_2Cl_2, *m/z*): 593.1 [M-Cl]. Anal. Found: C, 41.5; H, 3.4; N, 4.2; Cl, 16.6%. Anal. Calcd: C, 42.0; H, 3.5; N, 4.5; Cl, 16.9%. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) 8.58 (ddd, ^3J (^{1}H−^{1}H) = 5.6 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, ^5J (^{1}H−^{1}H) = 0.6 Hz, 1H, pyridyl CH ortho to N), 8.22 (ddd, ^3J (^{1}H−^{1}H) = 7.8 Hz, ^4J (^{1}H−^{1}H) = 1.6 Hz, ^5J (^{1}H−^{1}H) = 0.6 Hz, 1H, pyridyl CH meta to N, ortho to amide), 7.95 (vtd, ^3J (^{1}H−^{1}H) = 7.7 Hz, ^3J (^{1}H−^{1}H) = 7.7 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, 1H, pyridyl CH para to N), 7.89 (br. d, ^4J(^{1}H−^{1}H) = 2.6 Hz, 1H, CH ortho to Cl and NCOR), 7.50 (ddd, ^3J (^{1}H−^{1}H) = 6.5 Hz, ^3J (^{1}H−^{1}H) = 5.6 Hz, ^4J (^{1}H−^{1}H) = 1.7 Hz, 1H, pyridyl CH para to amide), 7.33 (br. d, ^3J (^{1}H−^{1}H) = 8.5 Hz, 1H, CH meta to NCOR) 7.07 (dd, ^3J (^{1}H−^{1}H) = 8.6 Hz, ^4J (^{1}H−^{1}H) = 2.6 Hz, 1H, CH para to NCOR), 1.49 (s, 15H, $C\underline{C}H_3$). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 300 K) 167.8 (NCO), 154.5 (CCON), 149.5 (CH ortho to N on pyridyl ring), 147.3 (CNCO), 138.7 (C para to N on pyridyl ring), 132.6 (CCl meta to NCO), 130.8 (CCl ortho to NCO) 129.8 (CH meta to NCOR), 128.5 (CH ortho to NCOR), 127.5 (CH para to CO and meta to N on pyridyl ring), 127.0 (CH ortho to CONR), 125.8 (CH para to NCOR), 87.0 (5 × $\underline{C}CH_3$), 8.7 (5 × $C\underline{C}H_3$).

*Synthesis of IrCp*Cl($C_{12}H_7F_2N_2O$), 6.* Pyridine-2-carboxylic acid (2,4-difluoro-phenyl) amide (0.07 g, 0.30 mmol) and [IrCp*Cl_2]$_2$ (0.10 g, 0.13 mmol) were dissolved in ethanol (30 mL) and the solution was refluxed for 30 min. Ammonium hexafluorophosphate (0.10g, 0.61 mmol) was added and the mixture was refluxed overnight. The resulting yellow solution was evaporated to dryness, redissolved in dichloromethane (50 mL) and washed with water (2 × 10 mL) and brine (10 mL), dried using sodium sulfate and filtered. **6** was recrystallized by dichloromethane/hexane layer diffusion (0.06 g, 0.10 mmol, 40%). ES-MS (CH_2Cl_2, *m/z*): 561.1 [M-Cl]. Anal. Found: C: 43.8, H: 3.8, N: 4.4%. Anal. Calcd: C, 44.3; H, 3.7; N, 4.7%. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) 8.58 (br. d, ^3J (^{1}H−^{1}H) = 5.6 Hz, 1H, pyridyl CH ortho to N), 8.18 (br. d, ^3J (^{1}H−^{1}H) = 7.5 Hz, 1H, pyridyl CH meta to N, ortho to amide), 7.94 (vdt (ddd), ^3J (^{1}H−^{1}H) = 7.8

