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Arene ruthenium complexes with phosphinoferrocene amino acid conjugates: Synthesis, characterization and cytotoxicity

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ABSTRACT

A series of heterodinuclear *p*-cymene ruthenium ferrocene complexes, [(η^6-*p*-MeC$_6$H$_4$Pr^i)RuCl$_2$(Ph$_2$PfcCONHRCO$_2$Me-κ*P*)] (R = (*S*)-Me: **6**, R = (*S*)-CHMe$_2$: **7**, R = (*S*)-CH$_2$OMe: **8**, R = (*S*)-CH$_2$SMe: **9**, R = (*S*)-CH$_2$CH$_2$CO$_2$Me: **10**) have been synthesized from *p*-cymene ruthenium dichloride dimer and phosphinoferrocene ligands bearing carboxamide substituents derived from amino acids, Ph$_2$PfcCONHRCO$_2$Me (R = (*S*)-Me: **1**, R = (*S*)-CHMe$_2$: **2**, R = (*S*)-CH$_2$OMe: **3**, R = (*S*)-CH$_2$SMe: **4**, R = (*S*)-CH$_2$CH$_2$CO$_2$Me: **5**, fc = ferrocene-1,1′-diyl). All new compounds, **3**–**10**, were fully characterized by elemental analysis, multinuclear NMR and IR spectroscopy and electrospray ionisation mass spectrometry, and their electrochemical properties were studied by cyclic voltammetry at a platinum disc electrode. The cytotoxicity of **6**–**10** was studied on human ovarian cancer cells. The related glycine derivatives [(η^6-arene)RuCl$_2$(Ph$_2$PfcCONHCH$_2$CO$_2$Me-κ*P*)] (arene = C$_6$H$_6$: **11a**, arene = *p*-MeC$_6$H$_4$Pr^i: **11b**, arene = C$_6$Me$_6$: **11c**), [(η^6-arene)RuCl(MeCN)(Ph$_2$PfcCONHCH$_2$CO$_2$Me-κ*P*)][PF$_6$] (arene = C$_6$H$_6$: **12a**, arene = *p*-MeC$_6$H$_4$Pr^i: **12b**, arene = C$_6$Me$_6$: **12c**), [(η^6-arene)Ru(MeCN)$_2$(Ph$_2$PfcCONHCH$_2$CO$_2$Me-κ*P*)][PF$_6$]$_2$ (arene = C$_6$H$_6$: **13a**, arene = *p*-MeC$_6$H$_4$Pr^i: **13b**, arene = C$_6$Me$_6$: **13c**) and [(η^6-*p*-MeC$_6$H$_4$Pr^i)RuCl$_2$(Ph$_2$PfcCONHCH$_2$CONH$_2$-κ*P*)] (**14**), which we reported recently, were also included in the cytotoxicity study. The arene ruthenium ferrocene complexes show moderate to good *in vitro* anticancer activity towards human ovarian cancer cells, the IC$_{50}$ values of the most active derivative **13c** being 4.1 ± 0.8 μM for the A2780 cell line and 6.9 ± 0.01 μM for the cisplatin-resistant derivative A2780cisR.

1. Introduction

Arene ruthenium compounds such as the prototype complexes [(*p*-Pr^{i}C$_6$H$_4$Me)RuCl$_2$(pta)] (pta=1,3,5-triaza-7-phosphatricyclo[3.3.1.1.^{3,7}]decane (termed RAPTA-C) [1] and [(C$_6$H$_5$Ph)RuCl(en)]$^+$ (en=1,2-ethylenediamine) [2] have antitumoral and/or antimetastatic properties *in vitro* and *in vivo*. The anticancer potential of these types of compounds has been partially explained by their dual character, with the hydrogen bonding capacity of the pta or en ligands counterbalanced by the lipophilicity of the arene ligand [3], while the mechanism of cytotoxic action is thought to involve hydrolysis of the Ru–Cl bond followed by reaction with the biomolecular target or targets [4]. The underlying design of arene ruthenium anticancer agents and the current understanding of their mode of action is summarised in several review articles [5–9].

In addition to half-sandwich arene ruthenium compounds, ferrocene compounds show excellent anticancer properties inhibiting the development of tumors *in vivo* [10]. It has been shown that tethering biologically active groups to the ferrocenyl unit increases their potency, possibly due to the combined action of the organic molecule with Fenton chemistry of the Fe-centre [11]. Ferrocene has also been covalently linked to both platinum [12-13] and gold [14] centres in order to achieve enhanced effects between the two active metals. In addition, ferrocenoyl pyridine arene ruthenium complexes have been prepared and studied for *in vitro* anticancer activity [15].

In general, iron compounds are well tolerated *in vivo*, and similarly, ruthenium compounds exhibit low general toxicity compared to their platinum counterparts, which is probably due to two main reasons. First, ruthenium compounds specifically accumulate in rapidly dividing cells, such as in tumors, due to possible HSA transport [16] or the ability of ruthenium(III) to mimic iron in

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binding to transferrin [17], the protein which delivers iron to cells, and transferrin receptors are over-expressed in cancer cells [18]. Second, the majority of ruthenium drugs comprise ruthenium in the +3 oxidation state and it has been proposed that in this oxidation state ruthenium is less active and is reduced *in vivo* to more active ruthenium(II) complexes, a process favored in the hypoxic environment of a tumor [18]. However, it should be noted that ruthenium(II) compounds also exhibit a low general toxicity and, since cancer cells can also become oxidizing at certain stages of their growth cycle, oxidation of the ruthenium cannot be excluded [19].

As part of our ongoing studies focused on the chemistry of phosphinoferrocene carboxamides [20] prepared by amidation of ferrocene phosphinocarboxylic acids with amino acid esters [21,22], we recently described the synthesis of η^6-arene ruthenium complexes containing phosphinoferrocene–glycine conjugates as P-monodentate ligands and established their catalytic potential for the oxidation of secondary alcohols to ketones with *tert*-butyl hydroperoxide [23]. Considering the successful applications of ruthenium complexes as anticancer agents and the fact that the amino acid residue in our ligands typically remains uncoordinated and can thus serve as a directing group in biological systems, we decided to evaluate cytotoxicity of these compounds. To this end, we extended the series of the known heterobimetallic Fe–Ru complexes $[(\eta^6\text{-arene})RuCl_n(MeCN)_{2-n}(Ph_2PfcCONHCH(R)CO_2Me\text{-}\kappa P)]^{(2-n)+}$ (R = H, n = 0–2) [23] by other (chiral) derivatives (R = Me, $CHMe_2$, CH_2OMe, CH_2SMe, $CH_2CH_2CO_2Me$, n = 2) and studied their antiproliferative effects on A2870 and A2870cisR human ovarian cancer cell lines.

