

# Arene–ruthenium complexes with ferrocene-derived ligands: Synthesis and characterization of complexes of the type [Ru( $\eta^6$ -arene)(NC<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>NHOC–C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>5</sub>)Cl<sub>2</sub>] and [Ru( $\eta^6$ -arene)(NC<sub>3</sub>H<sub>3</sub>N(CH<sub>2</sub>)<sub>2</sub>O<sub>2</sub>C–C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>5</sub>)Cl<sub>2</sub>]

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## ABSTRACT

Arene–ruthenium complexes of general formula [Ru( $\eta^6$ -arene)(L)Cl<sub>2</sub>] where L = NC<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>NHOC–C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>5</sub>, arene = *p*-<sup>i</sup>PrC<sub>6</sub>H<sub>4</sub>Me (**1**) or C<sub>6</sub>Me<sub>6</sub> (**2**); L = NC<sub>3</sub>H<sub>3</sub>N(CH<sub>2</sub>)<sub>2</sub>O<sub>2</sub>C–C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>5</sub>, arene = *p*-<sup>i</sup>PrC<sub>6</sub>H<sub>4</sub>Me (**3**) or C<sub>6</sub>Me<sub>6</sub> (**4**), and diruthenium–arene complexes of general formula [Ru( $\eta^6$ -arene)Cl<sub>2</sub>]<sub>2</sub>(L) where L = 1,1'-(NC<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>NHOC)–C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>4</sub>, arene = *p*-<sup>i</sup>PrC<sub>6</sub>H<sub>4</sub>Me (**5**) or C<sub>6</sub>Me<sub>6</sub> (**6**); L = 1,1'-(NC<sub>3</sub>H<sub>3</sub>N(CH<sub>2</sub>)<sub>2</sub>O<sub>2</sub>C)–C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>4</sub>, arene = *p*-<sup>i</sup>PrC<sub>6</sub>H<sub>4</sub>Me (**7**) or C<sub>6</sub>Me<sub>6</sub> (**8**) have been synthesized and characterized. The molecular structures of **1** and **3** were confirmed by single-crystal X-ray diffraction. The *in vitro* anticancer activities of complexes **1–8** have been studied comparatively to the uncoordinated ligands. The complexes exhibit fairly low cytotoxicities in comparison to related ferrocene-derived arene–ruthenium complexes.

**Keywords:** Ruthenium Anticancer agents Bioorganometallic chemistry Arene ligands Ferrocene-derived ligands

Dedicated to Prof. Gérard Jaouen on the occasion of his 65th birthday.

## 1. Introduction

The design and synthesis of metal-based anti-tumor drugs have been extensively studied following the discovery of the anticancer activity of cisplatin by Rosenberg [1], which remains the most commonly used anti-tumor drug in the world [2]. The quest for other platinum-based drugs arises from the high toxicity of cisplatin which gives rise to unwanted side effects and consequently limits its administered dose [3], and the resistance of some tumors to cisplatin [4]. In addition to the development of platinum drugs, other metal-based anticancer agents have been developed, which combine good cytotoxic activity with reduced general toxicity and side effects. In this respect, iron and ruthenium-based drugs appear to be good alternatives to platinum drugs, and considerable advances have been made on anticancer drugs based on these metals [5,6], taking into account that iron and ruthenium compounds are well tolerated *in vivo*, and exhibit low general toxicity compared to their platinum counterparts. For ruthenium, this feature has been ascribed to two main reasons: first, the accumulation of ruthenium compounds in tumors, due to the ability of ruthenium

to mimic iron in binding to transferrin (receptors of transferrin are over-expressed on cancer cells) [7,8]; and second, the well-accepted phenomena of “activation by reduction” from Ru(III) → Ru(II) *in vivo*, which is favored in the hypoxic environment of a tumor [7].

It has been shown that simple ferrocene compounds exhibit good cytotoxicities *in vitro* and inhibit the development of tumors *in vivo* [9]. Jaouen has shown that appending the ferrocenyl unit to biologically active molecules led to complexes with an increased potency and tumor specificity possibly due to the combined action of the organic molecule with Fenton chemistry of the Fe center [10]. Ferrocene has been linked to others transition-metals such as platinum [11,12] and gold [13] centers in order to achieve synergic effects between the two active metals.

Arenes are known to stabilize ruthenium in its +2 oxidation state, the active form of such complexes, therefore arene–ruthenium complexes have become intensively studied anticancer agents in recent years. The first complex evaluated was [Ru( $\eta^6$ -benzene)(metronidazole)Cl<sub>2</sub>], which presented a higher activity compared to the anti-tumor drug metronidazole itself [14], and more recently [Ru( $\eta^6$ -arene)(pta)Cl<sub>2</sub>] [15] (pta = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane), [Ru( $\eta^6$ -arene)(YZ)Cl][PF<sub>6</sub>] [16] (YZ = chelating diamine) as well as dinuclear compounds [17],

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and the tri [18] and tetranuclear clusters [19] such as  $[\text{H}_3\text{Ru}_3(\eta^6\text{-C}_6\text{H}_6)(\eta^6\text{-C}_6\text{Me}_6)_2\text{O}]^+$  and  $[\text{H}_4\text{Ru}_4(\eta^6\text{-C}_6\text{H}_6)_4]^{2+}$  have been studied *in vitro* for their activity.

In a recent study arene-ruthenium fragments coordinated to pyridyl-ferrocene ligands [20] were found to exhibit good cytotox-

icities against A2780 and A2780cisR (cisplatin resistant) ovarian carcinoma cell lines, and subsequently we designed a new series of arene-ruthenium complexes containing ferrocene-derived ligands. In this paper we describe these new compounds of general formula  $[\text{Ru}(\eta^6\text{-arene})\text{Cl}_2]_2(\text{L})$  bearing terminal ( $n = 1$ ), or bridging ( $n = 2$ ) ferrocene derivatives as ligands L. The synthesis, characterization, and *in vitro* cytotoxic activity on A2780 cell line of these ferrocene-containing arene-ruthenium complexes, and the free ligands, are reported.

## 2. Results and discussion

### 2.1. Synthesis and characterization of 1–4

In order to access new potential cytotoxic arene-Ru(II) complexes coordinated to ferrocene-derived ligands the four following ligands were designed. The ligands **L**<sup>1</sup> and **L**<sup>3</sup> contain pyridyl connectors for coordination to ruthenium, and ligands **L**<sup>2</sup> and **L**<sup>4</sup> contain imidazolyl connectors (Chart 1).

