Anticancer activity of opened arene ruthenium metalla-assemblies†

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Cationic tetranuclear and hexanuclear opened metalla-assemblies incorporating 5,15-bis(4-pyridyl)-10,20-diphenylporphyrin (bpp) or 5,10,15-tris(4-pyridyl)-20-phenylporphyrin (tpp) panels and dinuclear arene ruthenium clips $[(p\text{-cymene})_2Ru_2(OO\cap OO)_2]^{2+}$ ($OO\cap OO$ = oxalato, 2,5-dioxydo-1,4-benzoquinonato (dobq)) have been assembled in the presence of silver triflate. All complexes were characterised by NMR, IR and UV-visible spectroscopy and electrospray ionisation mass spectrometry. The cytotoxicities of the tetranuclear and hexanuclear ruthenium complexes have been established on ovarian A2780 and A2780cisR cancer cell lines. The compounds are quite cytotoxic, the most active metalla-assembly being $[Ru_6(p\text{-cymene})_6(dobq)_3(tpp)_2]^{6+}$, with IC_{50} values of 2.1 μM and 3.8 μM against A2780 and A2780cisR cells, respectively.

Introduction

With a view to increase the range of tumours treatable by platinum-based complexes multinuclear platinum compounds have been developed.[1] The trinuclear compound $[(NH_3)_2ClPtNH_2(CH_2)_6NH_2Pt(NH_3)_2NH_2(CH_2)_6NH_2PtCl(NH_3)_2](NO_3)_4$ (BBR3464) was found to be 2 to 3 orders of magnitude more active than cisplatin in several cell lines *in vivo* and reached phase II clinical trials although it was finally abandoned due to poor stability in human plasma.[2] The dinuclear compound $[(NH_3)_2ClPtNH_2(CH_2)_6NH_2(CH_2)_2NH_2(CH_2)_6NH_2PtCl(NH_3)_2](NO_3)_4$ (CT-3610) and its alkylcarboxylate analogues were shown to possess a better stability profile in human plasma compared to BBR3464 and consequently were considered for clinical development.[3] In an extension to this "multinuclearity approach" a number of macromolecular platinum compounds have been evaluated: including a polymer-linked diaminocyclohexyl platinum chemotherapeutic (AP5346),[4] hyperbranched polyglycerol polymers with carboxylic groups that coordinate platinum[5] and anionic poly(aminoamine) dendritic vehicles for platinum compounds.[6] Such compounds could specifically target tumours by exploiting their unique extracellular environment, *i.e.* their hypervasculature, defective vascular architecture, and impaired lymphatic drainage,[7] and is referred to as the "enhanced permeability and retention" (EPR) effect. Indeed, it has become common to target cancers *via* the application of macromolecules which may accumulate in cancer cells, but are unable to permeate healthy cells.[8]

Ruthenium complexes have also been evaluated as putative anticancer agents, and they appear to exert their cytotoxic effect *via* different modes of actions to those of platinum drugs.[9] Moreover, ruthenium complexes exhibit a low general toxicity and are effective against tumours that do not respond well to cisplatin.[10] Two mononuclear ruthenium complexes have recently entered phase-II clinical trials.[11,12] However, compared to platinum, the "multinuclearity approach" remains an under exploited concept for ruthenium-based drugs,[13] especially within the family of organoruthenium chemotherapeutics.[14]

The dinuclear arene ruthenium complexes $[(p\text{-cymene})_2Ru_2(OO\cap OO)Cl_2]$ ($OO\cap OO = MeC_5H_2O_2N(CH_2)_nNC_5H_2MeO_2$) show relevant cytotoxicities towards human cancer cell lines and unique DNA binding properties.[15] Similarly, the Ru_2Fe trinuclear complex $[(p\text{-cymene})_2Ru_2(N\cap N)Cl_2]$ ($N\cap N = NC_5H_4OOC\text{-}C_5H_4FeC_5H_4\text{-}COOC_5H_4N$) is equally cytotoxic against A2780 and A2780cisR (cisplatin resistant) cancer cells,[16] and the dinuclear complex $[(indane)_2Ru_2(2,3\text{-bis}(2\text{-pyridyl})pyrazine)Cl_2]$ is a potential photochemical agent.[17] Among other multinuclear arene ruthenium compounds, the trinuclear arene ruthenium clusters possess remarkable cytotoxicity[18] and a series of tetranuclear arene ruthenium complexes containing a porphyrin core demonstrate excellent photodynamic properties.[19] Recently, a dendritic scaffold was used to deliver arene ruthenium units to cancer cells.[20] These large systems have the potential to exploit the EPR effect to accumulate preferentially in cancer cells.

Recently, we have prepared a series of metalla-assemblies and studied their biological applications.[21] Rectangular tetranuclear arene ruthenium complexes containing 1,2-bis(4-pyridyl)ethylene linkers and 2,5-dioxydo-1,4-benzoquinonato (dobq) bridges were found to be more active against A2780 cancer cells (IC_{50} = 6 μM) than the smaller 4,4′-bipyridine containing assemblies,[22] and the water-soluble hexacationic arene ruthenium assembly $[Ru_6(p\text{-cymene})_6(dobq)_3(tpt)_2]^{6+}$ (tpt = 2,4,6-tris(pyridin-4-yl)-1,3,5-triazine) was shown to possess an energy-independent uptake pathway, good cytotoxicity, and able to act as a Trojan horse against cancer cells by carrying cytotoxic guest molecules.[23]

We have now extended this synthetic strategy to larger metalla-assemblies incorporating polypyridyl-porphyrin panels, 5,15-bis(4-pyridyl)-10,20-diphenylporphyrin (bpp) and 5,10,15-tris(4-pyridyl)-20-phenylporphyrin (tpp), connected by dinuclear arene ruthenium clips $[Ru_2(p\text{-cymene})_2(OO\cap OO)_2]^{2+}$ ($OO\cap OO$ = oxalato, 2,5-dioxydo-1,4-benzoquinonato). Herein

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we describe the synthesis and characterisation of the tetracationic metalla-assemblies, $[Ru_4(p\text{-cymene})_4(oxalato)_2(bpp)_2]^{4+}$ and $[Ru_4(p\text{-cymene})_4(dobq)_2(bpp)_2]^{4+}$, and the hexacationic metalla-assemblies, $[Ru_6(p\text{-cymene})_6(oxalato)_3(tpp)_2]^{6+}$ and $[Ru_6(p\text{-cymene})_6(dobq)_3(tpp)_2]^{6+}$, and their *in vitro* activity against human ovarian cancer cell lines.