2. Results and discussion

The new phosphinoferrocene amino acid conjugates $Ph_2PfcCONHRCO_2Me$ (R = (*S*)-CH_2OMe: **3**, R = (*S*)-CH_2SMe: **4**, R = (*S*)-$CH_2CH_2CO_2Me$: **5**, fc = ferrocene-1,1′-diyl) were obtained by amide coupling reactions of 1′-(diphenylphosphino)ferrocene-1-carboxylic acid (Hdpf) [27] and the corresponding amino acid esters in the presence of 1-hydroxybenzotriazole and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide as peptide coupling reagents (Scheme 1), by analogy to the known derivatives **1** (R = (*S*)-Me) and **2** (R = (*S*)-$CHMe_2$), described earlier [21,22].

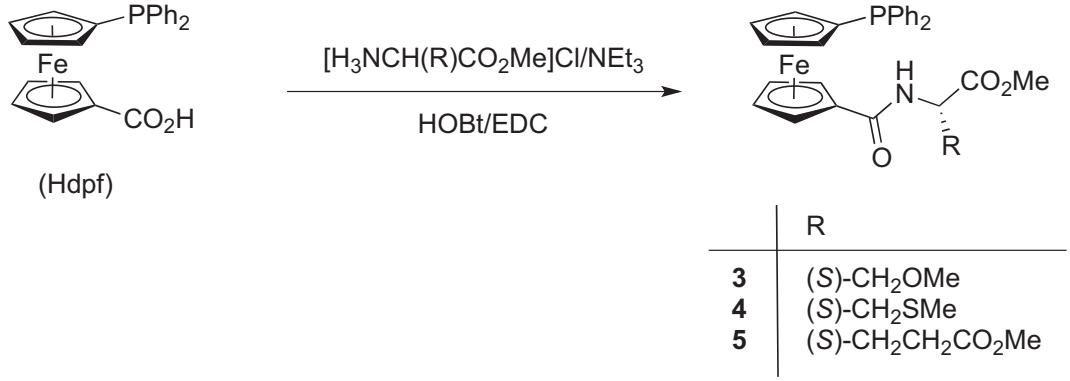
Compounds **3**–**5** were characterized by multinuclear (^{1}H, ^{31}P{^{1}H}, ^{13}C{^{1}H}) NMR and IR spectroscopy, and high-resolution mass spectroscopy. The ^{1}H and ^{13}C{^{1}H} NMR spectra display the characteristic signals of the 1′-(diphenylphosphino)ferrocene-1-yl moiety, possessing a stereogenic centre (namely eight signals due to diastereotopic ferrocene protons and a multiplet of the phosphine phenyl groups) as well as the signals of the carboxamide pendants. In addition to the signals of the amino acid side chain, the characteristic resonance of the NH group is observed as a CH-coupled doublet at δ_H 6.5–6.6 ppm, while those of the methyl esters groups are seen as singlets at δ_H ca. 3.75 ppm and δ_C 52–53 ppm. The ^{31}P{^{1}H} NMR spectra display a singlet at δ_P ca. −18 ppm. The positive-ion ESI mass spectra show the pseudomolecular ions $[M + K]^+$, $[M + Na]^+$ and $[M + H]^+$. The presence of the amide and ester groups is clearly manifested in the IR spectra via strong bands due to ν_{CO} at ca. 1740 cm^{-1} and by amide I (1638–1651 cm^{-1}) and amide II vibrations (1518–1533 cm^{-1}).

The phosphinoferrocene amides, **1**–**5**, react with *p*-cymene ruthenium dichloride dimer in chloroform to give the corresponding *p*-cymene ruthenium complexes $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)RuCl_2(Ph_2PfcCONHRCO_2Me\text{-}\kappa P)]$ (R = (*S*)-Me: **6**, R = (*S*)-$CHMe_2$: **7**, R = (*S*)-CH_2OMe: **8**, R = (*S*)-CH_2SMe: **9**, R = (*S*)-$CH_2CH_2CO_2Me$: **10**) in high yield (Scheme 2). Complexes **6**–**10** are red, air-stable solids, which can be purified by column chromatography on silica.

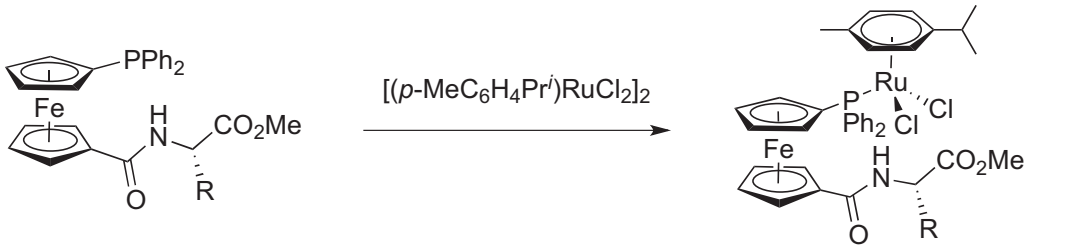
Compounds **6**–**10** were fully characterized by ^{1}H and ^{31}P{^{1}H} NMR and IR spectroscopy, ESI mass spectroscopy and satisfactory elemental analysis. The ^{1}H NMR spectra of **6**–**10** are similar to those of the corresponding free ligands but also contain additional signals due to the coordinated *p*-cymene (a pair of AA′BB′ type doublets in the range δ_H = 4.8–5.3 ppm). The ^{31}P{^{1}H} NMR spectra show a single resonance close to δ_P +18 ppm, while the positive-ion ESI mass spectra display ions attributable to $[M + Na]^+$ and $[M - Cl]^+$. As for the ligands **1**–**5**, the IR spectra of the complexes **6**–**10** also exhibit strong bands at ca. 1740 cm^{-1} (carbonyl) and 1638–1651 cm^{-1} (amide I) and 1518–1533 cm^{-1} (amide II).

The heterodinuclear *p*-cymene ruthenium ferrocene complexes **6**–**10** have been studied by cyclic voltammetry at a Pt disc electrode in acetonitrile. Representative cyclic voltammograms are shown in Fig. 1 and the pertinent data are presented in Table 1. In line with their glycine analogues studied earlier [23], complexes **6**–**10** undergo two successive oxidations. The first redox process occurring at ca. 0.27 V *versus* the ferrocene/ferrocenium reference is a reversible, one-electron oxidation attributable to the oxidation of the ferrocene moiety to the corresponding ferrocenium. The following oxidation at ca. 0.86 V is electrochemically irreversible and can be assigned to oxidation occurring at the Ru(II) centre, very likely multi-electron in nature.

The *in vitro* anticancer activity of the *p*-cymene ruthenium complexes **6**–**10** containing phosphinoferrocene chiral amino acid conjugates has been studied on the human ovarian cancer cell lines A2780 and A2780cisR, the latter having acquired resistance to cisplatin. The related glycine derivatives $[(\eta^6\text{-arene})RuCl_2(Ph_2PfcCONHCH_2CO_2Me\text{-}\kappa P)]$ (arene = C_6H_6: **11a**, arene = *p*-$MeC_6H_4Pr^i$: **11b**, arene = C_6Me_6: **11c**), $[(\eta^6\text{-arene})RuCl(MeCN)(Ph_2PfcCONHCH_2CO_2Me\text{-}\kappa P)][PF_6]$ (arene = C_6H_6: **12a**, arene = *p*-$MeC_6H_4Pr^i$: **12b**,



Scheme 1. Synthesis of the new phosphinoferrocene amides **3**–**5**. HOBt = 1-hydroxybenzotriazole, EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide.