The complexes  $[\text{Ru}(\eta^6\text{-arene})\text{Cl}_2]_2$  (arene = *p*-<sup>i</sup>PrC<sub>6</sub>H<sub>4</sub>Me or C<sub>6</sub>Me<sub>6</sub>) [21] react in dichloromethane at room temperature with two equivalents of the pyridyl-ferrocene ligand (NC<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>NHOC-C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>5</sub>) **L**<sup>1</sup> to afford the complexes  $[\text{Ru}(\eta^6\text{-}p\text{-}^i\text{PrC}_6\text{H}_4\text{Me})(\text{L}^1)\text{Cl}_2]$  (**1**) and  $[\text{Ru}(\eta^6\text{-C}_6\text{Me}_6)(\text{L}^1)\text{Cl}_2]$  (**2**), respectively. The analogous reaction between the arene-ruthenium complexes and the imidazolyl-ferrocene ligand (NC<sub>3</sub>H<sub>3</sub>N(CH<sub>2</sub>)<sub>2</sub>O<sub>2</sub>C-C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>5</sub>) **L**<sup>2</sup> affords the complexes  $[\text{Ru}(\eta^6\text{-}p\text{-}^i\text{PrC}_6\text{H}_4\text{Me})(\text{L}^2)\text{Cl}_2]$  (**3**) and  $[\text{Ru}(\eta^6\text{-C}_6\text{Me}_6)(\text{L}^2)\text{Cl}_2]$  (**4**) (Scheme 1). In contrast, the reaction of  $[\text{Ru}(\eta^6\text{-arene})\text{Cl}_2]_2$  with 1 equiv. of the dipyriddy-ferrocene ligand (1,1'-(NC<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>NHOC)<sub>2</sub>-C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>4</sub>) **L**<sup>3</sup> gives  $[\text{Ru}(\eta^6\text{-}p\text{-}^i\text{PrC}_6\text{H}_4\text{Me})\text{Cl}_2]_2(\text{L}^3)$  (**5**) and  $[\text{Ru}(\eta^6\text{-C}_6\text{Me}_6)\text{Cl}_2]_2(\text{L}^3)$  (**6**) and the reaction with 1 equiv. of the di-imidazolyl-ferrocene ligand (1,1'-(NC<sub>3</sub>H<sub>3</sub>N(CH<sub>2</sub>)<sub>2</sub>O<sub>2</sub>C)<sub>2</sub>-C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>4</sub>) **L**<sup>4</sup> yields  $[\text{Ru}(\eta^6\text{-}p\text{-}^i\text{PrC}_6\text{H}_4\text{Me})\text{Cl}_2]_2(\text{L}^4)$  (**7**) and  $[\text{Ru}(\eta^6\text{-C}_6\text{Me}_6)\text{Cl}_2]_2(\text{L}^4)$  (**8**) (Scheme 2). All the products are obtained by precipitation as air-stable orange to red powders (see Section 3).

Compounds **1–8** are soluble in halogenated solvents and polar organic solvents such as tetrahydrofuran, methanol or dimethylsulfoxide and also slightly soluble in water. All complexes were characterized by <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR spectroscopy, by mass spectrometry as well as by elemental analysis (see Section 3).

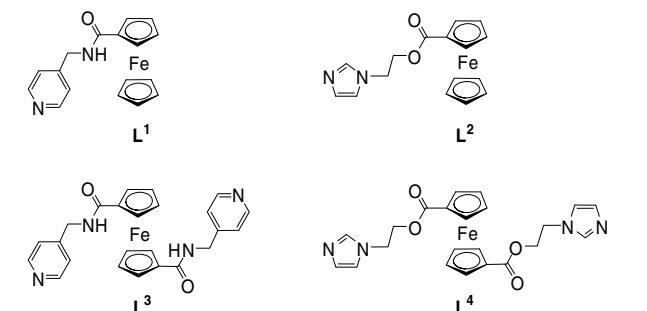
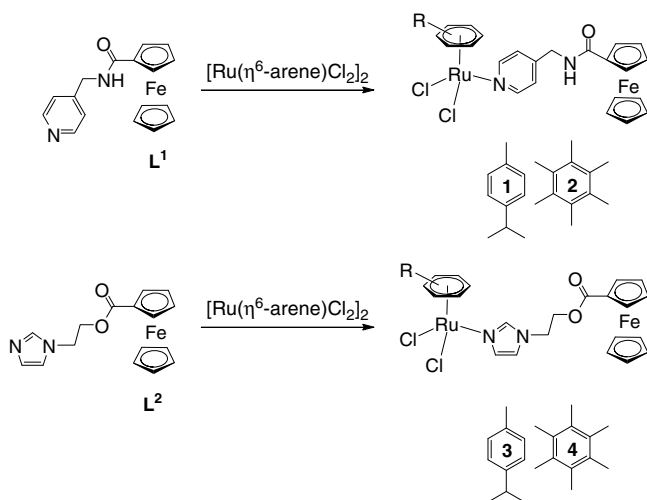
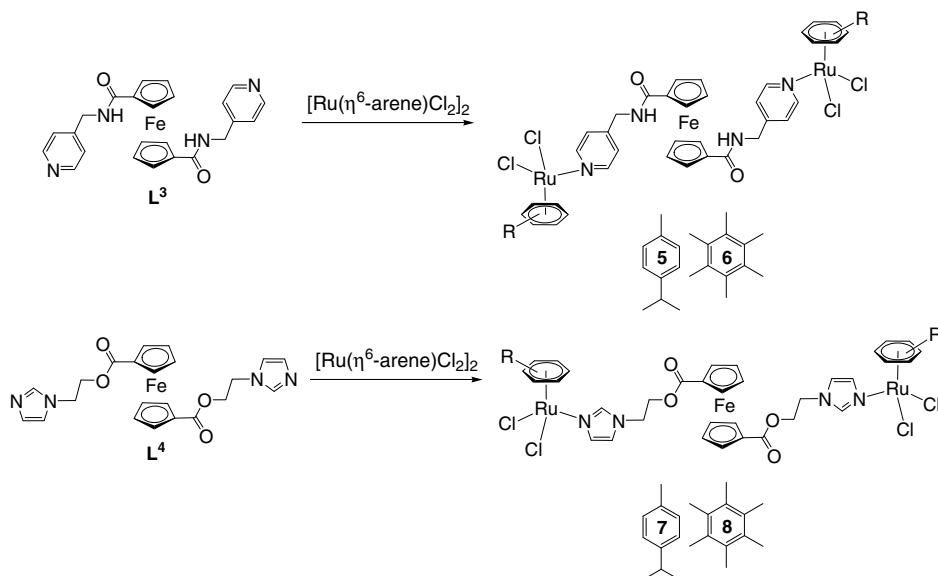


Chart 1.



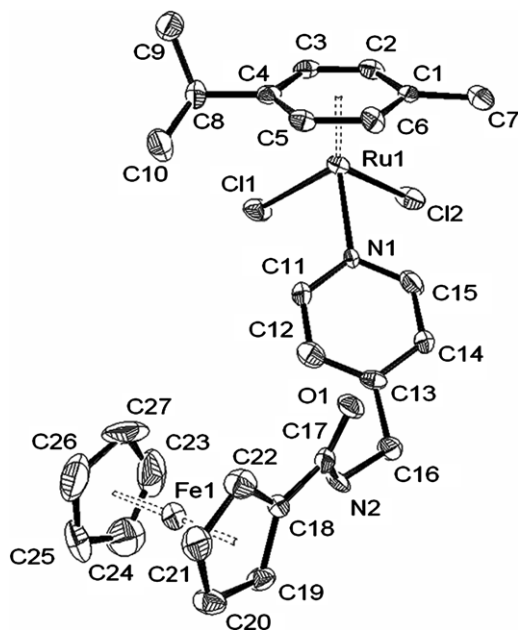
Scheme 1. Synthesis of complexes 1–4.



Scheme 2. Synthesis of complexes 5–8.

The single-crystal X-ray structure analysis of **1** confirms the expected structure which is presented in Fig. 1 with selected bond parameters. The ruthenium center in **1** possesses a pseudo-octahedral geometry and the ferrocene adopts an eclipsed conformation. The metric parameters around the metallic core compare well with those of the "ester" analogue  $[\text{Ru}(\eta^6\text{-}p\text{-}\text{PrC}_6\text{H}_4\text{Me})(\text{NC}_5\text{H}_4\text{O}_2\text{C-C}_5\text{H}_4\text{FeC}_5\text{H}_5)\text{Cl}_2]$  and other related imidazolyl species [22].