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Hz, ^3J (^{1}H−^{1}H) = 7.5 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, 1H, pyridyl CH para to N), 7.75 (vbr. q (ddd), ^3J (^{1}H−^{1}H) = 8.6 Hz, ^3J (^{1}H−^{1}H) = 8.6 Hz, ^4J (^{1}H−^{19}F) = 8.6 Hz, 1H, phenyl CH ortho to NCO and F), 7.51 (ddd, ^3J (^{1}H−^{1}H) = 7.3 Hz, ^3J (^{1}H−^{1}H) = 5.8 Hz, ^4J (^{1}H−^{1}H) = 1.7 Hz, 1H, pyridyl CH para to amide), 6.86 (m, 2H, CH ortho to F groups and CH ortho and para to F), 1.45 (s, 15H, 5 × CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, 300 K) 168.4 (NCO), 159.9 (dd, ^1J (^{13}C−^{19}F) = 245.1 Hz, ^4J (^{13}C−^{19}F) = 11.1 Hz, CF), 157.6 (dd, ^1J (^{13}C−^{19}F) = 294.4 Hz, ^4J (^{13}C−^{19}F) = 11.8 Hz, CF), 154.4 (CCON), 149.6 (CH ortho to N on pyridyl ring), 138.6 (CH para to N on pyridyl ring), 132.2 (dd, ^2J (^{13}C−^{19}F) =13.2 Hz, ^4J (^{13}C−^{19}F) = 3.9 Hz, CNCO), 128.8 (dd, ^3J (^{13}C−^{19}F) = 9.3 Hz, ^3J (^{13}C−^{19}F) = 4.1 Hz, CH ortho to NCO), 127.5 (CH para to CONR), 126.7 (CH ortho to CO and meta to N on pyridyl ring), 111.0 (dd, ^2J (^{13}C−^{19}F) =21.5 Hz, ^4J (^{13}C−^{19}F) = 3.5 Hz, CH meta to NCO and para to F), 103.4 (vt (dd), ^2J (^{13}C−^{19}F) =25.5 Hz, ^2J (^{13}C−^{19}F) =25.5 Hz, CH ortho to F groups), 86.6 (5 × CCH_3), 8.4 (5 × CCH_3).

*Synthesis of IrCp*Cl($C_{12}H_7F_2N_2O$), **7**.* Pyridine-2-carboxylic acid (2,5-difluoro-phenyl) amide (0.07 g, 0.30 mmol) and [IrCp*Cl_2]$_2$ (0.10 g, 0.13 mmol) were dissolved in ethanol (30 mL) and the solution was refluxed for 30 min. Ammonium hexafluorophosphate (0.10 g, 0.61 mmol) was added and the mixture was refluxed overnight. The resulting yellow solution was evaporated to dryness, redissolved in dichloromethane (50 mL), washed with water (2 × 10 mL) and brine (10 mL), dried using sodium sulfate, and filtered. **7** was recrystallized by dichloromethane/hexane layer diffusion (0.07 g, 0.12 mmol, 47%). ES-MS (CH_2Cl_2, m/z): 561.1 [M-Cl]. Anal. Found: C, 44.5; H, 3.7; N, 4.6%. Anal. Calcd: C, 44.3; H, 3.7; N, 4.7%. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) 8.59 (ddd, ^3J (^{1}H−^{1}H) = 5.5 Hz, ^3J (^{1}H−^{1}H) = 1.4 Hz, ^3J (^{1}H−^{1}H) = 0.7 Hz, 1H, pyridyl CH ortho to N), 8.19 (ddd, ^3J (^{1}H−^{1}H) = 7.8 Hz, ^4J (^{1}H−^{1}H) = 1.6 Hz, ^5J (^{1}H−^{1}H) = 0.7 Hz, 1H, pyridyl CH meta to N, ortho to amide), 7.95 (vdt (ddd), ^3J (^{1}H−^{1}H) = 7.7 Hz, ^3J (^{1}H−^{1}H) = 7.7 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, 1H, pyridyl CH para to N), 7.48−7.58 (m, 2H, pyridyl CH para to amide and phenyl CH ortho to NCO and F), 7.07 (vtd (ddd), ^3J (^{1}H−^{1}H) = 5.1 Hz, ^3J (^{1}H−^{1}H) = 9.2 Hz, ^4J (^{1}H−^{1}H) = 9.2 Hz, 1H, phenyl CH meta to amide), 6.77 − 6.85 (m, 1H, phenyl CH para to NCO) 1.46 (s, 15H, 5 × CH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, 300 K) 168.2 (NCO), 159.8 (dd, ^1J(^{13}C−^{19}F) = 242.5 Hz, ^4J(^{13}C−^{19}F) = 2.3 Hz, CF meta to NCO), 153.4 (dd, ^1J(^{13}C−^{19}F) = 242.4 Hz, ^4J(^{13}C−^{19}F) = 