	R
1	(*S*)-Me
2	(*S*)-$CHMe_2$
3	(*S*)-CH_2OMe
4	(*S*)-CH_2SMe
5	(*S*)-$CH_2CH_2CO_2Me$

	R
6	(*S*)-Me
7	(*S*)-$CHMe_2$
8	(*S*)-CH_2OMe
9	(*S*)-CH_2SMe
10	(*S*)-$CH_2CH_2CO_2Me$

Scheme 2. Synthesis of the heterodinuclear *p*-cymene ruthenium ferrocene complexes **6**–**10**.

arene = C_6Me_6: **12c**), [(η^6-arene)Ru(MeCN)$_2$($Ph_2PfcCONHCH_2$-CO_2Me-κ*P*)][PF_6]$_2$ (arene = C_6H_6: **13a**, arene = *p*-$MeC_6H_4Pr^i$: **13b**, arene = C_6Me_6: **13c**) and [(η^6-*p*-$MeC_6H_4Pr^i$)$RuCl_2$($Ph_2PfcCONHCH_2$-$CONH_2$-κ*P*)] (**14**), reported recently [23], were also included in the cytotoxicity study, see Scheme 3 and Table 1.

The IC_{50} cell survival rates for A2780 and A2780cisR cancer cells are summarized in Table 1, together with the Fe(II)/Fe(III) and Ru(II)/Ru(III) redox potentials. Most compounds show only moderate cytotoxicities, only **7**, **12c** and **13c** approach that of cisplatin in the A2789 cell line (IC_{50} 1.6 μM for A2780 and 8.6 μM for A2780 [15]). There is no clear-cut correlation between redox potentials and cytotoxicities, suggesting that catalytic glutathione oxidation, assumed for some other cytotoxic arene ruthenium complexes [24–26], in particular for dinuclear trithiolato derivatives [25,26] is not involved.

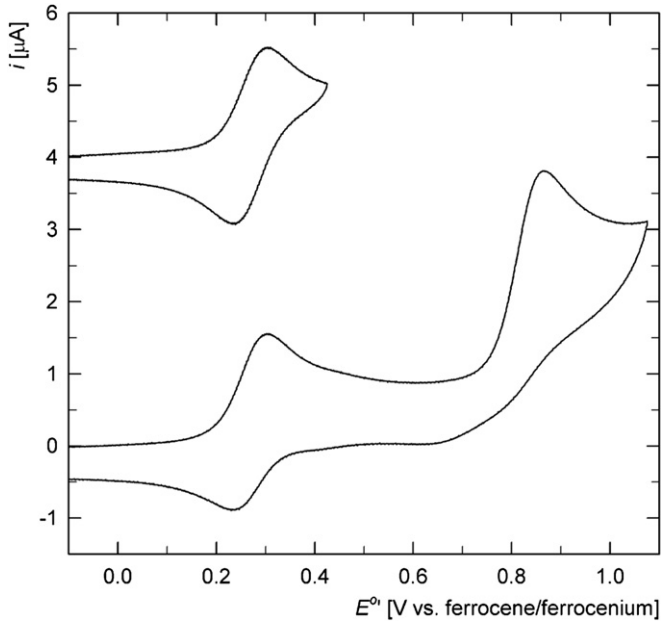


Fig. 1. A partial (top) and full (bottom) cyclic voltammogram of **9** as recorded in acetonitrile at a Pt disc electrode (scan rate: 200 mV s^{-1}). The partial voltammogram is shifted by +4 μA to avoid overlaps.

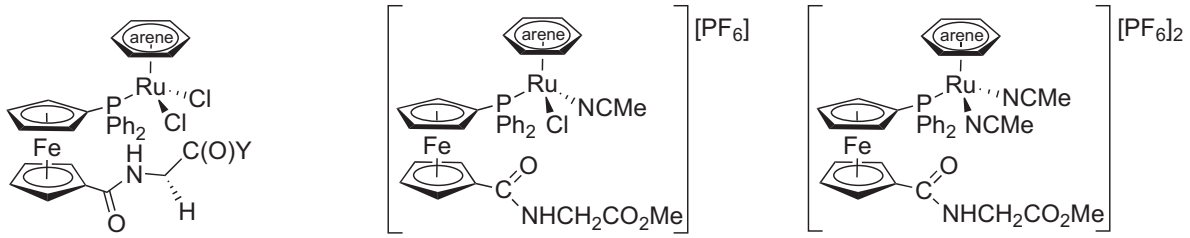
The cytotoxicity of the neutral dichloro complexes bearing the simplest glycine-based ligand and various arene donors increases significantly (IC_{50}: **11c** < **11b** < **11a**) upon increasing the number of alkyl substituents at the Ru-bound arene for both cell lines and, hence, correlates with the redox potentials of both the Fe(II/III) and Ru(II/III) couples. A similar trend is seen also for the dicationic complexes **13a**–**c**, whereas the IC_{50} values of **12a**–**c** suggest a different trend (IC_{50}: **12c** < **12a** < **12b**).

The variation of the amino acid pendant, that is to say R in the neutral complexes of the type [(η^6-*p*-cymene)$RuCl_2$(Ph_2Pfc-$CONHCHRCO_2Me$-κ*P*)] also influences the cytotoxicity, albeit less obviously. From the results in Table 1, one can conclude that simple alkyl groups increase the cytoxicity (decrease IC_{50}) towards both types of the cancer cells. Compounds possessing functional substituents (R = CH_2OMe, CH_2SMe, and $CH_2CH_2CO_2Me$), however, cause higher IC_{50} values. Finally, the bis-amide complex **14** is the least cytotoxic (highest IC_{50} values) in this series, which implies that the group attached to the O-terminus of the amino acid chain plays a significant role in determining the biological activity.

Table 1
Electrochemical and cytotoxicity data for human ovarian cancer cell lines of the arene ruthenium phosphinoferrocene amino acid conjugates **6**–**14**.