In the crystal packing of **1**, two molecules form a dimeric structure through  $\text{N-H}\cdots\text{Cl}$  and  $\text{C-H}\cdots\text{Cl}$  hydrogen-bonds and  $\pi$ -stack-



**Fig. 1.** ORTEP diagram of complex **1** ·  $\text{CHCl}_3$ . Hydrogen atoms and solvating  $\text{CHCl}_3$  molecule are omitted for clarity. Selected bond lengths (Å) and angles (°): Ru1–Cl1 2.397(2), Ru1–Cl2 2.408(2), Ru1–N1 2.131(4), N2–C16 1.452(7), N2–C17 1.351(8), C17–O1 1.233(7), C17–C18 1.483(7), C11–Ru1–Cl2 87.85(6), N1–Ru1–Cl1 87.01(14), N1–Ru1–Cl2 85.67(13), C16–N2–C17 120.0(5), O1–C17–N2 121.9(5), O1–C17–C18 120.9(6).

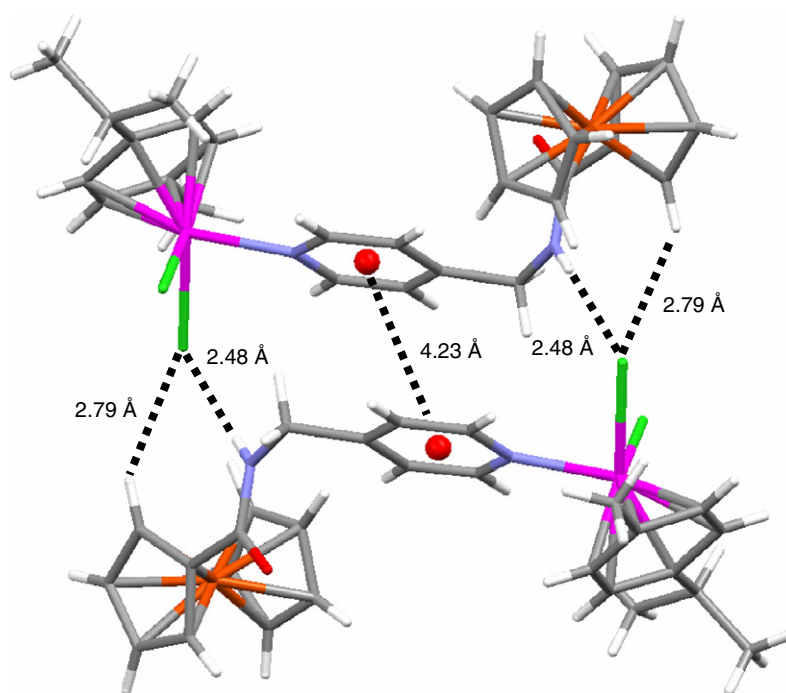
ing interactions between the parallel aromatic rings of two adjacent complexes, see Fig. 2. The centroid–centroid separation of the slipped parallel  $\pi$ -interacting system is 4.23 Å, while the  $\text{N}\cdots\text{Cl}$  and  $\text{C}\cdots\text{Cl}$  distances of the hydrogen-bonds are 3.301(5) and 3.595(6) Å with  $\text{N-H}\cdots\text{Cl}$  and  $\text{C-H}\cdots\text{Cl}$  angles of 160.6 and 145.3°, respectively.

Complex **3** crystallizes with two independent molecules per asymmetric unit, see Fig. 3. In both forms the ferrocene is found in an eclipsed conformation and the ruthenium center adopts a pseudo-octahedral geometry. The bond lengths and angles fit well with those of **1** and other analogues [20,22] although the spatial orientation of the ferrocene unit differs significantly between the two independent molecules. Indeed, in the first molecule, the ferrocene group points away from the *p*-cymene ligand, while in the second molecule, the ferrocene group faces the *p*-cymene ligand. Thus, in the crystal packing of **3**, the two ferrocene units face one another in a staggered conformation: the iron–iron distance between the two ferrocene units being 5.4566(8) Å.

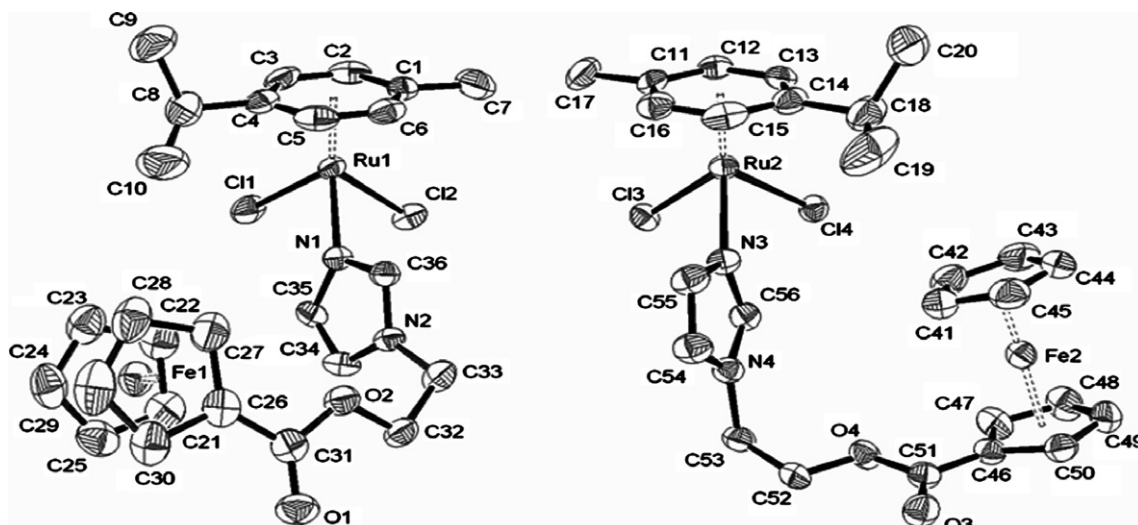
## 2.2. Cytotoxicity of **L**<sup>1</sup>–**L**<sup>4</sup> and **1**–**8**

The cytotoxicity of the ligands **L**<sup>1</sup>–**L**<sup>4</sup> and complexes **1**–**8** towards the A2780 ovarian cancer cell line was evaluated *in vitro* using the MTT assay which measures mitochondrial dehydrogenase activity as an indication of cell viability (see Section 3). The compounds are incubated at various concentrations in the A2780 cells and the cell viability measured after an incubation period of 72 h. Each experiment is conducted in duplicate and the  $\text{IC}_{50}$  values listed in Table 1 are calculated as an average over the two experiments.

The ligands **L**<sup>1</sup>–**L**<sup>4</sup> have  $\text{IC}_{50}$  values all greater than 329  $\mu\text{M}$ , whereas the complexes **1**–**8** are more cytotoxic with  $\text{IC}_{50}$  values in the range 103–390  $\mu\text{M}$ . Although the complexes can be described as only slightly cytotoxic towards A2780 cancer cells, they are more active than other ruthenium compounds described in the literature such as  $[\text{Ru}(\eta^6\text{-}p\text{-}\text{PrC}_6\text{H}_4\text{Me})(\text{pta})\text{Cl}_2]$  (>300  $\mu\text{M}$ ) [23a] and  $[\text{Ru}(\eta^5\text{-C}_5\text{H}_5)(\text{pta})_2\text{Cl}]$  (>1000  $\mu\text{M}$ ) [23b].



**Fig. 2.** Dimeric structure of **1** showing the hydrogen-bonded network and the intermolecular  $\pi$ -stacking interaction (symmetry code: 1–*x*, 1–*y*, –*z*).