Results and discussion

The tetranuclear arene ruthenium metalla-assemblies, $[Ru_4(p\text{-cymene})_4(OO{\cap}OO)_2(bpp)_2]^{4+}$ ($OO{\cap}OO$ = oxalato, **1**; 2,5-dioxydo-1,4-benzoquinonato (dobq), **2**) (Fig. 1), are readily prepared from the known dinuclear complexes $[Ru_2(p\text{-cymene})_2(oxalato)Cl_2]$[24] and $[Ru_2(p\text{-cymene})_2(dobq)Cl_2]$[23a] and the commercially available porphyrin derivative 5,15-bis(4-pyridyl)-10,20-diphenylporphyrin (bpp). The coordinatively unsaturated intermediates, $[Ru_2(p\text{-cymene})_2(oxalato)]^{2+}$ and $[Ru_2(p\text{-cymene})_2(dobq)]^{2+}$, formed upon addition of silver triflate, react at room temperature in the presence of the bpp ligands to give the corresponding tetranuclear cations **1** and **2**. These opened metalla-assemblies are isolated as triflate salts, *i.e.* $[Ru_4(p\text{-cymene})_4(oxalato)_2(bpp)_2][CF_3SO_3]_4$ ($[\mathbf{1}][CF_3SO_3]_4$) and $[Ru_4(p\text{-cymene})_4(dobq)_2(bpp)_2][CF_3SO_3]_4$ ($[\mathbf{2}][CF_3SO_3]_4$), respectively. Despite a molecular weight of 2946.9 g mol^{-1} for $[\mathbf{1}][CF_3SO_3]_4$ and 3047.0 g mol^{-1} for $[\mathbf{2}][CF_3SO_3]_4$, and their relatively high charge, these two tetranuclear metalla-assemblies are quite soluble in $(CH_3)_2CO$, CH_3CN and DMSO and sparingly soluble in CH_2Cl_2, $CHCl_3$ and H_2O.

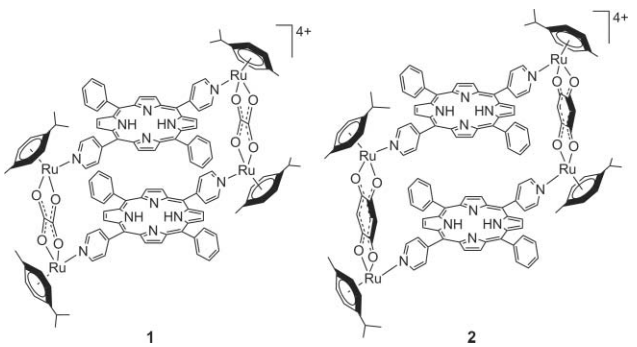

Fig. 1 Structure of the metalla-assemblies **1** and **2**.

The hexanuclear derivatives **3** and **4** are obtained following the same strategy, but using the tridentate porphyrin panels, 5,10,15-tris(4-pyridyl)-20-phenylporphyrin (tpp). Cations **3** and **4** are also isolated as triflate salts, *i.e.* $[Ru_6(p\text{-cymene})_6(oxalato)_3(tpp)_2][CF_3SO_3]_6$ ($[\mathbf{3}][CF_3SO_3]_6$) and $[Ru_6(p\text{-cymene})_6(dobq)_3(tpp)_2][CF_3SO_3]_6$ ($[\mathbf{4}][CF_3SO_3]_6$) (Fig. 2). Despite their higher charge, **3** and **4** possess a similar solubility to $[\mathbf{1}][CF_3SO_3]_4$ and $[\mathbf{2}][CF_3SO_3]_4$, with the molecular weight of the salts being 3803.6 and 3953.8 g mol^{-1} for $[\mathbf{3}][CF_3SO_3]_6$ and $[\mathbf{4}][CF_3SO_3]_6$, respectively.

The IR spectra of $[\mathbf{1–2}][CF_3SO_3]_4$ and $[\mathbf{3–4}][CF_3SO_3]_6$ are dominated by absorptions of the coordinated polypyridyl-porphyrin panels with, in particular, the in-plane N–H deformation around 1220 cm^{-1},[25] and the bands assigned to the C=C and C=N skeletal modes of the porphyrins located between 1620 and 1400 cm^{-1}.[26] Moreover, the bands associated with the $OO{\cap}OO$ bridges, including the strong C=O stretching vibration (≈ 1630 cm^{-1}), are

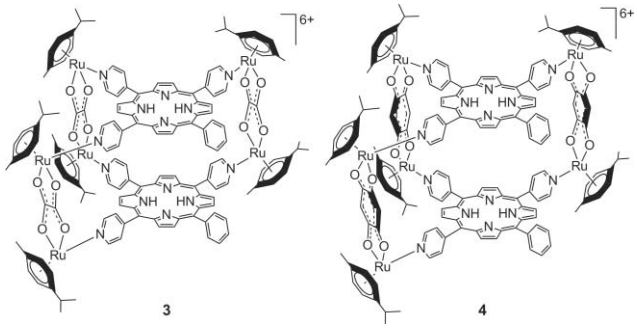

Fig. 2 Structures of the metalla-assemblies **3** and **4**.

only slightly shifted with respect to the dinuclear complexes $[Ru_2(p\text{-cymene})_2(oxalato)Cl_2]$[24] and $[Ru_2(p\text{-cymene})_2(dobq)Cl_2]$.[23a] In addition to the porphyrin and $OO{\cap}OO$ absorptions, strong stretching vibrations due to the triflate anions [1260 (s), 1030 (s), 638 (m) cm^{-1}] are also observed in the IR spectra of the salts $[\mathbf{1–2}][CF_3SO_3]_4$ and $[\mathbf{3–4}][CF_3SO_3]_6$.