Data	$E^{\circ\prime}$ [V][a]		IC_{50} [μM]	
Compound	$Fe^{II/III}$	$Ru^{II/III}$	A2780	A2780cisR
6	0.270	0.860	16.5 ± 1.6	31 ± 8.8
7	0.265	0.860	7.8 ± 0.1	14.5 ± 0.02
8	0.265	0.860	50.2 ± 6.7	50.3 ± 11.3
9	0.275	0.865	42.5 ± 2.5	48.6 ± 15.7
10	0.270	0.865	41.3 ± 0.7	42.6 ± 7.9
11a	0.315[b]	0.935[b]	35.4 ± 6.7	30.2 ± 11.7
11b	0.285[b]	0.850[b]	17.4 ± 3.2	14.4 ± 4
11c	0.245[b]	0.710[b]	8.7 ± 0.1	7.6 ± 1.2
12a	0.430[b]	n.o.[b]	32.3 ± 1.1	32 ± 13.6
12b	0.410[b]	n.o.[b]	48.9 ± 4	53.6 ± 12.7
12c	0.385[b]	n.o.[b]	7.5 ± 1	11.9 ± 1.5
13a	0.540[b]	n.o.[b]	22 ± 7.9	20.9 ± 4.2
13b	0.530[b]	n.o.[b]	12.2 ± 2	5.9 ± 0.6
13c	0.510[b]	n.o.[b]	4.1 ± 0.8	6.9 ± 0.01
14	0.260[b]	0.850[b]	98.3 ± 19.4	118.5 ± 4.5

[a] The potentials are given relative to the ferrocene/ferrocenium couple. $E^{\circ\prime} = ½(E_{pa} + E_{pc})$, where E_{pa} (E_{pc}) denote the anodic (cathodic) peak potential in cyclic voltammetry.
[b] Data from reference [23]; n.o. = not observed.



	arene	Y
11a	C_6H_6	OMe
11b	*p*-$MeC_6H_4Pr^i$	OMe
11c	C_6Me_6	OMe
14	*p*-$MeC_6H_4Pr^i$	NH_2

	arene
12a	C_6H_6
12b	*p*-$MeC_6H_4Pr^i$
12c	C_6Me_6

	arene
13a	C_6H_6
13b	*p*-$MeC_6H_4Pr^i$
13c	C_6Me_6

Scheme 3. Arene ruthenium phosphinoferrocene glycine conjugates [23] included in this study.

3. Experimental

3.1. Materials

The syntheses were performed in a nitrogen atmosphere with exclusion of direct day light. The starting materials $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)RuCl_2]_2$ [28], Hdpf [27], ligands **1** and **2** [21,22] and the glycine-derived complexes **11**–**14** [23] were prepared according to literature procedures. Amino acid methyl ester hydrochlorides, (*S*)-$[H_3NCH(CH_2EMe)CO_2Me]Cl$ (E = O, S) were obtained upon reacting the respective amino acid with thionyl chloride in dry methanol [29]. Chloroform and dichloromethane were dried by standing over CaH_2 and distilled under nitrogen. Methanol was distilled from MeONa. Other chemicals and solvents used for crystallizations and in chromatography were used without further purification.

3.2. Spectroscopy

NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer (^1H, 400.13 MHz; $^{13}C\{^1H\}$, 100.62 MHz; and $^{31}P\{^1H\}$, 161.98 MHz) at 296 K. Chemical shifts (δ/ppm) are given relative to the residual peak of the solvent ($CDCl_3$, $\delta_H = 7.26$; $\delta_C = 77.16$) or to external 85% aqueous H_3PO_4 ($\delta_P = 0$). Infrared spectra were recorded with a Perkin–Elmer FTIR 1720-X spectrometer using KBr pellets. Electrospray ionization (ESI) mass spectra were obtained in positive-ion mode with an LCQ Finnigan mass spectrometer. Optical rotations were determined with an Autopol III (Rudolph Research) automatic polarimeter at room temperature.

3.3. Electrochemistry

Electrochemical measurements were performed with a multipurpose potentiostat μAUTOLAB III (EcoChemie) at room temperature (ca. 25 °C) using a standard Metrohm three-electrode cell equipped with a platinum disc (2 mm diameter) as the working electrode, platinum sheet auxiliary electrode, and double-junction Ag/AgCl (3 M KCl) reference electrode. Samples were dissolved in acetonitrile (Sigma–Aldrich, absolute) to give solutions containing ca. 1 mM of the analyte and 0.1 M $[Bu_4N][PF_6]$ (Fluka, purissimum for electrochemistry). The solutions were deaerated by bubbling with argon before the measurement and then kept under an argon blanket. The potentials are given relative to ferrocene/ferrocenium reference. The redox potential of the ferrocene/ferrocenium couple was 0.425 V vs. Ag/AgCl (3 M KCl).

3.4. Cell culture and cell growth

Human A2780 and A2780cisR ovarian carcinoma cell lines were obtained from the European Centre of Cell Cultures (ECACC, Salisbury, UK) and maintained in culture as described by the provider. The cells were routinely grown in RPMI 1640 medium containing 10% fetal calf serum (FCS) and antibiotics at 37 °C and 6% CO_2. For the evaluation of growth inhibition tests, the cells were seeded in 96-well plates (Costar, Integra Biosciences, Cambridge, USA) and grown for 24 h in complete medium. Compounds **6**–**13** and rHSA solutions were diluted directly in culture medium to the required concentration and added to the cell culture for 72 h incubation. The MTT (MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test was performed for the last 2 h without changing the culture medium and was performed in triplicate. Briefly, following drug exposure, MTT (Sigma) was added to the cells at the final concentration of 0.2 mg/mL and incubated for 2 h, then the culture medium was aspirated and the violet formazan precipitate dissolved in 0.1 N HCl in 2-propanol. The optical density was quantified at 540 nm using a multiwell plate reader (iEMS Reader MF, Labsystems, US), and the percentage of surviving cells was calculated from the ratio of absorbance of treated to untreated cells. The IC_{50} values for the inhibition of cell growth were determined by fitting the plot of the percentage of surviving cells against the drug concentration using a sigmoidal function (Origin v7.5).

3.5. General procedure for the synthesis of the phosphinoferrocene amides ***3***–***5***

A suspension of Hdpf (414 mg, 1.00 mmol) and 1-hydroxybenzotriazole monohydrate (184 mg, 1.20 mmol) in dichloromethane (10 mL) was cooled in an ice bath and treated with neat 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (0.21 mL, 1.20 mmol). The resultant mixture was stirred at 0 °C for 15 min, whereupon the solids dissolved to give a clear orange-red solution. A solution of the corresponding amino acid methyl ester hydrochloride $[H_3NCH(R)CO_2Me]Cl$ (1.30 mmol) and triethylamine (0.20 mL, 1.40 mmol) in dichloromethane (20 mL) was introduced, and the cooling bath was removed. The reaction mixture was stirred overnight at room temperature and then washed successively with 10% aqueous citric acid (50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and brine (50 mL). The organic phase was separated, dried over $MgSO_4$ and evaporated under vacuum. The orange oily residue was purified by column chromatography (silica gel,

dichloromethane/methanol, 50:1 v/v). A single orange band was collected and evaporated to afford the analytically pure amide.