**Fig. 3.** ORTEP diagram of the two forms present in the crystal of complex **3**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°) for the Ru1 molecule: Cl1–Ru1 2.4153(9), Cl2–Ru1 2.4229(9), N1–Ru1 2.119(2), C32–O2 1.446(4), C31–O1 1.198(4), C26–C31 1.473(5), Cl1–Ru1–Cl2 85.82(4), N1–Ru1–Cl1 88.65(7), N1–Ru1–Cl2 81.45(8), C35–N1–Ru1 128.6(2), C36–N1–Ru1 123.5(2), C31–O2–C32 115.2(3), O1–C31–O2 123.2(3), O1–C31–C26 125.2(4), C33–C32–O2–C31 168.0(3), O2–C32–C33–N2 –57.9(4), C26–C31–O2–C32 –170.7(3). Selected bond lengths (Å) and angles (°) for the Ru2 molecule: Cl3–Ru2 2.4251(9), Cl4–Ru2 2.4273(9), N3–Ru2 2.131(2), C52–O4 1.444(4), C51–O3 1.209(4), C46–C51 1.450(5), Cl3–Ru2–Cl4 87.04(3), N3–Ru2–Cl3 83.97(8), N3–Ru2–Cl4 106.09(12), C55–N3–Ru2 126.5(2), C56–N3–Ru2 127.2(2), C51–O4–C52 115.5(2), O3–C51–O4 122.6(3), O3–C51–C46 125.7(3), C53–C52–O4–C51 170.6(3), O4–C52–C53–N4 –78.9(4), C46–C51–O4–C52 –179.4(3).

**Table 1**  
IC<sub>50</sub> values of ligands **L**<sup>1–4</sup> and complexes **1–8** in A2780 human ovarian cancer cells after 72 h

| Compound              | IC <sub>50</sub> (μM) |
|-----------------------|-----------------------|
| <b>L</b> <sup>1</sup> | 329                   |
| <b>L</b> <sup>2</sup> | 335                   |
| <b>L</b> <sup>3</sup> | >500                  |
| <b>L</b> <sup>4</sup> | 410                   |
| <b>1</b>              | 390                   |
| <b>2</b>              | 225                   |
| <b>3</b>              | 130                   |
| <b>4</b>              | 103                   |
| <b>5</b>              | 341                   |
| <b>6</b>              | 235                   |
| <b>7</b>              | 230                   |
| <b>8</b>              | 170                   |

Some structure–activity relationships can be made from an analysis of **1–8**. For each pair of related complexes the hexamethylbenzene derivative is more active than the *p*-cymene derivative, presumably due to the greater hydrophobicity of the hexamethylbenzene ring which facilitates transport of the complex into the cancer cell. Furthermore, the imidazolyl-linked complexes are more cytotoxic than their related pyridyl-linked counterparts. The reason for this could be related to the differences in the strength of these different groups to coordinate to the arene–ruthenium(II) fragment, differences in the transmission of electronic effects between the metal centers or due to the relative stability of the amide and ester bonds. Other arene–ruthenium complexes with imidazolyl-groups have been reported and also show interesting *in vitro* characteristics [24]. The higher cytotoxicities of the ester-linked complexes relative to the amide-linked systems could be a consequence of the ester-linkage which is more prone to hydrolytic cleavage by esterases present in the cell cytoplasm [25]. Potentially, the release of the ferrocene unit activates it once inside the cell.

It is particularly interesting that the complexes containing two arene–ruthenium fragments (**5–8**) have similar activities to the mono-ruthenium complexes (**1–4**). However, this result contrasts with the results obtained for arene–ruthenium complexes connected via a shorter linkage [20] which were about twice as

cytotoxic as compared to their mononuclear counterparts. These complexes were also more cytotoxic than the compounds reported herein with IC<sub>50</sub> values in the range 15–50 μM in the same cell line.

Despite the low cytotoxicities of **1–8** a number of ruthenium-based compounds have been found to show very good *in vivo* activity although they display only a low *in vitro* cytotoxicity [15,26]. Indeed, there does not appear to be a close correlation between *in vitro* and *in vivo* activity for ruthenium compounds and alternative assays that avoid use of animals are under development [27].

### 3. Experimental

#### 3.1. General remarks

All reagents were purchased either from Aldrich or Fluka and used as received. The complexes [Ru(η<sup>6</sup>-arene)Cl<sub>2</sub>]<sub>2</sub>, ferrocene carboxylic acid chloride and 1,1'-ferrocene dicarboxylic acid chloride were prepared according to literature methods [22,28]. NMR spectra were recorded on a Bruker AMX 400 spectrometer using the residual proton resonance of the deuterated solvent as an internal standard. Elemental analyses were performed by the Laboratory of Pharmaceutical Chemistry, University of Geneva (Switzerland) or by the Mikroelementaranalytisches Laboratorium, ETH Zürich (Switzerland). Electrospray mass spectra were performed by the Service Analytique Facultaire of the University of Neuchâtel (Switzerland).

#### 3.1.1. Synthesis of ligands **L**<sup>1–4</sup>

**3.1.1.1.** (NC<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>NHOC–C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>5</sub>) (**L**<sup>1</sup>). In a Schlenk tube, a solution of ferrocene carboxylic acid (1 g, 4.34 mmol), *N,N'*-dicyclohexylcarbodiimide (1.67 g, 8.69 mmol), 4-(dimethylamino)pyridine (1.06 g, 8.69 mmol), 4-pyrrolidinopyridine (1.29 g, 8.69 mmol) and 4-picolyamine (1.32 mL, 13.04 mmol) was dissolved in anhydrous dichloromethane (50 mL). The solution was stirred under inert atmosphere at room temperature for 2 days, then the solution was filtered on celite and the product was obtained as an orange powder after purification on silica gel (eluent: methanol/ethyl acetate 1:2). Yield: 54%, 753 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.60 (d, 2H, NC<sub>5</sub>H<sub>4</sub>, <sup>3</sup>J = 6.0 Hz), 7.28 (d, 2H,

$\text{NC}_5\text{H}_4$ ,  $^3J = 6.0$  Hz), 6.09 (br, 1H, NH), 4.71 (t, 2H,  $\text{CH}_{\text{Fc}}$ ,  $^3J = 2.0$  Hz), 4.59 (d, 2H,  $\text{NHCH}_2$ ,  $^3J = 6.0$  Hz), 4.39 (t, 2H,  $\text{CH}_{\text{Fc}}$ ,  $^3J = 2.0$  Hz), 4.21 (s, 5H,  $\text{CH}_{\text{Fc}}$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.61$  (CONH), 150.15 ( $\text{NC}_5\text{H}_4$ ), 147.93 ( $\text{NC}_5\text{H}_4$ ), 122.38 ( $\text{NC}_5\text{H}_4$ ), 95.0, 70.74, 69.78, 68.18 ( $\text{CH}_{\text{Fc}}$ ), 42.41 ( $\text{CH}_2$ ). ESI-MS:  $m/z = 321.1$   $[\text{M}+\text{H}]^+$ .

3.1.1.2.  $(\text{NC}_3\text{H}_3\text{N}(\text{CH}_2)_2\text{O}_2\text{C}-\text{C}_5\text{H}_4\text{FeC}_5\text{H}_5)$  (**L**<sup>2</sup>). In a Schlenk tube, freshly prepared ferrocene carboxylic acid chloride (1 g, 4.0 mmol), 1-(2-hydroxyethyl)imidazole (542 mg, 4.48 mmol) and triethylamine (3 mL) were dissolved in anhydrous dichloromethane (30 mL). The solution was stirred under an inert atmosphere at room temperature for 3 days, then the solution was filtered on celite and the product was obtained as an orange powder after purification on silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{acetone}$  1:1). Yield: 48%, 680 mg.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.61$  (s, 1H,  $\text{NC}_3\text{H}_3\text{N}$ ), 7.13 (s, 1H,  $\text{NC}_3\text{H}_3\text{N}$ ), 7.05 (s, 1H,  $\text{NC}_3\text{H}_3\text{N}$ ), 4.78 (t, 2H,  $\text{COOCH}_2$ ,  $^3J = 1.8$  Hz), 4.47 (t, 2H,  $\text{CH}_{\text{Fc}}$ ,  $^3J = 5.2$  Hz), 4.43 (t, 2H,  $\text{COOCH}_2\text{CH}_2$ ,  $^3J = 1.8$  Hz), 4.30 (t, 2H,  $\text{CH}_{\text{Fc}}$ ,  $^3J = 5.2$  Hz), 4.14 (s, 5H,  $\text{CH}_{\text{Fc}}$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.44$  (COO), 137.55 ( $\text{NC}_3\text{H}_3\text{N}$ ), 129.97 ( $\text{NC}_3\text{H}_3\text{N}$ ), 118.98 ( $\text{NC}_3\text{H}_3\text{N}$ ), 71.70, 70.15, 69.94, 69.87 ( $\text{CH}_{\text{Fc}}$ ), 63.02 ( $\text{CH}_2$ ), 46.01 ( $\text{CH}_2$ ). ESI-MS:  $m/z = 347.05$   $[\text{M}+\text{Na}]^+$ .