2.9 Hz, CF ortho to NCO), 154.4 (CCON), 149.6 (CH ortho to N on pyridyl ring), 138.7 (CH para to N on pyridyl ring), 137.1 (dd, ^2J(^{13}C−^{19}F) = 15.7 Hz, ^3J(^{13}C−^{19}F) = 11.3 Hz, CNCO), 127.6 (CH para to CONR), 126.8 (CH ortho to CO and meta to N on pyridyl ring), 115.7 (dd, ^2J (^{19}F−^{13}C) = 23.9 Hz, ^3J (^{19}F−^{13}C) = 9.7 Hz, CH meta to NCO), 114.9 (dd, ^2J (^{19}F−^{13}C) = 24.7 Hz, ^3J (^{19}F−^{13}C) = 2.9 Hz, CH ortho to NCO) 112.1(dd, ^2J (^{19}F−^{13}C) = 24.3 Hz, ^3J (^{19}F−^{13}C) = 7.9 Hz, CH para to NCO), 86.7 (5 × CCH_3), 8.4 (5 × CCH_3).

*Synthesis of RhCp*Cl($C_{12}H_8ClN_2O$), **8**.* Pyridine-2-carboxylic acid (3-chloro-phenyl) amide (0.06 g, 0.26 mmol) and sodium bicarbonate (0.02 g, 0.26 mmol) was added to a stirred suspension of [RhCp*Cl_2]$_2$ (0.12 g, 0.13 mmol) in methanol (25 mL). The mixture was heated to reflux for 18 h. The resulting solution was evaporated to dryness and the crude product recrystallized from hot methanol to give red crystals of **8** suitable for X-ray crystallography. The bulk sample was purified using layer diffusion with a dichloromethane/hexane solvent system (0.15 g, 0.30 mmol, 76%). ES-MS (CH_2Cl_2, m/z): 469.1 [M-Cl]. Anal. Found: C, 50.8; H, 4.9; N, 4.9%. Anal. Calcd (with 0.33 molecules of dichloromethane): C, 50.3; H, 4.5; N, 5.3%. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) 8.63 (br. d, J (^{1}H−^{1}H) = 5.4 Hz, 1H, CH of pyridyl ortho to N), 8.16 (br. d, J (^{1}H−^{1}H) = 7.8 Hz, 1H, CH of pyridyl meta to N, ortho to CON), 7.95 (vtd (ddd), ^3J (^{1}H−^{1}H) = 7.7 Hz, ^3J (^{1}H−^{1}H) = 7.7 Hz, ^4J (^{1}H−^{1}H) = 1.4 Hz, 1H, CH of pyridyl para to N), 7.83 (vt (dd), ^4J (^{1}H−^{1}H) = 2.0 Hz, 1H, CH ortho to NCO and Cl), 7.72 (ddd, ^3J (^{1}H−^{1}H) = 8.0 Hz, ^4J (^{1}H−^{1}H) = 1.8 Hz, ^4J (^{1}H−^{1}H) = 1.0 Hz, 1H, CH of phenyl para to NCO), 7.54 (ddd, ^3J (^{1}H−^{1}H) = 6.5 Hz, ^3J (^{1}H−^{1}H) = 5.6 Hz, ^4J (^{1}H−^{1}H) = 1.6 Hz, 1H, CH of pyridyl meta to N, para to CON), 7.24 (masked vt (dd), ^3J (^{1}H−^{1}H) = 8.0 Hz, 1H, CH of phenyl meta to NCO and Cl), 7.06 (ddd, ^{1}H, ^3J (^{1}H−^{1}H) = 8.0 Hz, ^4J (^{1}H−^{1}H) = 2.1 Hz, ^4J (^{1}H−^{1}H) = 1.1 Hz, CH para to Cl), 1.43 (s, 15H, 5 × CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 300 K) 168.6 (NCO), 156.3 (CCON), 149.7 (CH ortho to N on pyridyl ring), 149.6 (CNCO), 138.9 (C para to N on pyridyl ring), 133.5 (CCl), 128.9 (CH meta to Cl and NCO), 127.4 (CH para to CO and meta to N on pyridyl ring), 127.1 (CH ortho to NCO and Cl), 126.1 (CH ortho to CO and meta to N on pyridyl ring), 125.5 (CH ortho to Cl and meta to NCO), 124.0 (CH para to Cl), 94.7 (d, ^1J(^{13}C-^{103}Rh) = 8.0 Hz, CCH_3), 8.6 (CCH_3).

