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

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Novel rhodium, iridium and ruthenium half-sandwich complexes containing (*N,N*)-bound picolinamide ligands have been prepared for use as anti-cancer agents. The complexes show promising cytotoxicities, with the presence, position and number of halides having a significant effect on the corresponding IC_{50} value. A ruthenium complex is more cytotoxic than cisplatin on HT-29 cells and it remains active 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 anti-cancer agents.[1-5] Rhodium and iridium complexes, however, remain relatively unexplored.[6-20] 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 anti-cancer agents, whereby the more hydrophobic quinaldamide complexes are more active than their picolinamide analogues.[21] In collaboration with Sadler, we have also shown that osmium congeners have also shown potential as cytotoxic agents.[4] More recently, we reported a preliminary investigation into two iridium-Cp* chloride

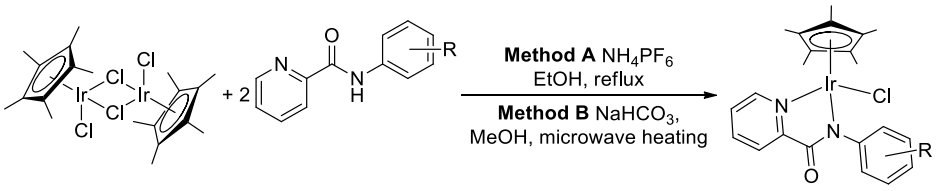
picolinamide complexes and their IC50 values for both HT-29 and MCF-7 cell lines.[16] In our continued study to optimise the design and potency of organometallic anti-cancer agents, we have extended our range of neutral complexes to include halide substituents on the phenyl ring for ruthenium *para-cymene* and rhodium-/iridium-Cp* in order to determine structure activity relationships. It is known that cancerous cells are in a hypoxic environment whereby the median oxygen partial pressure is approximately 10 mm Hg.[22] Many cytotoxic drugs are significantly less active when tested *in vitro* on cells in a hypoxic environment compared to normoxic conditions.[23] 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 in hypoxic conditions.

Results and Discussion

Synthesis of Compounds

Scheme 1 shows the synthesis of the group 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 1b)**. The ruthenium-*para*-cymene picolinamide complexes, **9**-**12**, and quinaldamide complex, **13**, were prepared according to **Scheme 1c)** and **Scheme 1d)** 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 of compounds **3**, **4** and **9**-**13**.

a)



1 R = H

2 R = 2'-Cl

3 R = 3'-Cl

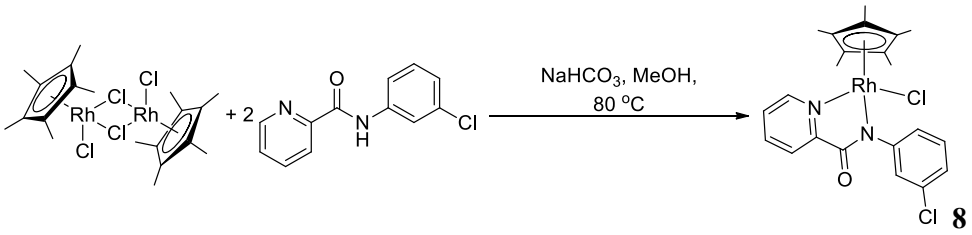
4 R =2',4'-dichloro

5 R = 2',5'-dichloro

6 R = 2',4'-difluoro

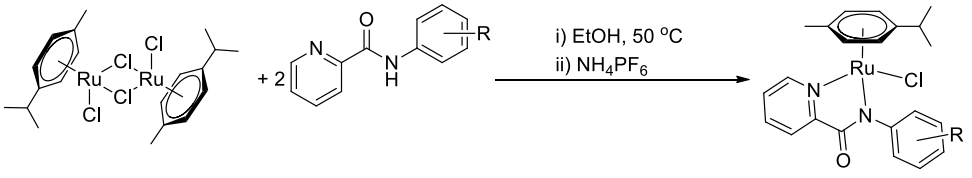
7 R = 2',5'-difluoro

b)



8

c)



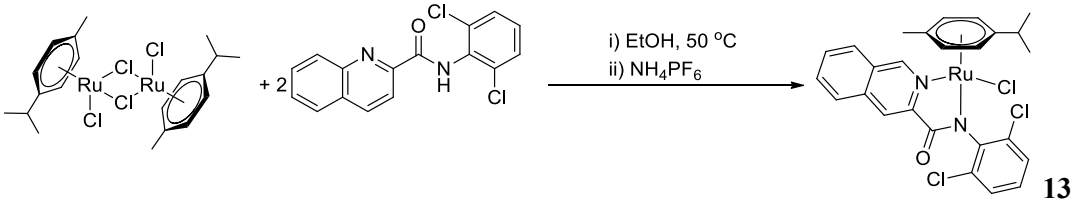
9 R = 2'-Cl

10 R = 3'-Cl

11 R =2',4'-dichloro

12 R = 2',5'-dichloro

d)