3.1.1.3.  $(1,1'-(\text{NC}_5\text{H}_4\text{CH}_2\text{NHOC})_2-\text{C}_5\text{H}_4\text{FeC}_5\text{H}_4)$  (**L**<sup>3</sup>). In a Schlenk tube, freshly prepared 1,1'-ferrocene dicarboxylic acid chloride (500 mg, 1.61 mmol), 4-picolylamine (0.65 mL, 6.43 mmol) and 1 mL of triethylamine were dissolved in anhydrous dichloromethane (30 mL). The solution was stirred under inert atmosphere at room temperature for 6 h, then the solution was filtered on celite and the product was obtained as a red powder after purification on silica gel (eluent: ethanol). Yield: 47%, 344 mg.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.54$  (d, 4H,  $\text{NC}_5\text{H}_4$ ,  $^3J = 6.0$  Hz), 7.58 (t, 2H, NH,  $^3J = 6.0$  Hz), 7.27 (d, 4H,  $\text{NC}_5\text{H}_4$ ,  $^3J = 6.0$  Hz), 4.55 (d, 4H,  $\text{NHCH}_2$ ,  $^3J = 6.0$  Hz), 4.51 (t, 4H,  $\text{CH}_{\text{Fc}}$ ,  $^3J = 2.0$  Hz), 4.39 (t, 4H,  $\text{CH}_{\text{Fc}}$ ,  $^3J = 2.0$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.93$  (CONH), 149.98 ( $\text{NC}_5\text{H}_4$ ), 147.82 ( $\text{NC}_5\text{H}_4$ ), 122.55 ( $\text{NC}_5\text{H}_4$ ), 78.05, 71.19, 70.94 ( $\text{CH}_{\text{Fc}}$ ), 42.59 ( $\text{CH}_2$ ). ESI-MS:  $m/z = 477.10$   $[\text{M}+\text{Na}]^+$ .

3.1.1.4.  $(1,1'-(\text{NC}_3\text{H}_3\text{N}(\text{CH}_2)_2\text{O}_2\text{C})_2-\text{C}_5\text{H}_4\text{FeC}_5\text{H}_4)$  (**L**<sup>4</sup>). In a Schlenk tube, freshly prepared 1,1'-ferrocene dicarboxylic acid chloride (500 mg, 1.61 mmol), 1-(2-hydroxyethyl)imidazole (721 mg, 6.43 mmol) and pyridine (0.5 mL) were dissolved in anhydrous dichloromethane (30 mL). The solution was stirred under inert atmosphere at room temperature for 6 h, then the solution was filtered on celite and the product was obtained as a red powder after purification on silica gel (eluent: ethanol). Yield: 36%, 267 mg.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.69$  (s, 2H,  $\text{NC}_3\text{H}_3\text{N}$ ), 7.17 (s, 2H,  $\text{NC}_3\text{H}_3\text{N}$ ), 7.10 (s, 2H,  $\text{NC}_3\text{H}_3\text{N}$ ), 4.72 (s, 4H,  $\text{CH}_{\text{Fc}}$ ), 4.46 (t, 4H,  $\text{COOCH}_2$ ,  $^3J = 5.2$  Hz), 4.36 (s, 4H,  $\text{CH}_{\text{Fc}}$ ), 4.32 (t, 4H,  $\text{COOCH}_2\text{CH}_2$ ,  $^3J = 5.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 169.79$  (COO), 137.95 ( $\text{NC}_3\text{H}_3\text{N}$ ), 129.92 ( $\text{NC}_3\text{H}_3\text{N}$ ), 119.04 ( $\text{NC}_3\text{H}_3\text{N}$ ), 73.05, 72.01, 71.72 ( $\text{CH}_{\text{Fc}}$ ), 63.13 ( $\text{CH}_2$ ), 46.16 ( $\text{CH}_2$ ). ESI-MS:  $m/z = 463.13$   $[\text{M}+\text{H}]^+$ .

### 3.1.2. Synthesis of complexes 1–4

3.1.2.1. Synthesis of  $[\text{Ru}(\eta^6\text{-arene})(\text{L})\text{Cl}_2]$ . To a solution of  $[\text{Ru}(\eta^6\text{-arene})\text{Cl}_2]_2$  (100 mg) in dichloromethane (20 mL), 2 equiv. of solid **L**<sup>1</sup> or **L**<sup>2</sup> were added (**1** and **3**: 0.325 mmol, **2** and **4**: 0.3 mmol). The mixture was stirred at room temperature for 24 h. The product was isolated by precipitation with diethyl ether and dried *in vacuo* to afford an orange to red powder.

3.1.2.2.  $[\text{Ru}(\eta^6\text{-p-}^i\text{PrC}_6\text{H}_4\text{Me})(\text{NC}_5\text{H}_4\text{CH}_2\text{NHOC}-\text{C}_5\text{H}_4\text{FeC}_5\text{H}_5)\text{Cl}_2]$  (**1**). Yield: 86%, 176 mg.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.63$  (d, 2H,  $\text{NC}_5\text{H}_4$ ,  $^3J = 6.0$  Hz), 7.53 (br, 1H, NH), 7.02 (d, 2H,  $\text{NC}_5\text{H}_4$ ,  $^3J = 6.0$  Hz), 5.42 (d, 2H,  $\text{C}_6\text{H}_4$ ,  $^3J = 6.0$  Hz), 5.14 (d, 2H,  $\text{C}_6\text{H}_4$ ,  $^3J = 6.0$  Hz), 4.94 (s, 2H,  $\text{CH}_{\text{Fc}}$ ), 4.32 (s, 2H,  $\text{CH}_{\text{Fc}}$ ), 4.20 (s, 5H,  $\text{CH}_{\text{Fc}}$ ),

4.11 (d, 2H,  $\text{NHCH}_2$ ,  $^3J = 5.2$  Hz), 3.00 (sept, 1H,  $\text{CH}(\text{CH}_3)_2$ ,  $^3J = 7.0$  Hz), 1.99 (s, 3H,  $\text{CH}_3$ ), 1.31 (d, 6H,  $\text{CH}(\text{CH}_3)_2$ ,  $^3J = 7.0$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.24$  (CONH), 153.85 ( $\text{NC}_5\text{H}_4$ ), 152.85 ( $\text{NC}_5\text{H}_4$ ), 122.33 ( $\text{NC}_5\text{H}_4$ ), 103.88 ( $\text{C}-\text{CH}(\text{CH}_3)_2$ ), 97.21 ( $\text{C}-\text{CH}_3$ ), 83.15, 82.16 ( $\text{C}_6\text{H}_4$ ), 75.72, 70.64, 69.94, 69.15 ( $\text{CH}_{\text{Fc}}$ ), 41.56 ( $\text{CH}_2$ ), 30.90 ( $\text{CH}(\text{CH}_3)_2$ ), 22.46 ( $\text{CH}(\text{CH}_3)_2$ ), 18.42 ( $\text{CH}_3$ ). ESI-MS:  $m/z = 626.9$   $[\text{M}+\text{H}]^+$ . Anal. Calc. for  $\text{C}_{27}\text{H}_{30}\text{FeN}_2\text{O}_2\text{RuCl}_2$  (626.36) C, 51.77; H, 4.83; N, 4.47. Found: 51.42; H, 4.89; N, 4.20%.