*Synthesis of Ru-p-cymene Cl($C_{12}H_8ClN_2O$), **9**.* Pyridine-2-carboxylic acid (2-chloro-phenyl) amide (0.07 g, 0.32 mmol) was added to a solution of [Ru{η^6-*p*-cymene}Cl_2]$_2$ (0.10 g, 0.16 mmol) in ethanol (50 mL) and the mixture was warmed at 50 °C for 15 min then filtered over to ammonium hexafluorophosphate (0.10 g, 0.61 mmol). The resulting solution was stirred overnight then evaporated to dryness. The crude product was washed with petroleum ether (bp 40−60 °C) (3 × 10 mL) and recrystallized from methanol to yield orange crystals of **9** (0.076 g, 0.15 mmol, 47%). ES MS (+): m/z 503 [M$^+$]. Anal. Found: C, 50.20; H, 4.55; N, 5.30%. Anal. Calcd (with 1 molecule of H_2O): C, 50.77; H, 4.65; N, 5.38%. ^{1}H NMR (CD_3OD, 300.13 MHz, 300 K) δ 9.33 (d, 1H, ^3J(^{1}H−^{1}H) = 5.4 Hz, CH of C_5H_4N), 8.12 (t of d, 1H, ^3J(^{1}H−^{1}H) = 7.8 Hz, ^4J(^{1}H−^{1}H) = 1.5 Hz, CH of C_5H_4N), 7.96 (d of d, 1H, ^3J(^{1}H−^{1}H) = 7.8 Hz, ^4J(^{1}H−^{1}H) = 1.5 Hz, CH of C_5H_4N), 7.76 (d of d, 1H, ^3J(^{1}H−^{1}H) = 7.8 Hz, ^4J(^{1}H−^{1}H) = 1.5 Hz, CH of C_6H_4Cl), 7.69 (m, 1H, CH of C_5H_4N), 7.57 (d of d, 1H, ^3J(^{1}H−^{1}H) = 7.9 Hz, ^4J(^{1}H−^{1}H) = 1.6 Hz, CH of C_6H_4Cl), 7.25−7.38 (m, 2H, 2 × CH of C_6H_4Cl), 5.60 (d, 1H, ^3J(^{1}H−^{1}H) = 6.3 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 5.44−5.53 (m, 2H, 2 × CH of $H_3CC_6H_4C(H)(CH_3)_2$), 4.82 (m, 1H, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 2.69 (sept, 1H, ^3J(^{1}H−^{1}H) = 6.9 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 2.10 (s, 3H, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 1.10 (d, 3H, ^3J(^{1}H−^{1}H) = 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 1.00 (d, 3H, ^3J(^{1}H−^{1}H) = 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$). ^{13}C{^{1}H} NMR (CD_3OD, 75.47 MHz, 300 K) δ 169.0 (CONRu), 156.3 (CH of C_5H_4N), 156.2 (Quaternary C), 150.9 (Quaternary C), 140.8 (CH of C_5H_4N), 131.8 (Quaternary C), 131.1 (CH of C_6H_4Cl), 129.4 (CH of C_6H_4Cl), 129.0 (CH), 128.3 (CH of C_6H_4Cl), 126.9 (CH of C_5H_4N), 105.4 (Quaternary C of $H_3CC_6H_4C(H)(CH_3)_2$), 99.7 (Quaternary C of $H_3CC_6H_4C(H)(CH_3)_2$), 88.1 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 86.7 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 86.5 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 82.6 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 32.9 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 23.4 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 22.3 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 19.1 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$).