The metalla-assemblies **1–4** are stable in deuterated water at 60 °C for 48 h, in which no degradation is observed by NMR spectroscopy, whereas in DMSO the complexes are stable for several hours at room temperature. The decomplexation of the metalla-assemblies in DMSO-d_6 may be monitored by ^{1}H NMR spectroscopy, in which signals corresponding to free bpp and tpp ligands are gradually observed.

The chemical shift pattern for the protons of the bpp and *p*-cymene ligands in **1** and **2** are similar despite the different length of the bridging $OO{\cap}OO$ ligands. However, the signal of the N–H protons is shifted more upfield in the dobq derivative **2** than in the oxalato derivative **1**. The upfield shift of the signal of the N–H protons is consistent with a closed face-to-face arrangement of the two porphyrin units.[27] In the tetranuclear complexes, **1** and **2**, large and broad signals are observed for the pyridyl and pyrrole protons of the porphyrin panels (see ESI†) as well as for the signal of the N–H protons. In addition, the aromatic protons of the *p*-cymene ligands appear as four superimposed doublets in the region 6.5 to 6.0 ppm. In **2**, an additional singlet is observed at $\delta = 6.17$ ppm corresponding to the dobq protons. The ^{1}H NMR spectra of **3–4** are somewhat more complicated, not only due to the presence of diastereotopic protons in solution, which is in agreement with a chiral conformation as previously observed in the related metalla-assemblies $[Ru_6(p\text{-cymene})_6(oxalato)_3(tpt)_2]^{6+}$,[28] $[Ru_8(p\text{-cymene})_8(oxalato)_4(H_2TPyP)_2]^{8+}$ (H_2TPyP = 5,10,15,20-tetra(4-pyridyl)porphyrin)[29] and $[Ru_8(p\text{-cymene})_8(dobq)_4(H_2TPyP)_2]^{8+}$,[27] but as well due to the lost of a symmetry element present in **1** and **2**.

Indeed, each proton of **3–4** resonates at a distinct chemical shift, and accordingly the ^{1}H NMR spectrum of **4** contains 142 distinct resonances (see ESI†). The assignment of the signals was made using a combination of 1D and 2D NMR techniques (^{1}H, ^{13}C, HSQC, 10 ppm HSQC, COSY, see ESI†). Due to their chiral conformation the chemical shift patterns for the protons of the bpp and *p*-cymene ligands, as well as for the pyridyl and pyrrole protons of the porphyrin panels, cannot be compared to the patterns observed for the tetranuclear complexes **1** and **2**. Rather than attempting a partial attribution of some resonances, several 10 ppm HSQC experiments were recorded in order to improve the spectral resolution and determine the number of carbon signals at

a given proton chemical shift. In usual heteronuclear ^{1}H-^{13}C NMR experiments, recorded with the full spectral width, the signals possess a typical width as large as 1 ppm in the ^{13}C dimension, making it impossible to distinguish between close signals. The use of 10 ppm experiments resolves the overlap problem and allows the determination of the correct ^{13}C chemical shifts, which is straightforward in these types of aliased spectra.[30] For instance, Fig. 3 shows an excerpt of a 10 ppm HSQC recorded on **4** displaying the region of the H_α of the pyridyl groups. In the figure, the difficulty to distinguish between closed ^{13}C signals in a standard ^{1}H-^{13}C HSQC experiment is readily demonstrated (top), in which only ten distinct cross peaks are identified. Moreover, the 10 ppm HSQC experiment increases the resolution in the ^{13}C dimension by a factor of about 25, thus enabling all resonances to be separated, and the twelve independent signals of the H_α of the pyridyl groups could be resolved (Fig. 3). The other resonances present in the 10 ppm spectrum arise from signals that are back-folded into the smaller window. Therefore, the discrimination of the resonances and the determination of the chemical shifts in a 10 ppm spectrum become straightforward.

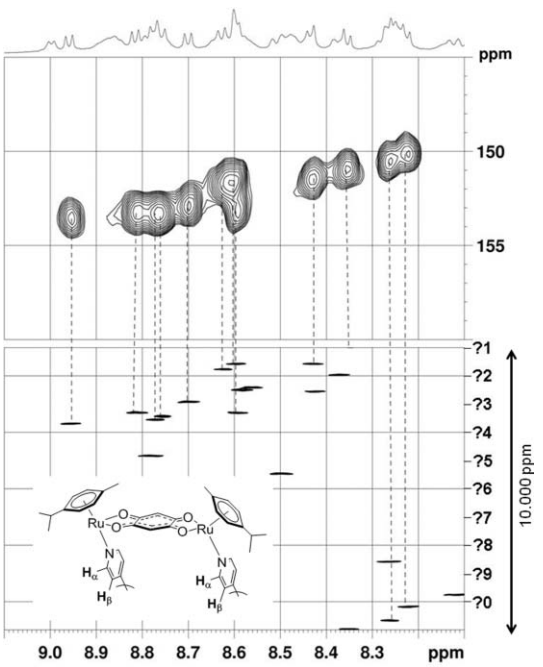

Fig. 3 Excerpts of the full-width HSQC (top) and 10 ppm HSQC (bottom) NMR spectra in CD_3CN of the metalla-assembly [**4**][CF_3SO_3]$_6$, showing the twelve independent signals of the H_α of the pyridyl groups (the question marks indicate unknown values).