3.1.2.3.  $[\text{Ru}(\eta^6\text{-C}_6\text{Me}_6)(\text{NC}_5\text{H}_4\text{CH}_2\text{NHOC}-\text{C}_5\text{H}_4\text{FeC}_5\text{H}_5)\text{Cl}_2]$  (**2**). Yield: 59%, 115 mg.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.40$  (d, 2H,  $\text{NC}_5\text{H}_4$ ,  $^3J = 6.4$  Hz), 7.64 (br, 1H, NH), 7.01 (d, 2H,  $\text{NC}_5\text{H}_4$ ,  $^3J = 6.4$  Hz), 4.94 (t, 2H,  $\text{CH}_{\text{Fc}}$ ,  $^3J = 2.0$  Hz), 4.29 (t, 2H,  $\text{CH}_{\text{Fc}}$ ,  $^3J = 2.0$  Hz), 4.19 (s, 5H,  $\text{CH}_{\text{Fc}}$ ), 4.15 (d, 2H,  $\text{NHCH}_2$ ,  $^3J = 6.0$  Hz), 1.93 (s, 18H,  $\text{CH}_3$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.97$  (CONH), 153.23 ( $\text{NC}_5\text{H}_4$ ), 152.28 ( $\text{NC}_5\text{H}_4$ ), 123.22 ( $\text{NC}_5\text{H}_4$ ), 91.25 ( $\text{C}-\text{CH}_3$ ), 75.91, 70.26, 69.74, 68.94 ( $\text{CH}_{\text{Fc}}$ ), 41.06 ( $\text{CH}_2$ ), 15.46 ( $\text{CH}_3$ ). ESI-MS:  $m/z = 633.06$   $[\text{M}-2\text{Cl}+\text{MeOH}+\text{H}_2\text{O}]^+$ . Anal. Calc. for  $\text{C}_{29}\text{H}_{34}\text{FeN}_2\text{O}_2\text{RuCl}_2 \cdot 1/5 \text{CH}_2\text{Cl}_2$  (671.40) C, 52.24; H, 5.16; N, 4.17. Found: C, 52.27; H, 5.38; N, 4.13%.

3.1.2.4.  $[\text{Ru}(\eta^6\text{-p-}^i\text{PrC}_6\text{H}_4\text{Me})(\text{NC}_3\text{H}_3\text{N}(\text{CH}_2)_2\text{O}_2\text{C}-\text{C}_5\text{H}_4\text{FeC}_5\text{H}_5)\text{Cl}_2]$  (**3**). Yield: 70%, 145 mg.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.99$  (s, 1H,  $\text{NC}_3\text{H}_3\text{N}$ ), 7.31 (s, 1H,  $\text{NC}_3\text{H}_3\text{N}$ ), 7.00 (s, 1H,  $\text{NC}_3\text{H}_3\text{N}$ ), 5.39 (d, 2H,  $\text{C}_6\text{H}_4$ ,  $^3J = 5.6$  Hz), 5.20 (d, 2H,  $\text{C}_6\text{H}_4$ ,  $^3J = 5.6$  Hz), 4.81 (s, 2H,  $\text{CH}_{\text{Fc}}$ ), 4.44 (ps s, 4H,  $\text{COOCH}_2$ ,  $\text{CH}_{\text{Fc}}$ ), 4.18 (ps s, 7H,  $\text{COOCH}_2\text{CH}_2$ ,  $\text{CH}_{\text{Fc}}$ ), 2.94 (sept, 1H,  $\text{CH}(\text{CH}_3)_2$ ,  $^3J = 6.8$  Hz), 2.12 (s, 3H,  $\text{CH}_3$ ), 1.24 (d, 6H,  $\text{CH}(\text{CH}_3)_2$ ,  $^3J = 6.8$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.50$  (COO), 140.41 ( $\text{NC}_3\text{H}_3\text{N}$ ), 132.35 ( $\text{NC}_3\text{H}_3\text{N}$ ), 120.17 ( $\text{NC}_3\text{H}_3\text{N}$ ), 102.85 ( $\text{C}-\text{CH}(\text{CH}_3)_2$ ), 97.39 ( $\text{C}-\text{CH}_3$ ), 82.59, 81.65 ( $\text{C}_6\text{H}_4$ ), 72.03, 70.44, 70.12, 69.95 ( $\text{CH}_{\text{Fc}}$ ), 62.68 ( $\text{CH}_2$ ), 47.53 ( $\text{CH}_2$ ), 30.84 ( $\text{CH}(\text{CH}_3)_2$ ), 22.44 ( $\text{CH}(\text{CH}_3)_2$ ), 18.70 ( $\text{CH}_3$ ). ESI-MS:  $m/z = 595.06$   $[\text{M}-\text{Cl}]^+$ . Anal. Calc. for  $\text{C}_{26}\text{H}_{30}\text{FeN}_2\text{O}_2\text{RuCl}_2$  (630.35) C, 49.54; H, 4.80; N, 4.44. Found: C, 49.40; H, 4.87; N, 4.35%.

3.1.2.5.  $[\text{Ru}(\eta^6\text{-C}_6\text{Me}_6)(\text{NC}_3\text{H}_3\text{N}(\text{CH}_2)_2\text{O}_2\text{C}-\text{C}_5\text{H}_4\text{FeC}_5\text{H}_5)\text{Cl}_2]$  (**4**). Yield: 63%, 124 mg.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.81$  (s, 1H,  $\text{NC}_3\text{H}_3\text{N}$ ), 7.37 (s, 1H,  $\text{NC}_3\text{H}_3\text{N}$ ), 7.12 (s, 1H,  $\text{NC}_3\text{H}_3\text{N}$ ), 4.80 (m, 4H,  $\text{CH}_2$ ,  $\text{CH}_{\text{Fc}}$ ), 4.40 (m, 4H,  $\text{CH}_2$ ,  $\text{CH}_{\text{Fc}}$ ), 4.19 (s, 5H,  $\text{CH}_{\text{Fc}}$ ), 1.96 (s, 18H,  $\text{CH}_3$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.24$  (COO), 139.48 ( $\text{NC}_3\text{H}_3\text{N}$ ), 131.56 ( $\text{NC}_3\text{H}_3\text{N}$ ), 118.98 ( $\text{NC}_3\text{H}_3\text{N}$ ), 90.75 ( $\text{C}-\text{CH}_3$ ), 71.82, 70.22, 69.96, 69.86 ( $\text{CH}_{\text{Fc}}$ ), 62.69 ( $\text{CH}_2$ ), 47.15 ( $\text{CH}_2$ ), 15.58 ( $\text{C}-\text{CH}_3$ ). ESI-MS:  $m/z = 623.07$   $[\text{M}-\text{Cl}]^+$ . Anal. Calc. for  $\text{C}_{28}\text{H}_{34}\text{FeN}_2\text{O}_2\text{RuCl}_2$  (658.40) C, 51.08; H, 5.21; N, 4.25. Found: C, 51.24; H, 5.32; N, 4.14%.