*Synthesis of Ru-p-cymene Cl($C_{12}H_8ClN_2O$), **10**.* Pyridine-2-carboxylic acid (3-chloro-phenyl) amide (0.07 g, 0.32 mmol) was added to a solution of [Ru{η^6-*p*-cymene}Cl_2]$_2$ (0.10 g, 0.16 mmol) in ethanol (50 mL) and the mixture was warmed at 50 °C for 15 min then filtered over to ammonium hexafluorophosphate (0.10 g, 0.61 mmol). The resulting solution was stirred overnight then evaporated to dryness. The crude product was washed with petroleum ether (bp 40−60 °C) (3 × 10 mL) and recrystallized from methanol to yield orange crystals of **10** (0.104 g, 0.21 mmol, 65%). ES MS (+): m/z 503 [M$^+$]. Anal. Found: C, 52.2; H, 4.4; N, 5.5%. Anal. Calcd: C, 52.6; H, 4.4; N, 5.6%. ^{1}H NMR (CD_3OD, 500.13 MHz, 300 K) δ 9.27 (br. d, 1H, ^3J(^{1}H−^{1}H) = 5.5 Hz, CH of C_5H_4N), 8.09 (t of d, 1H, ^3J(^{1}H−^{1}H) = 7.7 Hz, ^4J(^{1}H−^{1}H) = 1.4 Hz, CH of C_5H_4N), 7.95 (br. d, 1H, ^3J(^{1}H−^{1}H) = 7.8 Hz, CH of C_5H_4N), 7.64−7.68 (m, 2H, 2 × CH), 7.53 (m, 1H, CH of C_6H_4Cl), 7.39 (t, 1H, ^3J(^{1}H−^{1}H) = 8.0 Hz, CH of C_6H_4Cl), 7.23 (m, 1H, CH of C_6H_4Cl), 5.59 (d, 1H, ^3J(^{1}H−^{1}H) = 6.1 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 5.42 (d, 1H, ^3J(^{1}H−^{1}H) = 6.1 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 5.30 (d, 1H, ^3J(^{1}H−^{1}H) = 6.0 Hz, CH of $H_3CC_6H_4$ $C(H)(CH_3)_2$), 4.94 (d, 1H, ^3J(^{1}H−^{1}H) = 6.0 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 2.58 (sept, 1H, ^3J(^{1}H−^{1}H) = 6.9 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 2.16 (s, 3H, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 1.05−1.30 (m, 6H, 2 × CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$). ^{13}C{^{1}H} NMR (CD_3OD, 125.77 MHz, 300 K) δ 169.1 (CONRu), 156.2 (Quaternary C), 155.8 (CH of C_5H_4N), 154.4 (Quaternary C), 140.8 (CH of C_5H_4N), 134.9 (Quaternary C), 130.8 (CH of C_6H_4Cl), 128.6

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(CH), 127.5 (CH), 126.6 (CH of C_5H_4N), 126.0 (CH of C_6H_4Cl), 125.9 (CH of C_6H_4Cl), 103.7 (Quaternary C of $H_3CC_6H_4C(H)(CH_3)_2$), 101.9 (Quaternary C of $H_3CC_6H_4C(H)(CH_3)_2$), 86.3 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 85.9 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 85.5 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 85.3 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 32.2 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 22.5 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 22.1 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 18.9 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$). ES MS (+): m/z 467 $[M^+]$-Cl.