Electronic absorption spectra of the multinuclear metalla-assemblies **1–4** as well as the polypyridyl-porphyrin panels (bpp and tpp) were acquired in acetone at 10^{-5} M concentration in the range 250–800 nm, see Fig. 4. The visible-region electronic absorption spectra of all the compounds are characterised by intense absorptions due to the porphyrin panels, including the Soret band at around 400 nm and a series of Q bands between 500 and 700 nm. In complexes **1–4**, compared to the free porphyrins bpp and tpp, the Soret band is blue shifted and the full width at half-maximum ($\Delta\nu$) increases. In the case of metalla-assembly **4**, the full width at half-maximum ($\Delta\nu$ = 1870 cm^{-1}) is twice the

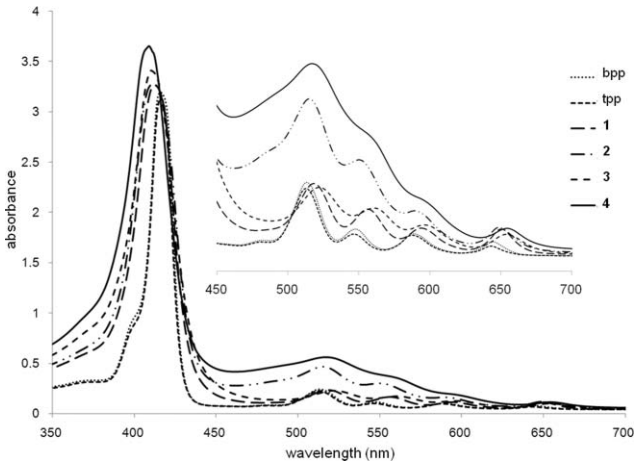

Fig. 4 Electronic absorption spectra of bpp, tpp and the metalla-assemblies **1–4** in acetone (10^{-5} M).

width of bpp (865 cm^{-1}) and the Soret band is blue shifted by 712 cm^{-1}. Moreover, a clear red shift of the Q bands is observed in **1–4**. These photophysical changes in the UV-visible spectra of **1–4** are characteristic of sandwich-type dimeric structures in which the porphyrin units are in a face-to-face geometry,[31] entirely consistent with the proposed structures.

The formation of the metalla-assemblies **1–4** was also confirmed by electrospray mass spectrometry with the four compounds displaying remarkable stability. The ESI-MS spectra show peaks corresponding to [**1**]$^{4+}$, [**1** + CF_3SO_3]$^{3+}$, [**2**]$^{4+}$, [**2** + CF_3SO_3]$^{3+}$, [**3** + $(CF_3SO_3)_2$]$^{4+}$, [**3** + $(CF_3SO_3)_3$]$^{3+}$, [**4** + $(CF_3SO_3)_2$]$^{4+}$ and [**4** + $(CF_3SO_3)_3$]$^{3+}$ at m/z 587.9, 833.5, 612.8, 866.8, 802.3, 1119.8, 839.9 and 1169.5, respectively (see ESI†). These peaks may be assigned unambiguously on the basis of their characteristic Ru_4 and Ru_6 isotope patterns.

The putative antitumour activity [**1–2**][CF_3SO_3]$_4$ and [**3–4**][CF_3SO_3]$_6$ was evaluated on A2780 (cisplatin sensitive) and A2780cisR (cisplatin resistant) human ovarian cancer cells. Although these compounds are highly charged it has been shown that highly charged metal complexes can not only traverse cell membranes, but some do so more effectively that neutral complexes or cations with low charges.[32] The cytotoxicities of the tetranuclear complexes **1** and **2** and the hexanuclear arene ruthenium complexes **3** and **4** are presented in Table 1. All compounds display good cytotoxicity towards both the sensitive and resistant cell lines with quite similar IC_{50} values. It is noteworthy, however, that the hexanuclear complexes **3** and **4** are slightly more cytotoxic than their tetranuclear counterparts **1** and **2**, which is consistent with the number of ruthenium centres per metalla-assemblies. In general, for arene ruthenium complexes an additive effect is observed as the number of ruthenium centres increases.[20] However, an additive effect is not always observed, for example, binuclear arene ruthenium complexes (connected *via* pyridone-based chelators) were found to be highly active in a colorectal carcinoma cell line in the absence of any activity for the mononuclear counterparts.[15c] Complexes **2** and **4** that contain the dobq ligand are more cytotoxic than the oxalato derivatives **1** and **3**, indicating that the length of the spacer is a relevant parameter in the design of these types of compounds. Overall, the cytotoxicities of these compounds are as

Table 1 IC_{50} values of **1–4** in A2780 and A2780cisR cell lines

Compound	A2780 (IC_{50}, μM)	A2780cisR (IC_{50}, μM)
1	11.0 ± 0.2	12.7 ± 3.0
2	5.6 ± 0.4	10.1 ± 1.2
3	3.1 ± 1.0	10.7 ± 2.6
4	2.1 ± 0.3	3.8 ± 0.8
cisplatin	1.6	8.6

good as the best observed for other multinuclear arene ruthenium complexes.[15-20]

Conclusions

A series of cationic metalla-assemblies based on dinuclear arene ruthenium clips and polypyridyl porphyrin panels have been prepared and characterised. The compounds are stable, and based on promising results obtained for related ruthenium compounds, were evaluated for *in vitro* anticancer activity. Large compounds such as these could potentially exploit the EPR effect for tumour targeting but as yet an *in vivo* study has not been performed to test this possibility. From the *in vitro* study, however, it was found that the number of ruthenium centres and the type of spacer used influence the cytotoxicity of these metalla-assemblies, and consequently, further studies to fine tune drug specificity would be worthwhile.