### 3.1.3. Synthesis of complexes 5–8

3.1.3.1. Synthesis of  $[\text{Ru}(\eta^6\text{-arene})\text{Cl}_2]_2$  (**2**). To a solution of  $[\text{Ru}(\eta^6\text{-arene})\text{Cl}_2]_2$  (100 mg) in dichloromethane (20 mL), 1 equiv. of solid **L**<sup>3</sup> or **L**<sup>4</sup> was added (**5** and **7**: 0.163 mmol, **6** and **8**: 0.15 mmol). The mixture was stirred at room temperature for 24 h. Then the product was isolated by precipitation with diethyl ether and dried *in vacuo* to afford an orange to red powder.

3.1.3.2.  $[\text{Ru}(\eta^6\text{-p-}^i\text{PrC}_6\text{H}_4\text{Me})\text{Cl}_2]_2(1,1'-(\text{NC}_5\text{H}_4\text{CH}_2\text{NHOC})_2-\text{C}_5\text{H}_4\text{FeC}_5\text{H}_5)$  (**5**). Yield: 62%, 105 mg.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.78$  (d, 4H,  $\text{NC}_5\text{H}_4$ ,  $^3J = 6.0$  Hz), 8.05 (br, 2H, NH), 7.22 (d, 4H,  $\text{NC}_5\text{H}_4$ ,  $^3J = 6.0$  Hz), 5.36 (d, 4H,  $\text{C}_6\text{H}_4$ ,  $^3J = 6.0$  Hz), 5.15 (d, 4H,  $\text{C}_6\text{H}_4$ ,  $^3J = 6.0$  Hz), 4.78 (s, 4H,  $\text{CH}_{\text{Fc}}$ ), 4.33 (s, 4H,  $\text{CH}_{\text{Fc}}$ ), 4.29 (d, 4H,  $\text{NHCH}_2$ ,  $^3J = 4.4$  Hz), 2.91 (sept, 2H,  $\text{CH}(\text{CH}_3)_2$ ,  $^3J = 6.8$  Hz), 1.95 (s, 6H,  $\text{CH}_3$ ), 1.26 (d, 12H,  $\text{CH}(\text{CH}_3)_2$ ,  $^3J = 6.8$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.87$  (CONH), 154.23 ( $\text{NC}_5\text{H}_4$ ), 151.70 ( $\text{NC}_5\text{H}_4$ ), 123.29 ( $\text{NC}_5\text{H}_4$ ), 103.27 ( $\text{C}-\text{CH}(\text{CH}_3)_2$ ), 97.30 ( $\text{C}-\text{CH}_3$ ), 83.05, 81.93 ( $\text{C}_6\text{H}_4$ ), 80.54, 72.09, 70.68 ( $\text{CH}_{\text{Fc}}$ ), 41.62 ( $\text{CH}_2$ ), 30.70 ( $\text{CH}(\text{CH}_3)_2$ ), 22.28 ( $\text{CH}(\text{CH}_3)_2$ ), 18.27 ( $\text{CH}_3$ ). ESI-MS:  $m/z = 725.14$   $[\text{M}-\text{Cl}-\text{C}_{10}\text{H}_{14}-\text{RuCl}_2]^+$ . Anal. Calc. for  $\text{C}_{44}\text{H}_{50}\text{FeN}_4\text{O}_2\text{Ru}_2\text{Cl}_4$  ·

CH<sub>2</sub>Cl<sub>2</sub> (1151.62) C, 46.93; H, 4.55; N, 4.87. Found: C, 46.55; H, 4.85; N, 4.58%.

3.1.3.3. [Ru( $\eta^6$ -C<sub>6</sub>Me<sub>6</sub>)Cl<sub>2</sub>]<sub>2</sub>(1,1'-(NC<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>NHOC)<sub>2</sub>-C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>4</sub>) (**6**). Yield: 79%, 133 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.52 (d, 4H, NC<sub>5</sub>H<sub>4</sub>, <sup>3</sup>J = 6.0 Hz), 7.92 (br, 2H, NH), 7.17 (d, 4H, NC<sub>5</sub>H<sub>4</sub>, <sup>3</sup>J = 6.0 Hz), 4.74 (s, 4H, CH<sub>FC</sub>), 4.37 (s, 4H, CH<sub>FC</sub>), 4.34 (d, 4H, NHCH<sub>2</sub>, <sup>3</sup>J = 5.6 Hz), 1.91 (s, 36H, CH<sub>3</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.06 (CONH), 153.89 (NC<sub>5</sub>H<sub>4</sub>), 151.67 (NC<sub>5</sub>H<sub>4</sub>), 123.47 (NC<sub>5</sub>H<sub>4</sub>), 91.43 (C-CH<sub>3</sub>), 75.91, 71.96, 70.95 (CH<sub>FC</sub>), 41.53 (CH<sub>2</sub>), 15.64 (CH<sub>3</sub>). ESI-MS: *m/z* = 404.9 [M+3H+(CH<sub>3</sub>)<sub>2</sub>CO+MeOH]<sup>3+</sup>. Anal. Calc. for C<sub>48</sub>H<sub>58</sub>FeN<sub>4</sub>O<sub>2</sub>Ru<sub>2</sub>Cl<sub>4</sub> · CH<sub>2</sub>Cl<sub>2</sub> (1207.73) C, 48.73; H, 5.01; N, 4.64. Found: C, 48.64; H, 5.39; N, 4.51%.

3.1.3.4. [Ru( $\eta^6$ -*p*-iPrC<sub>6</sub>H<sub>4</sub>Me)Cl<sub>2</sub>]<sub>2</sub>(1,1'-(NC<sub>3</sub>H<sub>3</sub>N(CH<sub>2</sub>)<sub>2</sub>O<sub>2</sub>C)<sub>2</sub>-C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>4</sub>) (**7**). Yield: 74%, 87 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.13 (s, 2H, NC<sub>3</sub>H<sub>3</sub>N), 7.31 (s, 2H, NC<sub>3</sub>H<sub>3</sub>N), 7.05 (s, 2H, NC<sub>3</sub>H<sub>3</sub>N), 5.43 (d, 4H, C<sub>6</sub>H<sub>4</sub>, <sup>3</sup>J = 5.4 Hz), 5.25 (d, 4H, C<sub>6</sub>H<sub>4</sub>, <sup>3</sup>J = 5.4 Hz), 4.75 (s, 4H, CH<sub>FC</sub>), 4.44 (s, 4H, CH<sub>FC</sub>), 4.22 (m, 8H, CH<sub>2</sub>), 2.93 (sept, 2H, CH(CH<sub>3</sub>)<sub>2</sub>, <sup>3</sup>J = 6.8 Hz), 2.12 (s, 6H, CH<sub>3</sub>), 1.25 (d, 12H, CH(CH<sub>3</sub>)<sub>2</sub>, <sup>3</sup>J = 6.8 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.82 (COO), 140.50 (NC<sub>3</sub>H<sub>3</sub>N), 131.99 (NC<sub>3</sub>H<sub>3</sub>N), 120.44 (NC<sub>3</sub>H<sub>3</sub>N), 102.58 (C-CH(CH<sub>3</sub>)<sub>2</sub>), 97.38 (C-CH<sub>3</sub>), 82.68 (C<sub>6</sub>H<sub>4</sub>), 81.41 (C<sub>6</sub>H<sub>4</sub>), 72.97, 72.38, 71.99 (CH<sub>FC</sub>), 63.10 (CH<sub>2</sub>), 47.44 (CH<sub>2</sub>), 30.70 (CH(CH<sub>3</sub>)<sub>2</sub>), 22.36 (CH(CH<sub>3</sub>)<sub>2</sub>), 18.55 (CH<sub>3</sub>). ESI-MS: *m/z* = 564.13 [M+2H+H<sub>2</sub>O+MeOH]<sup>2+</sup>.