*Synthesis of Ru-p-cymene Cl($C_{12}H_7Cl_2N_2O$), **11**.* Pyridine-2-carboxylic acid (2,4-dichloro-phenyl) amide (0.09 g, 0.32 mmol) was added to a solution of $[Ru\{\eta^6\text{-}p\text{-cymene}\}Cl_2]_2$ (0.10 g, 0.16 mmol) in ethanol (50 mL) and the mixture was warmed at 50 °C for 15 min then filtered over to ammonium hexafluorophosphate (0.10 g, 0.61 mmol). The resulting solution was stirred overnight then evaporated to dryness. The crude product was washed with petroleum ether (bp 40−60 °C) (3 × 10 mL) and recrystallized from methanol to yield orange crystals of **11** (0.098 g, 0.18 mmol, 57%). ES MS (+): m/z 501 $[M^+]$-Cl. Anal. Found: C, 49.1; H, 3.9; N, 5.2%. Anal. Calcd: C, 49.2; H, 3.9; N, 5.2%. ^{1}H NMR (CD_3OD, 500.13 MHz, 300 K) δ 9.31 (d, 1H, $^3J(^1H-^1H)$ = 5.0 Hz, CH of C_5H_4N), 8.11 (t of d, 1H, $^3J(^1H-^1H)$ = 7.7 Hz, $^4J(^1H-^1H)$ = 1.4 Hz, CH of C_5H_4N), 7.95 (br. d, 1H, $^3J(^1H-^1H)$ = 7.8 Hz, CH of C_5H_4N), 7.75 (d, 1H, $^3J(^1H-^1H)$ = 8.5 Hz, CH of $C_6H_3Cl_2$), 7.69 (m, 1H, CH of C_5H_4N), 7.60 (d, 1H, $^4J(^1H-^1H)$ = 2.3 Hz, CH of $C_6H_3Cl_2$), 7.36 (d of d, 1H, $^3J(^1H-^1H)$ = 8.5 Hz, $^4J(^1H-^1H)$ = 2.3 Hz, CH of $C_6H_3Cl_2$), 5.65 (d, 1H, $^3J(^1H-^1H)$ = 6.7 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 5.47−5.48 (m, 2H, 2 × CH of $H_3CC_6H_4C(H)(CH_3)_2$), 4.90 (d, 1H, ^3J ($^1H-^1H$) = 6.0 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 2.67 (sept, 1H, $^3J(^1H-^1H)$ = 6.9 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 2.10 (s, 3H, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 1.09 (d, 3H, $^3J(^1H-^1H)$ = 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 1.01 (d, 3H, $^3J(^1H-^1H)$ = 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.77 MHz, 300 K) δ 155.8 (CH of C_5H_4N), 155.6 (Quaternary C), 149.4 (Quaternary C), 140.5 (CH of C_5H_4N), 132.5 (Quaternary C), 132.2 (Quaternary C), 130.3 (CH of $C_6H_3Cl_2$), 130.1 (CH of $C_6H_3Cl_2$), 128.9 (CH of $C_6H_3Cl_2$), 128.7 (CH of C_5H_4N), 126.5 (CH of C_5H_4N), 105.0 (Quaternary C of $H_3CC_6H_4C(H)(CH_3)_2$), 99.9 (Quaternary C of $H_3CC_6H_4C(H)(CH_3)_2$), 87.2 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 86.3 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 85.9 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 82.7 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 32.3 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 22.9 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 22.0 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 18.8 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$).