13

Scheme 1 Synthesis of **a)** iridium-Cp*, **b)** rhodium-Cp*, **c)** ruthenium-*para*-cymene picolinamide complexes and **d)** a ruthenium-*para*-cymene quinaldamide complex

X-ray Crystallographic Data

Figure 1 shows the molecular structures of compounds **3**, **4** and **9**-**13**, with the 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 recrystallised 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 metal centre, whereby the *para*-cymene/Cp*/Cp‡ occupies 3 coordination sites and the angle between the centroid of the Cp*/Cp‡/*para*-cymene ring and the other coordinating atoms are between 125.9-135.1 degrees. The angle between the coordinated nitrogens and the metal centre is between 76.27 and 77.05 degrees. This is due to the rigidity of the picolinamide ligand. The angle between the nitrogens and chloride is between 81.04 and 89.59 degrees. The picolinamide ligands adopt non-planar 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.

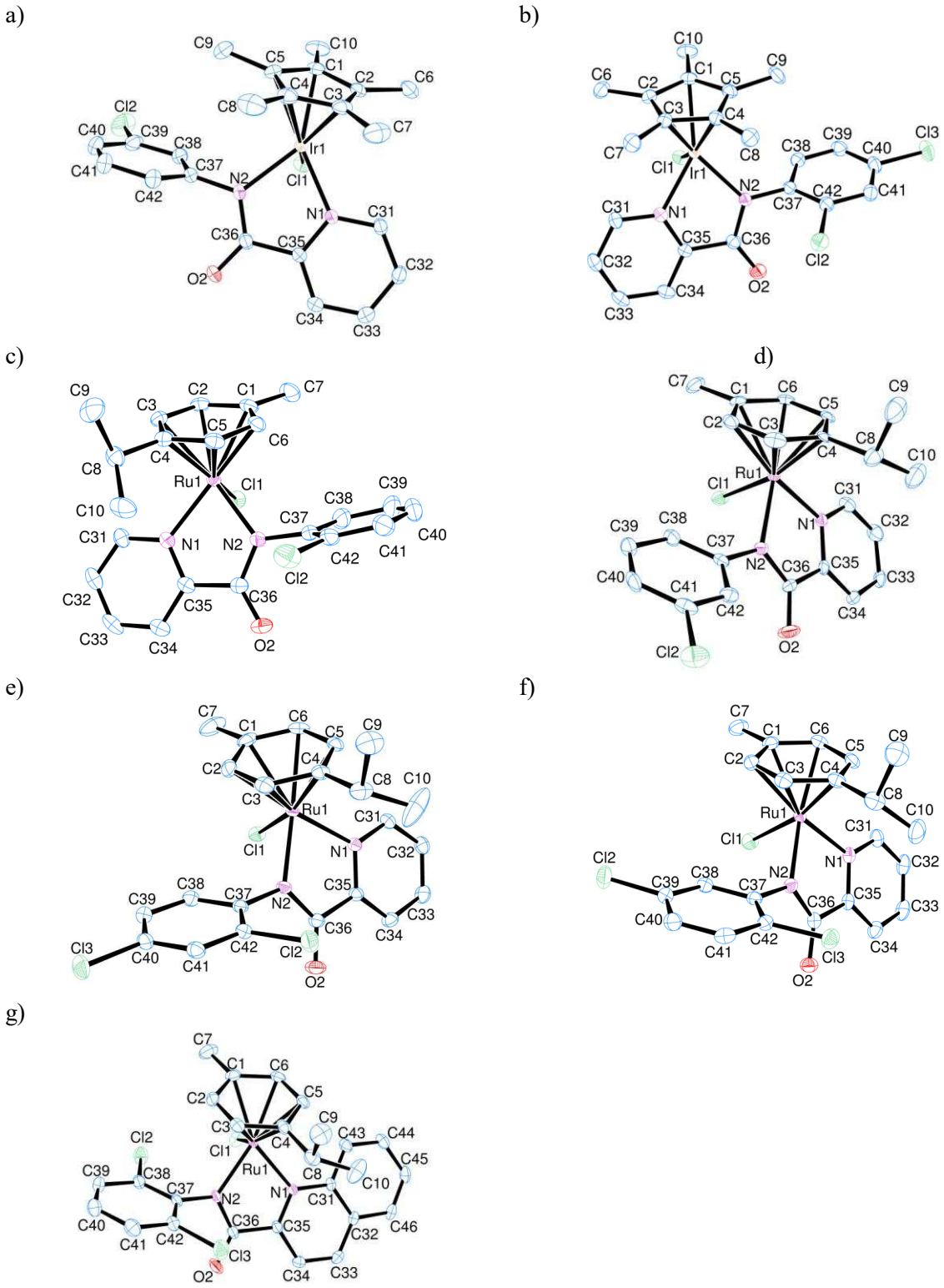


Figure 1. Molecular structures of compounds **a) 3**, **b) 4**, **c) 9**, **d) 10**, **e) 11**, **f) 12**, **g)** and **13**. Hydrogen atoms and solvent molecules are omitted for clarity. Displacement ellipsoids are at the 50% probability level.