*3.5.1. (S)-$Ph_2PfcCONHCH(CH_2OMe)CO_2Me$ (**3**)*

Orange solid. Yield: 493 mg (93%). $[\alpha]_D = -3$ ($c = 0.5$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.35 (s, 3H, CH_2OMe), 3.69 (dd, $^2J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 3.4 Hz, 1H, CH_2OMe), 3.77 (s, 3H, CO_2Me), 3.88 (dd, $^2J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 3.4 Hz, 1H, CH_2OMe), 4.15 (unresolved dq, 1H, fc), 4.22 (m, 3H, fc), 4.47 (dt, $J \approx 2.4$, 1.1 Hz, 1H, fc), 4.49 (dt, $J \approx 2.4$, 1.2 Hz, 1H, fc), 4.58 (dt, $J \approx 2.5$, 1.4 Hz, 1H, fc), 4.65 (dt, $J \approx 2.5$, 1.4 Hz, 1H, fc), 4.86 (dt, $^3J_{HH}$ = 8.3, 3.4 Hz, 1H, NHC*H*), 6.54 (d, $^3J_{HH}$ = 8.3 Hz, 1H, N*H*CH), 7.28–7.43 (m, 15H, PPh_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 52.58 (OMe), 52.72 (OMe), 59.41 (NHCH), 69.32 (*C*H fc), 69.78 (*C*H fc), 72.13 (*C*H fc), 72.18 (*C*H fc), 72.48 (OCH_2), 73.32 (2× d, J_{PC} = 4 Hz, *C*H fc), 74.44 (d, J_{PC} = 14 Hz, *C*H fc), 74.63 (d, J_{PC} = 14 Hz, *C*H fc), 75.89 (*C*–CONH fc), 128.39 (2× d, $^3J_{PC}$ = 7 Hz, *C*H PPh_2), 128.85 (2× *C*H PPh_2), 133.49 (d, $^2J_{PC}$ = 6 Hz, *C*H PPh_2), 133.69 (d, $^2J_{PC}$ = 6 Hz, *C*H PPh_2), 138.49 (d, $^1J_{PC}$ = 2 Hz, C_{ipso} PPh_2), 138.57 (d, $^1J_{PC}$ = 2 Hz, C_{ipso} PPh_2), 169.79 (CONH), 171.05 (CO_2Me); the signal due to *C*–P of fc was not found probably due to overlaps. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −17.6 (s). IR (KBr): ν_{NH} 3414 vs, ν_{CO} 1745 s, amide I 1638 vs, amide II 1522 vs cm^{-1}. MS (ESI+): *m*/*z* 568 ($[M + K]^+$), 552 ($[M + Na]^+$), 530 ($[M + H]^+$). HRMS (ESI+) calc. for $C_{28}H_{29}O_4NPFe$ $[M + H]^+$ 530.1178, found 530.1177.

*3.5.2. (S)-$Ph_2PfcCONHCH(CH_2SMe)CO_2Me$ (**4**)*

Orange solid. Yield: 475 mg (87 %). $[\alpha]_D = -3$ ($c = 0.5$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, CH_2SMe), 3.00 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, CH_2SMe), 3.05 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, CH_2SMe), 3.76 (s, 3H, CO_2Me), 4.18 (br s, 1H, fc), 4.23 (m, 3H, fc), 4.48 (dt, $J \approx 2.4$, 1.2 Hz, 1H, fc), 4.50 (dt, $J \approx 2.4$, 1.2 Hz, 1H, fc), 4.60 (dt, $J \approx 2.5$, 1.3 Hz, 1H, fc), 4.64 (dt, $J \approx 2.6$, 1.3 Hz, 1H, fc), 4.91 (ddd, $^3J_{HH}$ = 5.0, 6.0, 7.6 Hz, 1H, NHC*H*), 6.61 (d, $^3J_{HH}$ = 7.6 Hz, 1H, N*H*CH), 7.30–7.44 (m, 10H, PPh_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 16.15 (SMe), 36.56 (SCH_2), 51.42 (NHCH), 52.73 (OMe), 69.55 (*C*H fc), 69.72 (*C*H fc), 72.13 (2× *C*H fc), 73.23 (d, J_{PC} = 3 Hz, *C*H fc), 73.34 (d, J_{PC} = 4 Hz, *C*H fc), 74.43 (d, J_{PC} = 13 Hz, *C*H fc), 74.63 (d, J_{PC} = 14 Hz, *C*H fc), 75.88 (*C*–CONH fc), 128.41 (2× d, $^3J_{PC}$ = 7 Hz, *C*H PPh_2), 128.89 (*C*H PPh_2), 128.93 (*C*H PPh_2), 133.50 (d, $^2J_{PC}$ = 9 Hz, *C*H PPh_2), 133.70 (d, $^2J_{PC}$ = 9 Hz, *C*H PPh_2), 138.28 (d, $^1J_{PC}$ = 8 Hz, C_{ipso} PPh_2), 138.43 (d, $^1J_{PC}$ = 8 Hz, C_{ipso} PPh_2), 169.95 (CONH), 171.72 (CO_2Me); the signal due to *C*–P of fc was not found. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −17.6 (s). IR (KBr): ν_{NH} 3415 s, ν_{CO} 1744 s, amide I 1637 vs, amide II 1529 vs cm^{-1}. MS (ESI+): *m*/*z* 584 ($[M + K]^+$), 568 ($[M + Na]^+$), 546 ($[M + H]^+$). HRMS (ESI+) calc. for $C_{28}H_{29}O_3NPSFe$ $[M + H]^+$ 546.0950, found 546.0949.