*Synthesis of Ru-p-cymene Cl($C_{12}H_7Cl_2N_2O$), **12**.* Pyridine-2-carboxylic acid (2,5-dichloro-phenyl) amide (0.09 g, 0.32 mmol) was added to a solution of $[Ru\{\eta^6\text{-}p\text{-cymene}\}Cl_2]_2$ (0.10 g, 0.16 mmol) in ethanol (50 mL) and the mixture was warmed at 50 °C for 15 min then filtered over to ammonium hexafluorophosphate (0.10 g, 0.61 mmol). The resulting solution was stirred overnight then evaporated to dryness. The crude product was washed with petroleum ether (bp 40−60 °C) (3 × 10 mL) and recrystallized from methanol to yield orange crystals of **12** (0.11 g, 0.20 mmol, 62%). ES MS (+): m/z 501 $[M^+]$-Cl. Anal. Found: C, 47.3; H, 4.5; N, 5.0%. Anal. Calcd (with 1 molecule of H_2O): C 47.6; H 4.2; N 5.1%. ^{1}H NMR (CD_3OD, 500.13 MHz, 300 K) δ 9.31 (d, 1H, $^3J(^1H-^1H)$ = 5.5 Hz, CH of C_5H_4N), 8.11 (t of d, 1H, $^3J(^1H-^1H)$ = 7.7 Hz, $^4J(^1H-^1H)$ = 1.4 Hz, CH of C_5H_4N), 7.96 (d, 1H, $^3J(^1H-^1H)$ = 7.8 Hz, CH of C_5H_4N), 7.81 (d, 1H, $^4J(^1H-^1H)$ = 2.6 Hz, CH of $C_6H_3Cl_2$), 7.69 (m, 1H, CH of C_5H_4N), 7.54 (d, 1H, $^3J(^1H-^1H)$ = 8.6 Hz, CH of $C_6H_3Cl_2$), 7.27 (d of d, 1H, $^3J(^1H-^1H)$ = 8.6 Hz, $^4J(^1H-^1H)$ = 2.6 Hz, CH of $C_6H_3Cl_2$), 5.57 (d, 1H, $^3J(^1H-^1H)$ = 5.9 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 5.48−5.51 (m, 2H, 2 × CH of $H_3CC_6H_4C(H)(CH_3)_2$), 4.94 (d, 1H, $^3J(^1H-^1H)$ = 5.9 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 2.68 (sept, 1H, $^3J(^1H-^1H)$ = 6.9 Hz, CH of $H_3CC_6H_4C(H)(CH_3)_2$), 2.16 (s, 3H, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 1.11 (d, 3H, ^3J ($^1H-^1H$) = 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 1.00 (d, 3H, ^3J ($^1H-^1H$) = 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.77 MHz, 300 K) δ 168.6 (CONRu), 155.9 (CH of C_5H_4N), 155.6 (Quaternary C), 151.8 (Quaternary C), 140.5 (CH of C_5H_4N), 133.8 (Quaternary C), 131.8 (CH of $C_6H_3Cl_2$), 130.3 (Quaternary C), 128.9 (CH of $C_6H_3Cl_2$), 128.8 (CH of C_5H_4N), 127.7 (CH of $C_6H_3Cl_2$), 126.6 (CH of C_5H_4N), 105.5 (Quaternary C of $H_3CC_6H_4C(H)(CH_3)_2$), 98.9 (Quaternary C of $H_3CC_6H_4C(H)(CH_3)_2$), 88.1 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 86.9 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 82.2 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 32.3 (CH of $H_3CC_6H_4C(H)(CH_3)_2$), 22.8 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 21.9 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$), 18.8 (CH_3 of $H_3CC_6H_4C(H)(CH_3)_2$).