Compound	**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 weight	679.45	646.98	1058.82	502.39	536.83	568.87	586.88
Crystal system	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/m3	1.766	1.86	1.583	1.650	1.642	1.596	1.631
Absorption coefficient / mm-1	5.66	6.147	0.970	1.055	1.107	1.024	1.014
λ[Mo-K_α], Å				0.71073			
Temp, °C				150(2)			
Reflections Collected	90089	63960	41538	19466	52845	59908	48568
Independent Reflections	10785	6880	10185	8230	6471	5810	5471
Observed Reflections	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 1 Summary of the crystallographic data for Complexes **3**, **4**, and **9-13**

Compound	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)

Table 2 Selected bond lengths (Å) for compounds **3**,**4** and **9-13**, where M = Rh or Ir

Compound	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)

Table 3 Selected bond angles (°) for compounds **3**, **4**, and **9-13**, where M = Rh or Ir

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 hour exposure for the MCF-7 cells.

Compound	A2780 $IC_{50}/\mu M$[a]	Compound	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				

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.[a] The drugs were incubated

for 5 days. [b] The drugs were incubated for an hour. [c, d, e] and [f] refer to different sets of A2780 cells, with different IC_{50} values for cisplatin.

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 complex's anti-cancer 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. The dichloro substituted picolinamide complexes show even higher activity with IC_{50} values of 19 and 23 μM for compounds **6** and **7** respectively. As shown in both the mono and di chloro 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 seen 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.

The ruthenium picolinamide complexes, **9**-**12**, show a different trend to their iridium-Cp* analogues whereby the cytotoxicities are in the order **12**>**10**>**11**>**9** (where the phenyl ring substituents are 2,5-diCl, 3-Cl, 2,4-diCl and 2-Cl respectively) for all 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, for both cell lines after a five 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 towards MCF-7 cells after a one hour exposure compared to 5 days. Compound **12** is still the most active and, unlike the five 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. Due to this promising result, compound **12** was retested on MCF-7 cells in a hypoxic environment for a one hour exposure and it 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,[22] compound **12** retains its activity against hypoxic cells and is not

adversely affected by hypoxia. Compound **12** has the potential to eradicate both the aerobic and hypoxic fraction of tumour cells and it is therefore a promising candidate for *in vivo* applications.

Conclusions

Various Ru-*para*-cymene and Rh-/Ir-Cp* or functionalised 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 unfunctionalised picolinamide complex, **1**, shows modest activity which, 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 five day and one hour exposure respectively as well as being active under hypoxic conditions for the latter. This makes compound **12** a promising candidate for further studies.

Experimental Details

The picolinamide ligands[24] 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.[25] The full data set was recorded and the images processed using DENZO and SCALEPACK programs.[26] The

structures were solved by Stephanie Lucas or Christopher Pask. Structure solution by direct methods was achieved through the use of SHELXS86[27], SIR92[28] or SIR97[29] programs, and the structural model defined by full matrix least squares on F^2 using SHELX97.[27] Molecular graphics were plotted using ORTEP. Editing of Crystallographic Information files and construction of tables of bond lengths and angles was achieved using WC[30] and PLATON.[31] 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.

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 2×10^4cells cell/ml. 200 μL of growth media (RPMI 1640 supplemented with 10% foetal calf serum, sodium pyruvate (1 mM) and L-glutamine (2 mM)) was added to each well and the plates were incubated for 24 hours 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 dimethylsulphoxide at a concentration of 25 mM and diluted further with medium to obtain drug solutions ranging from 250 to 0.49 μM. The final dimethylsulphoxide concentration was 0.1% (v/v), which is non-toxic to cells. Drug solutions were applied to cells and incubated for either 1 hour or 5 days at 37 °C in an atmosphere of 5% CO_2. For 1 hour 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 $mgml^{-1}$) was added to each well and incubated for 3 hours at 37 °C in an atmosphere of 5% CO_2. The solutions were then removed and 150 μL of dimethylsulphoxide 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 3 times and a mean value obtained.