*3.5.3. (S)-$Ph_2PfcCONHCH(CH_2CH_2CO_2Me)CO_2Me$ (**5**)*

Orange solid. Yield: 531 mg (93 %). $[\alpha]_D = -11$ ($c = 0.5$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.09 (ddt, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 7.2, 8.3 Hz, 1H, $CH_2CH_2CO_2Me$), 2.26 (ddt, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 4.8, 7.2 Hz, 1H, $CH_2CH_2CO_2Me$), 2.45 (dt, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 7.3 Hz, 1H, $CH_2CH_2CO_2Me$), 2.50 (dt, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 7.3 Hz, 1H, $CH_2CH_2CO_2Me$), 3.65 (s, 3H, CH_2CO_2Me), 3.73 (s, 3H, $CHCO_2Me$), 4.11 (br s, 1H, fc), 4.22 (m, 2H, fc), 4.25 (br s, 1H, fc), 4.46 (dt, $J \approx 2.4$, 1.1 Hz, 1H, fc), 4.49 (dt, $J \approx 2.4$, 1.2 Hz, 1H, fc), 4.59 (dt, $J \approx 2.4$, 1.2 Hz, 1H, fc), 4.66 (dt, $J \approx 2.4$, 1.3 Hz, 1H, fc), 4.69 (dt, $^3J_{HH}$ = 4.7, 8.2 Hz, 1H, NHC*H*), 6.63 (d, $^3J_{HH}$ = 7.7 Hz, 1H, N*H*CH), 7.28–7.44 (m, 10H, PPh_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 27.10 ($CHCH_2$), 30.49 (CH_2CO_2Me), 51.97 (NHCH), 52.05 (OMe), 52.60 (OMe), 69.47 (*C*H fc), 69.64 (*C*H fc), 72.06 (*C*H fc), 72.12 (*C*H fc), 73.11 (d, J_{PC} = 3 Hz, *C*H fc), 73.24 (d, J_{PC} = 4 Hz, *C*H fc), 74.34 (d, J_{PC} = 13 Hz, *C*H fc), 74.56 (d, J_{PC} = 14 Hz, *C*H fc), 75.89 (*C*–CONH fc), 128.40 (2× d, $^3J_{PC}$ = 7 Hz, *C*H PPh_2), 128.87 (*C*H PPh_2), 128.91 (*C*H PPh_2), 133.50 (d, $^2J_{PC}$ = 8 Hz, *C*H PPh_2), 133.69 (d, $^2J_{PC}$ = 8 Hz, *C*H PPh_2), 138.26 (d, $^1J_{PC}$ = 8 Hz, C_{ipso} PPh_2), 138.47 (d, $^1J_{PC}$ = 8 Hz, C_{ipso} PPh_2), 170.18 (CONH), 172.55 (CO_2Me), 173.81 (CO_2Me); the signal due to *C*–P of fc was not found. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −17.6 (s). IR (KBr): ν_{NH} 3415 s, ν_{CO} 1741 vs, amide I 1630 vs, amide II 1533 vs cm^{-1}. MS (ESI+): *m*/*z* 610 ($[M + K]^+$), 594 ($[M + Na]^+$), 572 ($[M + H]^+$). HRMS (ESI+) calc. for $C_{30}H_{31}O_5NPFe$ $[M + H]^+$ 572.1284, found 572.1283.

*3.6. General procedure for the synthesis of the arene ruthenium complexes **6**–**10***

A solution of 0.2 mmol of the appropriate ligands **1**–**5** in $CHCl_3$ (5 mL) was added to 61 mg (0.1 mmol) of solid $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$, which dissolved rapidly in this mixture. After stirring the solution at room temperature for 3 h, the solvent was evaporated under vacuum, and the residue was purified by column chromatography on silica gel using chloroform/acetone (5:1 v/v) as the eluent. The products were isolated by evaporation and dried under vacuum. The elemental analyses showed all compounds to contain a small amount of chloroform (between 0.35 and 0.80 equivalents), which could not be removed even under high vacuum.

*3.6.1. (S)-$[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)RuCl_2(Ph_2PfcCONHCH(CO_2Me)Me\text{-}\kappa P)]$ (**6**)*

Red solid. Yield: 155 mg (96 %). $[\alpha]_D = +79$ ($c = 0.5$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.99 (d, $^3J_{HH}$ = 6.9 Hz, 3H, $CHMe_2$), 1.00 (d, $^3J_{HH}$ = 6.9 Hz, 3H, $CHMe_2$), 1.59 (d, $^3J_{HH}$ = 7.4 Hz, 3H, CH*Me*), 1.72 (s, 3H, η^6-C_6H_4Me), 2.52 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, *CH*Me_2), 2.96 (br s, 1H, fc), 3.62 (dt, $J \approx 2.4$, 1.2 Hz, 1H, fc), 3.78 (s, 3H, OMe), 4.40 (dt, $J \approx 2.4$, 1.2 Hz, 1H, fc), 4.46 (dq, $J \approx 2.5$, 1.3 Hz, 1H, fc), 4.47 (m, 2H, fc), 4.53 (dq, $J \approx 3.6$, 1.2 Hz, 1H, fc), 4.61 (pent, $^3J_{HH}$ = 7.4 Hz, 1H, NHC*H*), 4.86 (br s, 1H, fc), 4.99 (d, J_{HH} = 6.0 Hz, 1H, η^6-C_6H_4), 5.14 (d, J_{HH} = 6.1 Hz, 1H, η^6-C_6H_4), 5.23 (m, 2H, η^6-C_6H_4), 7.59 (d, $^3J_{HH}$ = 7.4 Hz, 1H, N*H*CH), 7.36–7.47 (m, 6H, PPh_2), 7.69–7.77 (m, 2H, PPh_2), 7.85–7.94 (m, 2H, PPh_2). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 17.6 (s). IR (KBr): ν_{NH} 3415 s, ν_{CO} 1740 s, amide I 1638 vs, amide II 1527 vs cm^{-1}. MS (ESI+): *m*/*z* 828 ($[M + Na]^+$), 770 ($[M - Cl]^+$). Anal. Calc. for $C_{37}H_{40}NO_3PCl_2FeRu \cdot 0.7\ CHCl_3$: C 50.93, H 4.61, N 1.58. Found: C 50.80, H 4.56, N 1.45.

*3.6.2. (S)-$[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)RuCl_2(Ph_2PfcCONHCH(CHMe_2)CO_2Me\text{-}\kappa P)]$ (**7**)*

Red solid. Yield: 150 mg (90 %). $[\alpha]_D = +52$ ($c = 0.5$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.99 (d, $^3J_{HH}$ = 6.9 Hz, 3H, η^6-$C_6H_4CHMe_2$), 1.01 (d, $^3J_{HH}$ = 7.0 Hz, 6H, $CHCHMe_2$), 1.03 (d, $^3J_{HH}$ = 6.9 Hz, 3H, η^6-$C_6H_4CHMe_2$), 1.69 (s, 3H, η^6-C_6H_4Me), 2.33 (d of sept, $^3J_{HH}$ = 6.9, 6.5 Hz, 1H, *CH*Me_2), 2.60 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, η^6-$C_6H_4CHMe_2$), 3.21 (br s, 1H, fc), 3.77 (s, 3H, OMe), 3.78 (dt, $J \approx 2.6$, 1.3 Hz, 1H, fc), 4.38 (m, 2H, fc), 4.46 (m, 3H, fc), 4.49 (dd, $^3J_{HH}$ = 8.6, 6.5 Hz, 1H, NHC*H*), 4.82 (br s, 1H, fc), 4.98 (d, J_{HH} = 6.1 Hz, 1H, η^6-C_6H_4), 5.17 (d, J_{HH} = 6.1 Hz, 1H, η^6-C_6H_4), 5.25 (m, 2H, η^6-C_6H_4), 6.72 (d, $^3J_{HH}$ = 8.6 Hz, 1H, N*H*CH), 7.37–7.50 (m, 6H, PPh_2), 7.72–7.82 (m, 2H, PPh_2), 7.84–7.93 (m, 2H, PPh_2). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 18.1 (s). IR (KBr): ν_{NH} 3419 s, ν_{CO} 1736 vs, amide I 1638 vs, amide II 1518 vs cm^{-1}. MS (ESI+): *m*/*z* 856 ($[M + Na]^+$), 798 ($[M - Cl]^+$). Anal. Calc. for $C_{39}H_{44}NO_3PCl_2FeRu \cdot 0.7\ CHCl_3$: C 51.99, H 4.91, N 1.53. Found: C 52.02, H 4.80, N 1.52.