Experimental

General details

The dinuclear *p*-cymene ruthenium complexes [Ru_2(*p*-cymene)$_2$(oxalato)Cl_2][24] and [Ru_2(*p*-cymene)$_2$(dobq)Cl_2][23a] were prepared according to published methods. The porphyrin derivatives were commercially available (either TriPorTech GmbH or Frontier Scientific) and used as received. All other reagents were purchased from Sigma-Aldrich and used as received. The ^1H, $^{13}C\{^1H\}$, HSQC, 10 ppm HSQC and COSY NMR spectra were recorded on a Bruker AvanceII 400 spectrometer using the residual protonated solvent as internal standard. *J* values are given in Hz. Infrared spectra were recorded as KBr pellets on a Perkin-Elmer FTIR 1720X spectrometer. UV-visible absorption spectra were recorded on an Uvikon 930 spectrophotometer using precision cells made of quartz (1 cm). Microanalyses were performed by the Laboratory of Pharmaceutical Chemistry, University of Geneva (Switzerland). Electrospray mass spectra were obtained in positive-ion mode with a Bruker FTMS 4.7T BioAPEX II mass spectrometer, University of Fribourg (Switzerland).

Compound synthesis

Metalla-assemblies: general synthetic procedure for 1–4. A mixture of dinuclear *p*-cymene ruthenium complexes [Ru_2(*p*-cymene)$_2$(oxalato)Cl_2] (**1**: 57 mg, 0.09 mmol; **3**: 85 mg, 0.13 mmol) or [Ru_2(*p*-cymene)$_2$(dobq)Cl_2] (**2**: 61 mg, 0.09 mmol; **4**: 92 mg, 0.13 mmol), $AgCF_3SO_3$ (**1**, **2**: 46 mg, 0.18 mmol; **3**, **4**: 69 mg, 0.27 mmol) and the corresponding porphyrin panels 5,15-bis(4-pyridyl)-10,20-diphenylporphyrin (**1**, **2**: 55 mg, 0.09 mmol) or 5,10,15-tris(4-pyridyl)-20-phenylporphyrin (**3**, **4**: 56 mg, 0.09 mmol) was stirred at 60 °C for 24 h and then the solution was filtered to remove silver chloride. The solvent was removed under vacuum and the residue was re-dissolved in dichloromethane (3 mL) and diethyl ether added to precipitate the products as red solids.

[**1**][CF_3SO_3]$_4$ (75 mg, 85%) (Found: C, 54.07; H, 3.95; N, 5.98. Calc. for $C_{132}H_{112}N_{12}F_{12}O_{20}S_4Ru_4$: C, 53.73; H, 3.80; N, 5.70%); λ_{max}((CH$_3$)$_2$CO)/nm 411 (ε/dm^3 mol^{-1} cm^{-1} 327 000), 515 (47 000), 550 (30 000), 589 (16 000) and 649 (12 000); ν_{max}/cm^{-1} 3436 m (NH), 3061 w (CH$_{p\text{-cym}}$), 1523 s (CO), 1258 s (CF_3); δ_H(400 MHz, CD_3CN) 4.25 (4 H, broad, NH), 1.58 (24 H, d, *J* 5.6, CH(C*H*$_3$)$_2$), 2.40 (12 H, s, CH_3), 3.13 (4 H, sept, C*H*(CH$_3$)$_2$), 6.04 (8 H, m, H$_{p\text{-cym}}$), 6.18 (8 H, m, H$_{p\text{-cym}}$), 7.25 (7 H, broad, H$_{phenyl}$), 8.17 (4 H, m, H$_{pyr}$), 8.35 (3 H, m, H$_{phenyl}$), 8.48 (4 H, m, H$_{pyr}$), 8.55 (4 H, d, *J* 7.4, H$_\beta$), 8.90 (4 H, d, H$_\alpha$); δ_C(100 MHz, CD_3CN) 18.4 (CH_3), 22.7 (CH(*C*H$_3$)$_2$), 32.2 (*C*H(CH$_3$)$_2$), 83.1 (CH$_{p\text{-cym}}$), 84.9 (CH$_{p\text{-cym}}$), 98.5 (*C*CH$_3$), 103.6 (*C*CH(CH$_3$)$_2$), 115.5 (C$_{pyr}$), 132.1 (CH$_{phenyl}$), 132.4 (CH$_{phenyl}$), 133.0 (CH$_\beta$), 133.4 (CH$_\beta$), 142.7 (C$_{phenyl}$), 142.8 (C$_{phenyl}$), 151.1 (CH$_\alpha$), 153.3 (CH$_\alpha$), 171.9 (CO); *m*/*z* (EI) 833.5 [**1** + CF_3SO_3]$^{3+}$, 587.9 [**1**]$^{4+}$.

[**2**][CF_3SO_3]$_4$ (79 mg, 86%) (Found: C, 55.38; H, 3.63; N, 4.92. Calc. for $C_{140}H_{116}N_{12}F_{12}O_{20}S_4Ru_4$: C, 55.12; H, 3.80; N, 5.51%); λ_{max}((CH$_3$)$_2$CO)/nm 413 (ε/dm^3 mol^{-1} cm^{-1} 326 000), 521 (23 000), 560 (16 000), 599 (11 000) and 654 (11 000); ν_{max}/cm^{-1} 3446 m (NH), 3066 w (CH$_{p\text{-cym}}$), 1631 s (CO), 1259 s (CF_3); δ_H(400 MHz, CD_3CN) 3.50 (4 H, broad, NH), 1.55 (24 H, d, *J* 5.8, CH(C*H*$_3$)$_2$), 2.39 (12 H, s, CH_3), 3.07 (4 H, sept, C*H*(CH$_3$)$_2$), 5.92 (8 H, d, *J* 6.0, H$_{p\text{-cym}}$), 6.10 (4 H, s, H$_{dobq}$), 6.13 (8 H, d, H$_{p\text{-cym}}$), 7.25 (7 H, broad, H$_{phenyl}$), 8.10 (4 H, m, H$_{pyr}$), 8.35 (3 H, m, H$_{phenyl}$), 8.42 (4 H, m, H$_{pyr}$), 8.58 (4 H, d, *J* 7.4, H$_\beta$), 8.75 (4 H, d, H$_\alpha$); δ_C(100 MHz, CD_3CN) 18.5 (CH_3), 22.6 (CH(*C*H$_3$)$_2$), 32.3 (*C*H(CH$_3$)$_2$), 83.2 (CH$_{p\text{-cym}}$), 84.8 (CH$_{p\text{-cym}}$), 98.4 (*C*CH$_3$), 103.7 (*C*CH(CH$_3$)$_2$), 115.6 (C$_{pyr}$), 125.7 (CH$_{phenyl}$), 132.8 (CH$_{phenyl}$), 132.9 (CH$_{phenyl}$), 133.0 (CH$_\beta$), 133.1 (CH$_\beta$), 141.3 (C$_{phenyl}$), 141.4 (C$_{phenyl}$), 151.0 (CH$_\alpha$), 153.3 (CH$_\alpha$), 171.8 (CO); *m*/*z* (EI) 866.8 [**2** + CF_3SO_3]$^{3+}$, 612.8 [**2**]$^{4+}$.