*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 minutes Ammonium hexafluorophosphate (0.10 g, 0.61 mmol) was added and the mixture was stirred at 80 °C for 20 hours. 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 recrystallised using vapour 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. Calculated (with 0.05 molecules of dichloromethane): C: 46.9, H: 4.3, N: 5.0, Cl: 6.9%. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) 8.57 (br. d, ^3J (^{1}H-^{1}H) = 5.4 Hz, 1H, pyridyl CH *ortho* to N), 8.17 (br. d, ^3J (^{1}H-^{1}H) = 8.0 Hz, 1H, pyridyl CH *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 $[Ir\{\eta^5\text{-}C_5(CH_3)_5\}Cl_2]_2$ (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 minutes. 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. Calculated: 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 (<u>C</u>CON), 150.4 (CH *ortho* to N on pyridyl ring), 147.2 (<u>C</u>NCO), 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 (<u>C</u>CH_3), 9.0 (C<u>C</u>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 minutes. 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. Calculated: 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 $[Ir\{\eta^5\text{-}C_5(CH_3)_5\}Cl_2]_2$ (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 minutes. 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. Calculated (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, ^{3}J (^{1}H-^{1}H) = 5.7 Hz, 1H, pyridyl CH *ortho* to N), 8.24 (br. d, ^{3}J (^{1}H-^{1}H) = 8.1 Hz, pyridyl CH *meta* to N, *ortho* to amide), 7.98 (vtd, ^{3}J (^{1}H-^{1}H) = 7.6 Hz, ^{4}J (^{1}H-^{1}H) = 1.4 Hz, 1H, pyridyl CH *para* to N), 7.86 (br. d, ^{3}J (^{1}H-^{1}H) = 8.6 Hz, 1H, phenyl CH *ortho* to amide, *meta* to both Cl), 7.54 (ddd, ^{3}J (^{1}H-^{1}H) = 7.5 Hz, ^{3}J (^{1}H-^{1}H) = 5.7 Hz, ^{4}J (^{1}H-^{1}H) = 1.4 Hz,, 1H, pyridyl CH *para* to amide), 7.47 (d, ^{4}J (^{1}H-^{1}H) = 2.4 Hz, 1H, phenyl CH *ortho* to both Cl), 7.25 (dd, ^{3}J (^{1}H-^{1}H) = 8.6 Hz, ^{4}J (^{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 $[Ir\{\eta^5\text{-}C_5(CH_3)_5\}Cl_2]_2$ (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 minutes. 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. Calculated: 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, $CC\underline{H}_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 300 K) 167.8 (NCO), 154.5 ($\underline{C}CON$), 149.5 (CH *ortho* to N on pyridyl ring), 147.3 ($\underline{C}NCO$), 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 minutes. 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) & brine (10 ml), dried using sodium sulfate and filtered. **6** was recrystallised 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. Calculated: 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 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 × $\underline{C}CH_3$), 8.4 (5 × $C\underline{C}H_3$).

*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 mins. 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) and washed with water (2 × 10 ml) & brine (10 ml), dried using sodium sulfate and filtered. **7** was recrystallised 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. Calculated: 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), ^{3}J (^{1}H-^{1}H) = 7.7 Hz, ^{3}J (^{1}H-^{1}H) = 7.7 Hz, ^{4}J (^{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), ^{3}J (^{1}H-^{1}H) = 5.1 Hz, ^{3}J (^{1}H-^{1}H) = 9.2 Hz, ^{4}J (^{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, ^{1}J(^{13}C-^{19}F) = 242.5 Hz, ^{4}J(^{13}C-^{19}F) = 2.3 Hz, CF *meta* to NCO), 153.4 (dd, ^{1}J(^{13}C-^{19}F) = 242.4 Hz, ^{4}J(^{13}C-^{19}F) = 2.9 Hz, CF *ortho* to NCO), 154.4 (<u>C</u>CON), 149.6 (CH *ortho* to N on pyridyl ring), 138.7 (CH *para* to N on pyridyl ring), 137.1 (dd, ^{2}J(^{13}C-^{19}F) = 15.7 Hz, ^{3}J(^{13}C-^{19}F) = 11.3 Hz, <u>C</u>NCO), 127.6 (CH *para* to CONR), 126.8 (CH *ortho* to CO and *meta* to N on pyridyl ring), 115.7 (dd, ^{2}J (^{19}F-^{13}C) = 23.9 Hz, ^{3}J (^{19}F-^{13}C) = 9.7 Hz, CH *meta* to NCO), 114.9 (dd, ^{2}J (^{19}F-^{13}C) = 24.7 Hz, ^{3}J (^{19}F-^{13}C) = 2.9 Hz, CH *ortho* to NCO) 112.1(dd, ^{2}J (^{19}F-^{13}C) = 24.3 Hz, ^{3}J (^{19}F-^{13}C) = 7.9 Hz, CH *para* to NCO), 86.7 (5 × <u>C</u>CH_3), 8.4 (5 × C<u>C</u>H_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 hours. The resulting solution was evaporated to dryness and the crude product recrystallised 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. Calculated (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), ^{3}J (^{1}H-^{1}H) = 7.7 Hz, ^{3}J (^{1}H-^{1}H) = 7.7 Hz, ^{4}J (^{1}H-^{1}H) = 1.4 Hz, 1H, CH of pyridyl *para* to N), 7.83 (vt (dd), ^{4}J (^{1}H-^{1}H) = 2.0 Hz, 1H, CH *ortho* to NCO and Cl), 7.72 (ddd, ^{3}J (^{1}H-^{1}H) = 8.0 Hz, ^{4}J (^{1}H-^{1}H) = 1.8 Hz, ^{4}J (^{1}H-^{1}H) = 1.0 Hz, 1H, CH of phenyl *para* to NCO), 7.54 (ddd, ^{3}J (^{1}H-^{1}H) = 6.5 Hz, ^{3}J (^{1}H-^{1}H) = 5.6 Hz, ^{4}J (^{1}H-^{1}H) = 1.6 Hz, 1H, CH of pyridyl *meta* to N, *para* to CON), 7.24 (masked vt (dd), ^{3}J (^{1}H-^{1}H) = 8.0 Hz, 1H, CH of phenyl *meta* to NCO and Cl), 7.06 (ddd, ^{1}H, ^{3}J (^{1}H-^{1}H) = 8.0 Hz, ^{4}J

(^{1}H-^{1}H) = 2.1 Hz, ^{4}J (^{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 (<u>C</u>CON), 149.7 (CH *ortho* to N on pyridyl ring), 149.6 (<u>C</u>NCO), 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, ^{1}J(^{13}C-^{103}Rh) = 8.0 Hz, <u>C</u>CH_3), 8.6 (C<u>C</u>H_3).