*Synthesis of Ru-p-cymene Cl($C_{12}H_7Cl_2N_2O$), **13**.* Quinoline-2-carboxylic acid (2,6-dichloro-phenyl)-amide (0.10 g, 0.32 mmol) was added to a solution of $[Ru\{\eta^6\text{-}p\text{-cymene}\}Cl_2]_2$ (0.10 g, 0.16 mmol) in ethanol (50 mL) and the mixture was warmed at 50 °C for 15 min then filtered over to ammonium hexafluorophosphate (0.10 g, 0.61 mmol). The resulting solution was stirred overnight then evaporated to dryness. The crude product was washed with petroleum ether (bp 40−60 °C) (3 × 10 mL) and recrystallized from methanol to yield orange crystals of **13** (0.09 g, 0.15 mmol, 48%). ES MS (+): m/z 551.0 $[M^+]$-Cl. Anal. Found: C. 53.3; H. 3.9; N. 4.7%. Anal. Calcd:C 53.2; H 4.0; N 4.8%. It was noticed that there was exchange between the deuterated NMR solvent and the protons of the methyl group on the *para*-cymene ring. ^{1}H NMR (CD_3OD, 500.13 MHz, 300 K) δ 8.95 (d, 1H, $^3J(^1H-^1H)$ = 8.8 Hz, CH of C_9H_6N), 8.61 (d, 1H, $^3J(^1H-^1H)$ = 8.4 Hz, CH of C_9H_6N), 8.12−8.14 (m, 2H, 2 × CH of C_9H_6N), 8.08 (m, 1H, CH of C_9H_6N), 7.86 (m, 1H, CH of C_9H_6N), 7.61 (d of d, 1H, $^3J(^1H-^1H)$ = 8.0 Hz, $^4J(^1H-^1H)$ = 1.4 Hz, CH of $C_6H_3Cl_2$), 7.56 (d of d, 1H, $^3J(^1H-^1H)$ = 8.0 Hz, $^4J(^1H-^1H)$ = 1.4 Hz, CH of $C_6H_3Cl_2$), 7.30 (t, 1H, $^3J(^1H-^1H)$ = 8.1 Hz, CH of $C_6H_3Cl_2$), 5.79 (m, 2H, 2 × CH of $DH_2CC_6H_4C(H)(CH_3)_2$), 5.47 (d, 1H, $^3J(^1H-^1H)$ = 6.0 Hz, CH of $DH_2CC_6H_4C(H)(CH_3)_2$), 4.87 (d, 1H, $^3J(^1H-^1H)$ = 5.5 Hz, CH of $DH_2CC_6H_4C(H)(CH_3)_2$), 2.55 (sept, 1H, $^3J(^1H-^1H)$ = 6.9 Hz, CH of $DH_2CC_6H_4C(H)(CH_3)_2$), 2.17 (s, 2H, CH_2D of $DH_2CC_6H_4C(H)(CH_3)_2$), 0.99 (d, 3H, $^3J(^1H-^1H)$ = 6.9 Hz, CH_3 of $DH_2CC_6H_4C(H)(CH_3)_2$), 0.66 (d, 3H, $^3J(^1H-^1H)$ = 6.9 Hz, CH_3 of $DH_2CC_6H_4C(H)(CH_3)_2$). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.77 MHz, 300 K) δ 170.7 (CONRu), 156.6 (Quaternary C), 149.3 (Quaternary C), 148.1 (Quaternary C), 141.4 (CH of C_9H_6N), 134.5 (Quaternary C), 134.3 (Quaternary C), 132.6 (CH of C_9H_6N), 132.1 (Quaternary C), 131.0 (CH of C_9H_6N), 130.8 (CH of $C_6H_3Cl_2$), 130.1 (CH), 130.0 (CH), 129.9 (CH of C_9H_6N), 127.9 (CH of $C_6H_3Cl_2$), 122.8 (CH of C_9H_6N), 105.1 (C of $DH_2CC_6H_4C(H)(CH_3)_2$), 85.5 (CH of $DH_2CC_6H_4C(H)(CH_3)_2$), 85.4 (CH of $DH_2CC_6H_4C(H)(CH_3)_2$), 85.3 (CH of $DH_2CC_6H_4C(H)(CH_3)_2$), 85.0 (CH of $DH_2CC_6H_4C(H)(CH_3)_2$), 32.6 (CH of $DH_2CC_6H_4C(H)(CH_3)_2$), 23.8 (CH_3 of $DH_2CC_6H_4C(H)(CH_3)_2$), 21.1 (CH_3 of $DH_2CC_6H_4C(H)(CH_3)_2$), 19.0 (CH_3 of $DH_2CC_6H_4C(H)(CH_3)_2$).

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic information files (CIFs) containing crystallographic data for compounds **3**, **4**, **9**, **10**, **11**, **12**, and **13**. These files were also deposited onto the CCDC with the codes 944704, 944705, 944706, 944707, 944708, 944709, and 944710. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript. The crystal structures were run and solved by Stephanie Lucas, Andrew Hebden and Christopher Pask.

Notes

The authors declare no competing financial interest.

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