[**3**][CF_3SO_3]$_6$ (97 mg, 85%) (Found: C, 48.27; H, 3.29; N, 5.02. Calc. for $C_{154}H_{136}N_{14}F_{18}O_{30}S_6Ru_6$: C, 48.53; H, 3.52; N, 5.15%); λ_{max}((CH$_3$)$_2$CO)/nm 410 (ε/dm^3 mol^{-1} cm^{-1} 341 000), 522 (23 000), 565 (16 000), 602 (12 000) and 656 (10 000); ν_{max}/cm^{-1} 3467 m (NH), 3069 w (CH$_{p\text{-cym}}$), 1631 s (CO), 1258 s (CF_3); δ_H(400 MHz, CD_3CN) 6.94 (4 H, s, NH), 1.54 (36 H, m, CH(C*H*$_3$)$_2$), 2.42 (18 H, s, CH_3), 3.14 (6 H, m, C*H*(CH$_3$)$_2$), 6.22 to 6.26 (12 H, m, H$_{p\text{-cym}}$), 6.36 to 6.42 (12 H, m, H$_{p\text{-cym}}$), 7.32 (1 H, m, H$_\beta$), 7.39 (2 H, m, H$_{phenyl}$), 7.65 (2 H, m, H$_{phenyl}$), 7.90 (3 H, m, H$_{pyr}$), 7.99 (4 H, m, H$_{phenyl}$), 8.10 (2 H, m, H$_{pyr}$), 8.26 (1 H, m, H$_\alpha$), 8. 30 (1 H, m, H$_{phenyl}$), 8.38 (1 H, d, *J* 7.5, H$_\beta$), 8.40 (1 H, m, H$_\alpha$), 8.55 (1 H, m, H$_\alpha$), 8.78 (1 H, m, H$_\alpha$), 8.86 (3 H, m, H$_{pyr}$), (1 H, m, H$_{pyr}$), 9.20 (m, 1 H, H$_{pyr}$), 9.42 (1 H, d, H$_\alpha$), 7.60 to 9.40 (broad, 6 H, H$_{pyr}$; 1 H, H$_{phenyl}$; 7 H, H$_\alpha$; 10 H, H$_\beta$); δ_C(100 MHz, CD_3CN)[33] 19.1 (CH_3), 19.2 (CH_3), 19.2 (CH_3), 22.1 (CH(*C*H$_3$)$_2$), 22.5 (CH(*C*H$_3$)$_2$), 22.6 (CH(*C*H$_3$)$_2$), 32.0 (*C*H(CH$_3$)$_2$), 32.2 (*C*H(CH$_3$)$_2$), 32.2 (*C*H(CH$_3$)$_2$), 85.5 (CH$_{p\text{-cym}}$), 88.3 (CH$_{p\text{-cym}}$), 99.6 (*C*CH$_3$), 121.0 (C$_{pyr}$), 125.1 (CH$_{phenyl}$), 125.2 (CH$_{phenyl}$), 127.1 (CH$_\beta$), 128.5 (CH$_{phenyl}$), 128.7 (CH$_{phenyl}$), 128.9 (CH$_{phenyl}$), 129.7 (CH$_{phenyl}$), 142.2 (C$_{phenyl}$), 153.2 (CH$_\alpha$), 153.3 (CH$_\alpha$), 184.4 (CO), 184.5 (CO); *m*/*z* (EI) 1119.8 [**3** + (CF_3SO_3)$_3$]$^{3+}$, 802.3 [**3** + (CF_3SO_3)$_2$]$^{4+}$.

[**4**][CF_3SO_3]$_6$ (98 mg, 82%) (Found: C, 50.27; H, 3.23; N, 4.52. Calc. for $C_{166}H_{142}N_{14}F_{18}O_{30}S_6Ru_6$: C, 50.42; H, 3.62; N, 4.96%);