Synthesis of Ru-para-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-*para*-cymene}Cl_2]$_2$ (0.10 g, 0.16 mmol) in ethanol (50 ml) and the mixture was warmed at 50 °C for 15 minutes 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 recrystallised 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. Calculated (with 1 molecule of H_2O): C 50.77; H 4.65; N 5.38%. ^{1}H NMR (CD_3OD, 300.13MHz, 300K) δ 9.33 (d, 1H, ^{3}J(^{1}H-^{1}H)= 5.4 Hz, CH of C_5<u>H</u>$_4$N), 8.12 (t of d, 1H, ^{3}J(^{1}H-^{1}H)= 7.8 Hz, ^{4}J(^{1}H-^{1}H)= 1.5 Hz, CH of C_5<u>H</u>$_4$N), 7.96 (d of d, 1H, ^{3}J(^{1}H-^{1}H)= 7.8 Hz, ^{4}J(^{1}H-^{1}H)= 1.5 Hz, CH of C_5<u>H</u>$_4$N), 7.76 (d of d, 1H, ^{3}J(^{1}H-^{1}H)= 7.8 Hz, ^{4}J(^{1}H-^{1}H)= 1.5 Hz, CH of C_6<u>H</u>$_4$Cl), 7.69 (m, 1H, CH of C_5<u>H</u>$_4$N), 7.57 (d of d, 1H, ^{3}J(^{1}H-^{1}H)= 7.9 Hz, ^{4}J(^{1}H-^{1}H)= 1.6 Hz, CH of C_6<u>H</u>$_4$Cl), 7.25-7.38 (m, 2H, 2 x CH of C_6<u>H</u>$_4$Cl), 5.60 (d, 1H, ^{3}J(^{1}H-^{1}H)= 6.3 Hz, CH of H_3CC_6<u>H</u>$_4$C(H)(CH_3)$_2$), 5.44-5.53 (m, 2H, 2 x CH of H_3CC_6<u>H</u>$_4$C(H)(CH_3)$_2$), 4.82 (m, 1H, CH of H_3CC_6<u>H</u>$_4$C(H)(CH_3)$_2$), 2.69 (sept, 1H, ^{3}J(^{1}H-^{1}H)= 6.9 Hz, CH of $H_3CC_6H_4$C(<u>H</u>)(CH_3)$_2$), 2.10 (s, 3H, CH_3 of <u>H</u>$_3CC_6H_4$C(H)(CH_3)$_2$), 1.10 (d, 3H, ^{3}J(^{1}H-^{1}H)= 6.9 Hz, CH_3 of $H_3CC_6H_4$C(H)(C<u>H</u>$_3$)$_2$), 1.00 (d, 3H, ^{3}J(^{1}H-^{1}H)= 6.9 Hz, CH_3 of $H_3CC_6H_4$C(H)(C<u>H</u>$_3$)$_2$); ^{13}C{^{1}H} NMR (CD_3OD, 75.47MHz, 300K) 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 $H_3CC_6H_4$C(H)(CH_3)$_2$), 99.7 (Quaternary C of H_3C<u>C</u>$_6H_4$C(H)(CH_3)$_2$), 88.1 (CH of H_3C<u>C</u>$_6H_4$C(H)(CH_3)$_2$),

86.7 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 86.5 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 82.6 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 32.9 (CH of $H_3CC_6H_4\underline{C}(H)(CH_3)_2$), 23.4 ($CH_3$ of $H_3CC_6H_4C(H)(\underline{C}H_3)_2$), 22.3 ($CH_3$ of $H_3CC_6H_4C(H)(\underline{C}H_3)_2$), 19.1 ($CH_3$ of $H_3\underline{C}C_6H_4C(H)(CH_3)_2$).