*3.6.3. (S)-$[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)RuCl_2(Ph_2PfcCONHCH(CH_2OMe)CO_2Me\text{-}\kappa P)]$ (**8**)*

Red solid. Yield 157 mg (94 %). $[\alpha]_D = +26$ ($c = 0.5$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.96 (d, $^3J_{HH}$ = 6.9 Hz, 6H, η^6-$C_6H_4CHMe_2$), 1.76 (s, 3H, η^6-C_6H_4Me), 2.54 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, η^6-$C_6H_4CHMe_2$), 3.38 (s, 3H, CH_2OMe), 3.52 (dt, $J \approx 2.5$, 1.4 Hz 1H, fc), 3.69 (dd, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 3.7 Hz, 1H, CH_2OMe), 3.72 (dt, $J \approx 2.6$, 1.3 Hz 1H, fc), 3.78 (s, 3H, CO_2Me), 3.91 (dd, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 4.4 Hz,

1H, C*H*$_2$OMe), 4.27 (dt, $J \approx 2.5$, 1.2 Hz, 1H, fc), 4.30 (dt, $J \approx 2.6$, 1.3 Hz, 1H, fc), 4.44 (dq, $J \approx 2.4$, 1.3 Hz, 1H, fc), 4.48 (dq, $J \approx 2.4$, 1.2 Hz, 1H, fc), 4.53 (dq, $J \approx 2.5$, 1.3 Hz, 1H, fc), 4.73 (dq, $J \approx 2.5$, 1.2 Hz, 1H, fc), 4.80 (dt, $^3J_{HH} = 8.3$, 4.1 Hz, 1H, NHC*H*), 5.08 (d, $J_{HH} = 6.1$ Hz, 1H, η^6-C_6H_4), 5.13 (d, $J_{HH} = 6.1$ Hz, 1H, η^6-C_6H_4), 5.16 (d, $J_{HH} = 6.3$ Hz, 1H, η^6-C_6H_4), 5.19 (d, $J_{HH} = 6.2$ Hz, 1H, η^6-C_6H_4), 6.76 (d, $^3J_{HH} = 8.3$ Hz, 1H, N*H*CH), 7.38–7.49 (m, 6H, PPh$_2$), 7.77–7.91 (m, 4H, PPh$_2$). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 18.3 (s). IR (KBr): ν_{NH} 3418 s, ν_{CO} 1744 s, amide I 1651 vs, amide II 1524 vs cm^{-1}. MS (ESI+): *m*/*z* 858 ([M + Na]$^+$), 800 ([M − Cl]$^+$). Anal. Calc. for $C_{38}H_{42}NO_4PCl_2FeRu \cdot 0.45\ CHCl_3$: C 51.93, H 4.81, N 1.58. Found: C 51.86, H 4.74, N 1.49.

3.6.4. (S)-[(η^6-*p*-MeC_6H_4Pr^i)RuCl$_2$(Ph$_2$PfcCONHCH(CH$_2$SMe)CO$_2$Me-κP)] (**9**)

Red solid. Yield: 158 mg (93%). $[\alpha]_D = +36$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.98 (d, $^3J_{HH} = 6.9$ Hz, 3H, η^6-$C_6H_4CHMe_2$), 1.01 (d, $^3J_{HH} = 7.0$ Hz, 3H, η^6-$C_6H_4CHMe_2$), 1.73 (s, 3H, η^6-C_6H_4Me), 2.17 (s, 3H, CH$_2$S*Me*), 2.57 (sept, $^3J_{HH} = 7.0$ Hz, 1H, η^6-$C_6H_4CHMe_2$), 3.10 (d, $^3J_{HH} = 1.0$ Hz, 1H, C*H*$_2$SMe), 3.12 (d, $^3J_{HH} = 2.4$ Hz, 1H, C*H*$_2$SMe), 3.22 (virtual q, $J \approx 1.8$ Hz, 1H, fc), 3.63 (virtual q, $J \approx 1.8$ Hz, 1H, fc), 3.80 (s, 3H, CO_2Me), 4.40 (virtual t, $J \approx 1.9$ Hz, 1H, fc), 4.50 (m, 3H, fc), 4.79 (m, 1H of NHC*H* and 1H of fc), 5.04 (d, $J_{HH} = 6.0$ Hz, 1H, η^6-C_6H_4), 5.18 (m, 3H, η^6-C_6H_4), 7.20 (d, $^3J_{HH} = 8.1$ Hz, 1H, N*H*CH), 7.37–7.49 (m, 6H, PPh$_2$), 7.72–7.80 (m, 2H, PPh$_2$), 7.84–7.92 (m, 2H, PPh$_2$). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 17.9 (s). IR (KBr): ν_{NH} 3311 m, ν_{CO} 1739 vs, amide I 1651 vs, amide II 1525 vs cm^{-1}. MS (ESI+): *m*/*z* 874 ([M + Na]$^+$), 816 ([M − Cl]$^+$). Anal. Calc. for $C_{38}H_{42}NO_3PSCl_2FeRu \cdot 0.8\ CHCl_3$: C 49.20, H 4.55, N 1.48. Found: C 49.23, H 4.57, N 1.39.

3.6.5. (S)-[(η^6-*p*-MeC_6H_4Pr^i)RuCl$_2$(Ph$_2$PfcCONHCH(CH$_2$CH$_2$CO$_2$Me)CO$_2$Me-κP)] (**10**)

Red solid. Yield: 163 mg (93%). $[\alpha]_D = +77$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.05 (d, $^3J_{HH} = 7.0$ Hz, 6H, η^6-$C_6H_4CHMe_2$), 1.70 (s, 3H, η^6-C_6H_4Me), 2.33 (m, 2H, CH_2), 2.54 (m, 2H of CH_2 and 1H of η^6-$C_6H_4CHMe_2$), 2.92 (br s, 1H, fc), 3.68 (s, 3H, CH_2CO_2Me), 3.70 (unresolved dt, 1H, fc), 3.79 (s, 3H, $CHCO_2Me$), 4.37 (unresolved dq, 1H, fc), 4.47 (dt, $J \approx 2.5$, 1.3 Hz, 1H, fc), 4.51 (m, 2H, fc), 4.55 (m, 1H fc), 4.57 (m, 1H, NHC*H*), 4.81 (d, $J_{HH} = 5.9$ Hz, 1H, η^6-C_6H_4), 4.89 (br s, 1H, fc), 5.15 (d, $J_{HH} = 5.9$ Hz, 1H, η^6-C_6H_4), 5.23 (d, $J_{HH} = 6.0$ Hz, 1H, η^6-C_6H_4) 5.31 (d, $J_{HH} = 6.0$ Hz, 1H, η^6-C_6H_4), 7.36–7.45 (m, 6H, PPh$_2$), 7.48 (d, $^3J_{HH} = 8.1$ Hz, 1H, N*H*CH), 7.68–7.76 (m, 2H, PPh$_2$), 7.85–7.93 (m, 2H, PPh$_2$). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 17.6 (s). IR (KBr): ν_{NH} 3415 s, ν_{CO} 1737 vs, amide I 1650 vs, amide II 1524 vs cm^{-1}. MS (ESI+): *m*/*z* 900 ([M + Na]$^+$), 842 ([M − Cl]$^+$). Anal. Calc. for $C_{40}H_{44}NO_5PCl_2FeRu \cdot 0.35\ CHCl_3$: C 52.71, H 4.86, N 1.52. Found: C 52.65, H 4.75, N 1.42.