$\lambda_{max}((CH_3)_2CO)$/nm 409 ($\varepsilon$/dm^3 mol^{-1} cm^{-1} 365 000), 517 (56 000), 560 (36 000) and 654 (12 000); ν_{max}/cm^{-1} 3434 m (NH), 3059 w ($CH_{p\text{-cym}}$), 1522 s (CO), 1258 s (CF_3); δ_H(400 MHz, CD_3CN) –6.96 (2 H, s, NH), 6.76 (2 H, m, NH), 1.52 (36 H, m, $CH(CH_3)_2$), 2.45 (18 H, m, CH_3), 3.15 (6 H, m, $CH(CH_3)_2$), 5.80 to 6.30 (24 H, m, $H_{p\text{-cym}}$), 6.13 (1 H, s, H_{dobq}), 6.14 (1 H, s, H_{dobq}), 6.15 (1 H, s, H_{dobq}), 6.16 (1 H, s, H_{dobq}), 6.17 (1 H, s, H_{dobq}), 6.18 (1 H, s, H_{dobq}), 6.75 (1 H, m, H_{pyr}), 7.12 (1 H, m, H_{pyr}), 7.18 (1 H, m, H_β), 7.32 (1 H, m, H_β), 7.35 (2 H, m, H_{phenyl}), 7.50 (6 H, m, H_β), 7.65 (2 H, m, H_{phenyl}), 7.78 (4 H, m, H_β), 7.85 (3 H, m, H_{pyr}), 7.98 (4 H, m, H_{phenyl}), 8.05 (1 H, m, H_{phenyl}), 8.10 (2 H, m, H_{pyr}), 8.18 (5 H, m, H_{pyr}), 8.22 (1 H, m, H_α), 8.26 (1 H, m, H_α), 8. 30 (1 H, m, H_{phenyl}), 8.35 (1 H, m, H_α), 8.42 (1 H, m, H_α), 8.58 (1 H, m, H_α), 8.60 (1 H, m, H_α), 8.62 (1 H, m, H_α), 8.70 (1 H, m, H_α), 8.76 (1 H, m, H_α), 8.77 (1 H, m, H_α), 8.82 (1 H, m, H_α), 8.85 (3 H, m, H_{pyr}), 8.95 (1 H, m, H_α), 9.00 (1 H, m, H_{pyr}); δ_C(100 MHz, CD_3CN) 18.5 (CH_3), 18.5 (CH_3), 18.5 (CH_3), 18.6 (CH_3), 18.6 (CH_3), 18.7 (CH_3), 22.2 ($CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$), 22.6 ($CH(CH_3)_2$), 22.6 ($CH(CH_3)_2$), 22.7 ($CH(CH_3)_2$), 22.8 ($CH(CH_3)_2$), 22.8 ($CH(CH_3)_2$), 22.9 ($CH(CH_3)_2$), 22.9 ($CH(CH_3)_2$), 22.9 ($CH(CH_3)_2$), 32.4 ($CH(CH_3)_2$), 32.4 ($CH(CH_3)_2$), 32.4 ($CH(CH_3)_2$), 32.4 ($CH(CH_3)_2$), 32.5 ($CH(CH_3)_2$), 32.5 ($CH(CH_3)_2$), 82.8 ($CH_{p\text{-cym}}$), 82.9 ($CH_{p\text{-cym}}$), 82.9 ($CH_{p\text{-cym}}$), 83.1 ($CH_{p\text{-cym}}$), 83.2 ($CH_{p\text{-cym}}$), 83.3 ($CH_{p\text{-cym}}$), 83.5 ($CH_{p\text{-cym}}$), 83.8 ($CH_{p\text{-cym}}$), 83.9 ($CH_{p\text{-cym}}$), 83.9 ($CH_{p\text{-cym}}$), 84.0 ($CH_{p\text{-cym}}$), 84.0 ($CH_{p\text{-cym}}$), 84.2 ($CH_{p\text{-cym}}$), 84.3 ($CH_{p\text{-cym}}$), 84.3 ($CH_{p\text{-cym}}$), 84.4 ($CH_{p\text{-cym}}$), 84.4 ($CH_{p\text{-cym}}$), 84.8 ($CH_{p\text{-cym}}$), 84.9 ($CH_{p\text{-cym}}$), 85.0 ($CH_{p\text{-cym}}$), 85.1 ($CH_{p\text{-cym}}$), 85.1 ($CH_{p\text{-cym}}$), 85.1 ($CH_{p\text{-cym}}$), 85.1 ($CH_{p\text{-cym}}$), 99.6 (CCH_3), 99.6 (CCH_3), 99.7 (CCH_3), 99.8 (CCH_3), 99.8 (CCH_3), 99.8 (CCH_3), 102.6 (CH_{dobq}), 102.8 (CH_{dobq}), 102.9 (CH_{dobq}), 103.0 (CH_{dobq}), 103.0 (CH_{dobq}), 103.1 (CH_{dobq}), 104.6 ($CCH(CH_3)_2$), 104.7 ($CCH(CH_3)_2$), 104.7 ($CCH(CH_3)_2$), 105.0 ($CCH(CH_3)_2$), 105.1 ($CCH(CH_3)_2$), 105.2 ($CCH(CH_3)_2$), ($CCH(CH_3)_2$), 122.1 (C_{pyr}), 122.4 (C_{pyr}), 122.6 (C_{pyr}), 122.9 (C_{pyr}), 125.4 (CH_{phenyl}), 125.5 (CH_{phenyl}), 127.0 (CH_β), 127.2 (CH_β), 127.9 (CH_β), 128.3 (CH_β), 128.6 (CH_{phenyl}), 128.6 (CH_{phenyl}), 128.6 (CH_{phenyl}), 128.7 (CH_{phenyl}), 129.4 (CH_β), 129.7 (CH_{phenyl}), 129.8 (CH_{phenyl}), 129.9 (CH_β), 131.9 (CH_β), 132.0 (CH_β), 132.4 (CH_{phenyl}), 132.4 (CH_{phenyl}), 132.5 (CH_β), 133.4 (CH_β), 135.5 (CH_β), 136.0 (CH_β), 141.3 (C_{phenyl}), 141.8 (C_{phenyl}), 150.2 (CH_α), 150.7 (CH_α), 150.9 (CH_α), 151.4 (CH_α), 151.6 (CH_α), 151.8 (CH_α), 152.1 (CH_α), 152.4 (CH_α), 152.8 (CH_α), 152.9 (CH_α), 153.3 (CH_α), 153.5 (CH_α), 184.4 (CO), 184.5 (CO), 184.6 (CO), 184.6 (CO), 184.7 (CO), 184.7 (CO); *m*/*z* (EI) 1169.5 [**4** + $(CF_3SO_3)_3]^{3+}$, 839.9 [**4** + $(CF_3SO_3)_2]^{4+}$.