Synthesis of Ru-para-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-*para*-cymene}Cl_2]$_2$ (0.10 g, 0.16 mmol) in ethanol (50 ml) and the mixture was warmed at 50 °C for 15 minutes 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 recrystallised 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. Calc.: 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, $^3J(^1H\text{-}^1H)$=5.5 Hz, CH of $C_5\underline{H}_4N$), 8.09 (t of d, 1H, $^3J(^1H\text{-}^1H)$= 7.7 Hz, $^4J(^1H\text{-}^1H)$= 1.4 Hz, CH of $C_5\underline{H}_4N$), 7.95 (br. d, 1H, $^3J(^1H\text{-}^1H)$= 7.8 Hz, CH of $C_5\underline{H}_4N$), 7.64-7.68 (m, 2H, 2 x CH), 7.53 (m, 1H, CH of $C_6\underline{H}_4Cl$), 7.39 (t, 1H, $^3J(^1H\text{-}^1H)$= 8.0 Hz, CH of $C_6\underline{H}_4Cl$), 7.23 (m, 1H, CH of $C_6\underline{H}_4Cl$), 5.59 (d, 1H, $^3J(^1H\text{-}^1H)$= 6.1 Hz, CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 5.42 (d, 1H, $^3J(^1H\text{-}^1H)$= 6.1 Hz, CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 5.30 (d, 1H, $^3J(^1H\text{-}^1H)$= 6.0 Hz, CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 4.94 (d, 1H, $^3J(^1H\text{-}^1H)$= 6.0 Hz, CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 2.58 (sept, 1H, $^3J(^1H\text{-}^1H)$= 6.9 Hz, CH of $H_3CC_6H_4C(\underline{H})(CH_3)_2$), 2.16 (s, 3H, CH_3 of $\underline{H}_3CC_6H_4C(H)(CH_3)_2$), 1.05-1.30 (m, 6H, 2 x CH_3 of $H_3CC_6H_4C(H)(C\underline{H}_3)_2$); $^{13}C\{^1H\}$ NMR (CD_3OD, 125.77MHZ, 300K) 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 (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 $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 101.9 (Quaternary C of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 86.3 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 85.9 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 85.5 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 85.3 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 32.2 (CH of $H_3CC_6H_4\underline{C}(H)(CH_3)_2$), 22.5 ($CH_3$ of $H_3CC_6H_4C(H)(\underline{C}H_3)_2$), 22.1 ($CH_3$ of $H_3CC_6H_4C(H)(\underline{C}H_3)_2$), 18.9 ($CH_3$ of $H_3\underline{C}C_6H_4C(H)(CH_3)_2$); ES MS (+): m/z 467 [$M^+$]-Cl.

*Synthesis of Ru-para-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{η^6-*para*-cymene}Cl_2]$_2$ (0.10 g, 0.16 mmol) in ethanol (50 ml) and the mixture was warmed at 50 °C for 15 minutes 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 recrystallised 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. Calc.: C 49.2; H 3.9; N 5.2%. ^{1}H NMR (CD_3OD, 500.13MHz, 300K) δ 9.31 (d, 1H, $^3J(^1H\text{-}^1H)$= 5.0 Hz, CH of $C_5\underline{H}_4N$), 8.11 (t of d, 1H, $^3J(^1H\text{-}^1H)$= 7.7 Hz, $^4J(^1H\text{-}^1H)$= 1.4 Hz, CH of $C_5\underline{H}_4N$), 7.95 (br. d, 1H, $^3J(^1H\text{-}^1H)$= 7.8 Hz, CH of $C_5\underline{H}_4N$), 7.75 (d, 1H, $^3J(^1H\text{-}^1H)$= 8.5 Hz, CH of $C_6\underline{H}_3Cl_2$), 7.69 (m, 1H, CH of $C_5\underline{H}_4N$), 7.60 (d, 1H, $^4J(^1H\text{-}^1H)$= 2.3 Hz, CH of $C_6\underline{H}_3Cl_2$), 7.36 (d of d, 1H, $^3J(^1H\text{-}^1H)$= 8.5 Hz, $^4J(^1H\text{-}^1H)$= 2.3 Hz, CH of $C_6\underline{H}_3Cl_2$), 5.65 (d, 1H, $^3J(^1H\text{-}^1H)$= 6.7 Hz, CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 5.47-5.48 (m, 2H, 2 x CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 4.90 (d, 1H, ^3J ($^1H\text{-}^1H$) = 6.0 Hz, CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 2.67 (sept, 1H, $^3J(^1H\text{-}^1H)$= 6.9 Hz, CH of $H_3CC_6H_4C(\underline{H})(CH_3)_2$), 2.10 (s, 3H, CH_3 of $\underline{H}_3CC_6H_4C(H)(CH_3)_2$), 1.09 (d, 3H, $^3J(^1H\text{-}^1H)$= 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(C\underline{H}_3)_2$), 1.01 (d, 3H, $^3J(^1H\text{-}^1H)$= 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(C\underline{H}_3)_2$); $^{13}C\{^1H\}$ NMR (CD_3OD, 125.77MHZ, 300K) δ 155.8 (CH of $\underline{C}_5H_4N$), 155.6 (Quaternary C), 149.4 (Quaternary C), 140.5 (CH of $\underline{C}_5H_4N$), 132.5 (Quaternary C), 132.2 (Quaternary C), 130.3 (CH of $\underline{C}_6H_3Cl_2$), 130.1 (CH of $\underline{C}_6H_3Cl_2$), 128.9 (CH of $\underline{C}_6H_3Cl_2$), 128.7 (CH of $\underline{C}_5H_4N$), 126.5 (CH of $\underline{C}_5H_4N$), 105.0 (Quaternary C of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 99.9 (Quaternary C of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 87.2 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 86.3 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 85.9 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 82.7 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 32.3 (CH of $H_3CC_6H_4\underline{C}(H)(CH_3)_2$), 22.9 ($CH_3$ of $H_3CC_6H_4C(H)(\underline{C}H_3)_2$), 22.0 ($CH_3$ of $H_3CC_6H_4C(H)(\underline{C}H_3)_2$), 18.8 ($CH_3$ of $H_3\underline{C}C_6H_4C(H)(CH_3)_2$).