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References

[1] C.S. Allardyce, P.J. Dyson, D.J. Ellis, S.L. Heath, Chem. Commun. (2001) 1396–1397.
[2] R.E. Morris, R.E. Aird, P.d.S. Murdoch, H. Chen, J. Cummings, N.D. Hughes, S. Pearsons, A. Parkin, G. Boyd, D.I. Jodrell, P.J. Sadler, J. Med. Chem. 44 (2001) 3616–3621.
[3] P.J. Dyson, Chimia 61 (2007) 698–703.
[4] S.J. Dougan, P.J. Sadler, Chimia 61 (2007) 704–715;
C. Scolaro, A.B. Chaplin, C.G. Hartinger, A. Bergamo, M. Cocchietto, B.K. Keppler, G. Sava, P.J. Dyson, Dalton Trans. (2007) 5065–5072.
[5] W.H. Ang, P.J. Dyson, Eur. J. Inorg. Chem. (2006) 4003–4018.
[6] C.G. Hartinger, P.J. Dyson, Chem. Soc. Rev. 38 (2009) 391–401.
[7] M. Melchart, P.J. Sadler, in: G. Jaouen (Ed.), Bioorganometallics, Wiley-VCH, Weinheim, 2006, p. 39.
[8] L. Ronconi, P.J. Sadler, Coord. Chem. Rev. 251 (2007) 1633–1648.
[9] G. Süss-Fink, Dalton Trans. 39 (2010) 1673–1688.
[10] L.-V. Popova, V.N. Babin, Y.A. Belousov, Y.S. Nekrasov, A.E. Snegireva, N.P. Borodina, G.M. Shaposhnikova, O.B. Bychenko, P.M. Raevskii, Appl. Organomet. Chem. 7 (1993) 85–94;
P. Köpf-Maier, H. Köpf, E.W. Neuse, J. Cancer Res. Clin. 108 (1984) 336–340;
M. Görmen, P. Pigeon, S. Top, E.A. Hillard, M. Huché, C.G. Hartinger, F. de Montigny, M.-A. Plamont, A. Vessières, G. Jaouen, ChemMedChem 5 (2010) 2039–2050.
[11] E. Hillard, A. Vessieres, F. Le Bideau, D. Plazuk, D. Spera, M. Huché, G. Jaouen, ChemMedChem 1 (2006) 551–559. and references cited therein.
[12] W. Henderson, S.R. Alley, Inorg. Chim. Acta 322 (2001) 106–112.
[13] A. Rosenfeld, J. Blum, D. Gibson, A. Ramu, Inorg. Chim. Acta 201 (1992) 219–221.
[14] M. Viotte, B. Gautheron, M.M. Kubicki, I.E. Nifant'ev, S.P. Fricker, Met.-based Drugs 2 (1995) 311–326.
[15] M. Auzias, B. Therrien, G. Süss-Fink, P. Štěpnička, Wee Han Ang, P.J. Dyson, Inorg. Chem. 47 (2008) 578–583.
[16] A.K. Bytzek, K. Boeck, S. Hann, B.K. Keppler, C.G. Hartinger, G. Koellensperger, Metallomics 3 (2011) 1049–1055.
[17] M. Pongratz, P. Schluga, M.A. Jakupec, V.B. Arion, C.G. Hartinger, G. Allmaier, B.K. Keppler, J. Anal. At. Spectrom. 19 (2004) 46–51.
[18] L. Messori, F. Gonzales Vilchez, R. Vilaplana, F. Piccioli, E. Alessio, B.K. Keppler, Met.-based Drugs 7 (2000) 335–342;
A.R. Timerbaev, C.G. Hartinger, S.S. Aleksenko, B.K. Keppler, Chem. Rev. 106 (2006) 2224–2248;
C.G. Hartinger, W.H. Ang, A. Casini, L. Messori, B.K. Keppler, P.J. Dyson, J. Anal. At. Spectrom. 22 (2007) 960–967;
K. Polec-Pawlak, J.K. Abramski, O. Semenova, C.G. Hartinger, A.R. Timerbaev, B.K. Keppler, M. Jarosz, Electrophoresis 27 (2006) 1128–1135;
M.J. Clarke, S. Bitler, D. Rennert, M. Buchbinder, A.D. Kelman, J. Inorg. Biochem. 12 (1980) 79–87;
P. Schluga, C.G. Hartinger, A. Egger, E. Reisner, M. Galanski, M.A. Jakupec, B.K. Keppler, Dalton Trans. 14 (2006) 1796–1802.
[19] P.J. Dyson, G. Sava, Dalton Trans. (2006) 1929–1933.
[20] For a general review on the chemistry of phosphine-carboxamides, see: P. Štěpnička Chem. Soc. Rev. 41 (2012) 4273–4305.
[21] J. Tauchman, I. Císařová, P. Štěpnička, Organometallics 28 (2009) 3288–3302.
[22] J. Tauchman, I. Císařová, P. Štěpnička, Eur. J. Org. Chem. (2010) 4276–4287;
J. Tauchman, I. Císařová, P. Štěpnička, Dalton Trans. 40 (2011) 11748–11757.
[23] J. Tauchman, B. Therrien, G. Süss-Fink, P. Štěpnička, Organometallics 31 (2012) 3985–3994.
[24] S.J. Dougan, A. Habtemariam, S.E. McHale, S. Pearsons, P.J. Sadler, Proc. Natl. Acad. Sci. U S A 105 (2008) 11628–11633.
[25] F. Giannini, G. Süss-Fink, J. Furrer, Inorg. Chem. 50 (2011) 10552–10554.
[26] F. Giannini, J. Furrer, A.-F. Ibao, G. Süss-Fink, B. Therrien, O. Zava, M. Baquie, P.J. Dyson, P. Štěpnička, J. Biol. Inorg. Chem. 17 (2012) 951–960.
[27] J. Podlaha, P. Štěpnička, J. Ludvík, I. Císařová, Organometallics 15 (1996) 543–550.
[28] M.A. Bennett, T.-N. Huang, T.W. Matheson, A.K. Smith, Inorg. Synth. 21 (1982) 75.
[29] M. Brenner, W. Huber, Helv. Chim. Acta 36 (1953) 1109–1115.