3.1.3.5. [Ru( $\eta^6$ -C<sub>6</sub>Me<sub>6</sub>)Cl<sub>2</sub>]<sub>2</sub>(1,1'-(NC<sub>3</sub>H<sub>3</sub>N(CH<sub>2</sub>)<sub>2</sub>O<sub>2</sub>C)<sub>2</sub>-C<sub>5</sub>H<sub>4</sub>FeC<sub>5</sub>H<sub>4</sub>) (**8**). Yield: 83%, 140 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.13 (s, 2H, NC<sub>3</sub>H<sub>3</sub>N), 7.09 (s, 2H, NC<sub>3</sub>H<sub>3</sub>N), 6.99 (s, 2H, NC<sub>3</sub>H<sub>3</sub>N), 4.70 (t, 4H, CH<sub>FC</sub>, <sup>3</sup>J = 2.0 Hz), 4.44 (t, 4H, CH<sub>FC</sub>, <sup>3</sup>J = 2.0 Hz), 4.22 (t, 4H, COOCH<sub>2</sub>, <sup>3</sup>J = 4.8 Hz), 3.89 (t, 4H, COOCH<sub>2</sub>CH<sub>2</sub>, <sup>3</sup>J = 4.8 Hz), 2.01 (s, 36H, CH<sub>3</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.85 (COO), 140.06 (NC<sub>3</sub>H<sub>3</sub>N), 131.30 (NC<sub>3</sub>H<sub>3</sub>N), 120.75 (NC<sub>3</sub>H<sub>3</sub>N), 93.09, 90.96, 89.81 (C-CH<sub>3</sub>), 72.89, 72.65, 72.37 (CH<sub>FC</sub>), 63.50 (CH<sub>2</sub>), 47.42 (CH<sub>2</sub>), 15.92 (CH<sub>3</sub>). ESI-MS: *m/z* = 1131.90 [M+H]<sup>+</sup>.

### 3.2. Single crystal X-ray structure analysis

Single crystals of **1** · CHCl<sub>3</sub> and **3** were mounted on a Stoe Image Plate Diffraction equipped with a  $\phi$  circle goniometer, using Mo K $\alpha$  graphite monochromated radiation ( $\lambda$  = 0.71073 Å) with  $\phi$  range 0–200°. The structures were solved by direct methods using the program SHELXS-97 [29]. Refinement and all further calculations were carried out using SHELXL-97 [30]. The H-atoms were included in calculated positions and treated as riding atoms using the SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-square on *F*<sup>2</sup>. Crystallographic details are summarized in Table 2. Figs. 1 and 3 were drawn with ORTEP [31] and Fig. 2 with MERCURY [32].

### 3.3. Cytotoxicity study

The human A2780 ovarian cancer cell line was obtained from the European Collection of Cell Cultures (Salisbury, UK). Cells were grown routinely in RPMI medium containing glucose, 5% foetal calf serum (FCS) and antibiotics at 37 °C and 5% CO<sub>2</sub>. Cytotoxicity was determined using the MTT assay (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2 H-tetrazolium bromide). Cells were seeded in 96-well plates as monolayers with 100  $\mu$ L of cell solution (approximately 20,000 cells) per well and pre-incubated for 24 h in medium supplemented with 10% FCS. Compounds were dissolved first in DMSO and then added to the culture medium (final DMSO concentration = 0.5% v/v) and serially diluted to the appropriate concentration, 100  $\mu$ L of compound solution was added to each well and the plates were incubated for another 72 h.

**Table 2**

Crystallographic and selected experimental data for **1** · CHCl<sub>3</sub> and **3**

|                                                                           | <b>1</b> · CHCl <sub>3</sub>                                         | <b>3</b>                                                                           |
|---------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Chemical formula                                                          | C <sub>28</sub> H <sub>31</sub> Cl <sub>5</sub> FeN <sub>2</sub> ORu | C <sub>26</sub> H <sub>30</sub> Cl <sub>2</sub> FeN <sub>2</sub> O <sub>2</sub> Ru |
| Formula weight                                                            | 745.72                                                               | 630.34                                                                             |
| Crystal system                                                            | Monoclinic                                                           | Triclinic                                                                          |
| Space group                                                               | P2 <sub>1</sub> /c (no. 14)                                          | P $\bar{1}$ (no. 2)                                                                |
| Crystal color and shape                                                   | Orange block                                                         | Orange block                                                                       |
| Crystal size                                                              | 0.37 × 0.30 × 0.29                                                   | 0.35 × 0.27 × 0.16                                                                 |
| <i>a</i> (Å)                                                              | 14.450(3)                                                            | 11.8573(8)                                                                         |
| <i>b</i> (Å)                                                              | 27.116(5)                                                            | 12.8274(9)                                                                         |
| <i>c</i> (Å)                                                              | 7.863(2)                                                             | 19.0365(14)                                                                        |
| $\alpha$ (°)                                                              |                                                                      | 105.798(6)                                                                         |
| $\beta$ (°)                                                               | 103.68(3)                                                            | 103.102(6)                                                                         |
| $\gamma$ (°)                                                              |                                                                      | 96.764(5)                                                                          |
| <i>V</i> (Å <sup>3</sup> )                                                | 2993.5(11)                                                           | 2663.3(3)                                                                          |
| <i>Z</i>                                                                  | 4                                                                    | 4                                                                                  |
| <i>T</i> (K)                                                              | 203(2)                                                               | 203(2)                                                                             |
| <i>D</i> <sub>calc</sub> (g cm <sup>-3</sup> )                            | 1.655                                                                | 1.572                                                                              |
| $\mu$ (mm <sup>-1</sup> )                                                 | 1.461                                                                | 1.338                                                                              |
| Scan range (°)                                                            | 2.09 < $\theta$ < 26.06                                              | 1.68 < $2\theta$ < 25.68                                                           |
| Unique reflections                                                        | 5410                                                                 | 10045                                                                              |
| Observed reflections [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]                | 2509                                                                 | 6464                                                                               |
| <i>R</i> <sub>int</sub>                                                   | 0.0692                                                               | 0.0446                                                                             |
| Final <i>R</i> indices [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )] <sup>a</sup> | 0.0417, <i>wR</i> <sub>2</sub> 0.0831                                | 0.0304, <i>wR</i> <sub>2</sub> 0.0535                                              |
| <i>R</i> indices (all data)                                               | 0.1096, <i>wR</i> <sub>2</sub> 0.0937                                | 0.0587, <i>wR</i> <sub>2</sub> 0.0568                                              |
| Goodness-of-fit                                                           | 0.730                                                                | 0.800                                                                              |
| Max, Min $\Delta\rho$ (e (Å <sup>-3</sup> ))                              | 0.681, -1.290                                                        | 0.416, -0.569                                                                      |

<sup>a</sup> Structures were refined on *F*<sup>2</sup>: *wR*<sub>2</sub> = [ $\sum[w(F_o^2 - F_c^2)^2]/\sum w(F_o^2)^2$ ]<sup>1/2</sup>, where  $w^{-1} = [\sum(F_o^2) + (aP)^2 + bP]$  and  $P = [\max(F_o^2, 0) + 2F_c^2]/3$ .

Subsequently, MTT (5 mg/mL solution) was added to the cells and the plates were incubated for a further 2 h. The culture medium was aspirated, and the purple formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in DMSO. The optical density, directly proportional to the number of surviving cells, was quantified at 540 nm using a multi-well plate reader and the fraction of surviving cells was calculated from the absorbance of untreated control cells. Evaluation is based on means from two independent experiments, each comprising 3 microcultures per concentration level.

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### Appendix A. Supplementary material

CCDC 692820 and 692821 contain the supplementary crystallographic data for compounds **1** · CHCl<sub>3</sub> and **3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorgchem.2008.08.012.

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