*Synthesis of Ru-para-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{η^6-*para*-cymene}Cl_2]$_2$ (0.10 g, 0.16 mmol) in

ethanol (50 ml) and the mixture was warmed at 50 °C for 15 minutes 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 recrystallised 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. Calc. (with 1 molecule of H_2O): C 47.6; H 4.2; N 5.1%. ^{1}H NMR (CD_3OD, 500.13MHz, 300K) δ 9.31 (d, 1H, $^3J(^1H\text{-}^1H)$= 5.5 Hz, CH of $C_5\underline{H}_4N$), 8.11 (t of d, 1H, $^3J(^1H\text{-}^1H)$= 7.7 Hz, $^4J(^1H\text{-}^1H)$= 1.4 Hz, CH of $C_5\underline{H}_4N$), 7.96 (d, 1H, $^3J(^1H\text{-}^1H)$= 7.8 Hz, CH of $C_5\underline{H}_4N$), 7.81 (d, 1H, $^4J(^1H\text{-}^1H)$= 2.6 Hz, CH of $C_6\underline{H}_3Cl_2$), 7.69 (m, 1H, CH of $C_5\underline{H}_4N$), 7.54 (d, 1H, $^3J(^1H\text{-}^1H)$= 8.6 Hz, CH of $C_6\underline{H}_3Cl_2$), 7.27 (d of d, 1H, $^3J(^1H\text{-}^1H)$= 8.6 Hz, $^4J(^1H\text{-}^1H)$= 2.6 Hz, CH of $C_6\underline{H}_3Cl_2$), 5.57 (d, 1H, $^3J(^1H\text{-}^1H)$= 5.9 Hz, CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 5.48-5.51 (m, 2H, 2 x CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 4.94 (d, 1H, $^3J(^1H\text{-}^1H)$= 5.9 Hz, CH of $H_3CC_6\underline{H}_4C(H)(CH_3)_2$), 2.68 (sept, 1H, $^3J(^1H\text{-}^1H)$ = 6.9 Hz, CH of $H_3CC_6H_4C(\underline{H})(CH_3)_2$), 2.16 (s, 3H, CH_3 of $\underline{H}_3CC_6H_4C(H)(CH_3)_2$), 1.11 (d, 3H, ^3J ($^1H\text{-}^1H$) = 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(C\underline{H}_3)_2$), 1.00 (d, 3H, ^3J ($^1H\text{-}^1H$) = 6.9 Hz, CH_3 of $H_3CC_6H_4C(H)(C\underline{H}_3)_2$); $^{13}C\{^1H\}$ NMR (CD_3OD, 125.77MHZ, 300K) δ 168.6 (<u>C</u>ONRu), 155.9 (CH of $\underline{C}_5H_4N$), 155.6 (Quaternary C), 151.8 (Quaternary C), 140.5 (CH of $\underline{C}_5H_4N$), 133.8 (Quaternary C), 131.8 (CH of $\underline{C}_6H_3Cl_2$), 130.3 (Quaternary C), 128.9 (CH of $\underline{C}_6H_3Cl_2$), 128.8 (CH of $\underline{C}_5H_4N$), 127.7 (CH of $\underline{C}_6H_3Cl_2$), 126.6 (CH of $\underline{C}_5H_4N$), 105.5 (Quaternary C of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 98.9 (Quaternary C of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 88.1 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 86.9 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 82.2 (CH of $H_3C\underline{C}_6H_4C(H)(CH_3)_2$), 32.3 (CH of $H_3CC_6H_4\underline{C}(H)(CH_3)_2$), 22.8 ($CH_3$ of $H_3CC_6H_4C(H)(\underline{C}H_3)_2$), 21.9 ($CH_3$ of $H_3CC_6H_4C(H)(\underline{C}H_3)_2$), 18.8 ($CH_3$ of $H_3\underline{C}C_6H_4C(H)(CH_3)_2$).

Synthesis of Ru-para-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{η^6-*para*-cymene}Cl_2]$_2$ (0.10 g, 0.16 mmol) in ethanol (50 ml) and the mixture was warmed at 50 °C for 15 minutes 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 recrystallised

from methanol to yield orange crystals of **15** (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. Calc.:C 53.2; H 4.0; N 4.8%.^{1}H NMR (CD_3OD, 500.13MHz, 300K) δ 8.95 (d, 1H, $^3J(^1H\text{-}^1H)$= 8.8 Hz, CH of $C_9\underline{H}_6N$), 8.61 (d, 1H, $^3J(^1H\text{-}^1H)$= 8.4 Hz, CH of $C_9\underline{H}_6N$), 8.12-8.14 (m, 2H, 2 x CH of $C_9\underline{H}_6N$), 8.08 (m, 1H, CH of $C_9\underline{H}_6N$), 7.86 (m, 1H, CH of $C_9\underline{H}_6N$), 7.61 (d of d, 1H, $^3J(^1H\text{-}^1H)$= 8.0 Hz, $^4J(^1H\text{-}^1H)$= 1.4 Hz, CH of $C_6\underline{H}_3Cl_2$), 7.56 (d of d, 1H, $^3J(^1H\text{-}^1H)$= 8.0 Hz, $^4J(^1H\text{-}^1H)$= 1.4 Hz, CH of $C_6\underline{H}_3Cl_2$), 7.30 (t, 1H, $^3J(^1H\text{-}^1H)$= 8.1 Hz, CH of $C_6\underline{H}_3Cl_2$), 5.79 (m, 2H, 2 x CH of $DH_2CC_6\underline{H}_4C(H)(CH_3)_2$), 5.47 (d, 1H, $^3J(^1H\text{-}^1H)$ =6.0 Hz, CH of $DH_2CC_6\underline{H}_4C(H)(CH_3)_2$), 4.87 (d, 1H, $^3J(^1H\text{-}^1H)$= 5.5 Hz, CH of $DH_2CC_6\underline{H}_4C(H)(CH_3)_2$), 2.55 (sept, 1H, $^3J(^1H\text{-}^1H)$= 6.9 Hz, CH of $DH_2CC_6H_4C(\underline{H})(CH_3)_2$), 2.17 (s, 2H, CH_2D of $D\underline{H}_2CC_6H_4C(H)(CH_3)_2$), 0.99 (d, 3H, $^3J(^1H\text{-}^1H)$= 6.9 Hz, CH_3 of $DH_2CC_6H_4C(H)(C\underline{H}_3)_2$), 0.66 (d, 3H, $^3J(^1H\text{-}^1H)$= 6.9 Hz, CH_3 of $DH_2CC_6H_4C(H)(C\underline{H}_3)_2$); $^{13}C\{^1H\}$ NMR (CD_3OD, 125.77MHZ, 300K) δ 170.7 ($\underline{C}$ONRu), 156.6 (Quaternary C), 149.3 (Quaternary C), 148.1 (Quaternary C), 141.4 (CH of $\underline{C}_9H_6N$), 134.5 (Quaternary C), 134.3 (Quaternary C), 132.6 (CH of $\underline{C}_9H_6N$), 132.1 (Quaternary C), 131.0 (CH of $\underline{C}_9H_6N$), 130.8 (CH of $\underline{C}_6H_3Cl_2$), 130.1 (CH), 130.0 (CH), 129.9 (CH of $\underline{C}_9H_6N$), 127.9 (CH of $\underline{C}_6H_3Cl_2$), 122.8 (CH of $\underline{C}_9H_6N$), 105.1 (C of $DH_2C\underline{C}_6H_4C(H)(CH_3)_2$), 85.5 (CH of $DH_2C\underline{C}_6H_4C(H)(CH_3)_2$), 85.4 (CH of $DH_2C\underline{C}_6H_4C(H)(CH_3)_2$), 85.3 (CH of $DH_2C\underline{C}_6H_4C(H)(CH_3)_2$), 85.0 (CH of $DH_2C\underline{C}_6H_4C(H)(CH_3)_2$), 32.6 (CH of $DH_2CC_6H_4\underline{C}(H)(CH_3)_2$), 23.8 ($CH_3$ of $DH_2CC_6H_4C(H)(\underline{C}H_3)_2$), 21.1 ($CH_3$ of $DH_2CC_6H_4C(H)(\underline{C}H_3)_2$), 19.0 ($CH_3$ of $DH_2\underline{C}C_6H_4C(H)(CH_3)_2$).

ASSOCIATED CONTENT

(Word Style "TE_Supporting_Information"). **Supporting Information**. CIF files containing crystallographical data for compounds **1**, **2**, **5**, **6**, **11** and **12**. 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.

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Notes

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ABBREVIATIONS
Cp*, pentamethylcyclopentadienyl. C_g, centroid.

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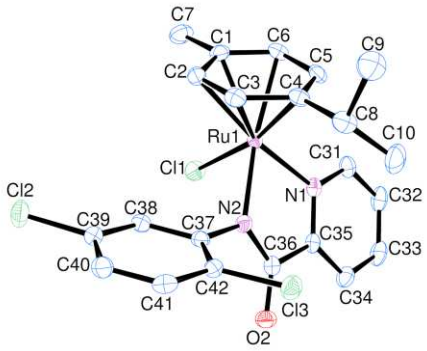
TOC Graphic



Novel rhodium, iridium and ruthenium half-sandwich complexes containing (*N,N*)-bound picolinamide ligands have been prepared for use as anti-cancer agents. The complexes show promising cytotoxicities, with the presence, position and number of halides having a significant effect on the corresponding IC_{50} value. A ruthenium complex is more cytotoxic than cisplatin on HT-29 cells and it remains active even under hypoxic conditions making it a promising candidate for in vivo studies.