Cell culture and inhibition of cell growth

Human A2780 and A2780cisR ovarian carcinoma cells 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 with GlutaMAX(tm) containing 5% foetal calf serum (FCS) and antibiotics (penicillin and ciproxin) at 37 °C and 5% CO_2. For the evaluation of growth inhibition tests, the cells were seeded in 96 well plates (25000 cells per well) and grown for 24 h in complete medium. Complexes were added to the required concentration and added to the cell culture and incubated at 37 °C for 72 h. The complexes were dissolved in DMSO and then diluted in complete medium to the required concentration. The DMSO concentration did not exceed 0.5% v/v and at this concentration DMSO did not show any effects on cells. Solutions of the compounds were applied by diluting a freshly prepared stock solution of the corresponding compound in aqueous RPMI medium with GlutaMAX™ (20 mM). Following drug exposure, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to the cells at a final concentration of 0.25 mg ml^{-1} and incubated for 2 h, then the culture medium was aspirated and the violet formazan (artificial chromogenic precipitate of the reduction of tetrazolium salts by dehydrogenases and reductases) dissolved in DMSO. The optical density of each well (96 well plates) was quantified three times in tetraplicates 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 logarithmic percentage of surviving cells against the logarithm of the drug concentration using a linear regression function. The median value and the median absolute deviation were obtained from the Excel(tm) software (Microsoft(tm)) and those values are reported in Table 1.

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References

1 (*a*) M. A. Jakupec, M. Galanski and B. K. Keppler, *Rev. Physiol., Biochem., Pharmacol.*, 2003, **146**, 1; (*b*) N. J. Wheate and J. G. Collins, *Curr. Med. Chem.: Anti-Cancer Agents*, 2005, **5**, 267; (*c*) G. Cossa, L. Gatti, F. Zunino and P. Perego, *Curr. Med. Chem.*, 2009, **16**, 2355.
2 T. A. Hensing, N. H. Hanna, H. H. Gillenwater, M. G. Camboni, C. Allievi and M. A. Socinski, *Anti-Cancer Drugs*, 2006, **17**, 697.
3 L. Gatti, P. Perego, R. Leone, P. Apostoli, N. Carenini, E. Corna, C. Allievi, U. Bastrup, S. De Munari, S. Di Giovine, P. Nicoli, M. Grugni, M. Natangelo, G. Pardi, G. Pezzoni, J. W. Singer and F. Zunino, *Mol. Pharmaceutics*, 2010, **7**, 207.
4 P. Sood, K. B. Thurmond, II, J. E. Jacob, L. K. Waller, G. O. Silva, D. R. Stewart and D. P. Nowotnik, *Bioconjugate Chem.*, 2006, **17**, 1270.
5 K. J. Haxton and H. M. Burt, *Dalton Trans.*, 2008, 5872.
6 M. J. Pisani, N. J. Wheate, F. R. Keene, J. R. Aldrich-Wright and J. G. Collins, *J. Inorg. Biochem.*, 2009, **103**, 373.
7 Y. Matsumura and H. Maeda, *Cancer Res.*, 1986, **46**, 6387.
8 (*a*) D. F. Baban and L. W. Seymour, *Adv. Drug Delivery Rev.*, 1998, **34**, 109; (*b*) H. Maeda, *Adv. Enzyme Regul.*, 2001, **41**, 189; (*c*) E. Gullotti and Y. Yeo, *Mol. Pharmaceutics*, 2009, **6**, 1041.
9 (*a*) M. Pongratz, P. Schluga, M. A. Jakupec, V. B. Arion, C. G. Hartinger, G. Allmaier and B. K. Keppler, *J. Anal. At. Spectrom.*, 2004, **19**, 46; (*b*) P. Schluga, C. G. Hartinger, A. Egger, E. Reisner, M. Galanski, M. A. Jakupec and B. K. Keppler, *Dalton Trans.*, 2006, 1796; (*c*) C. G. Hartinger, M. A. Jakupec, S. Zorbas-Seifried, M. Groessl, A. Egger, W. Berger, H. Zorbas, P. J. Dyson and B. K. Keppler, *Chem. Biodiversity*, 2008, **5**, 2140; (*d*) C. G. Hartinger and P. J. Dyson, *Chem. Soc. Rev.*, 2009, **38**, 391; (*e*) A. Levina, A. Mitra and P. A. Lay, *Metallomics*, 2009, **1**, 458.
10 (*a*) M. J. Clarke, *Coord. Chem. Rev.*, 2003, **236**, 209; (*b*) Y. K. Yan, M. Melchart, A. Habtemariam and P. J. Sadler, *Chem. Commun.*, 2005, 4764; (*c*) P. J. Dyson and G. Sava, *Dalton Trans.*, 2006, 1929.
11 J. M. Rademaker-Lakhai, D. Van den Bongard, D. Pluim, J. H. Beijnen and J. H. M. Schellens, *Clin. Cancer Res.*, 2004, **10**, 3717.
12 (*a*) G. Sava, R. Gagliardi, A. Bergamo, E. Alessio and G. Mestroni, *Anticancer Res.*, 1999, **19**, 969; (*b*) C. G. Hartinger, S. Zorbas-Seifried, M. A. Jakupec, B. Kynast, H. Zorbas and B. K. Keppler, *J. Inorg. Biochem.*, 2006, **100**, 891.

13 (*a*) F. R. Keene, J. A. Smith and J. G. Collins, *Coord. Chem. Rev.*, 2009, **253**, 2021; (*b*) D. P. Buck, C. B. Spillane, J. G. Collins and F. R. Keene, *Mol. BioSyst.*, 2008, **4**, 851; (*c*) A. Herman, J. M. Tanski, M. F. Tibbetts and C. M. Anderson, *Inorg. Chem.*, 2008, **47**, 274; (*d*) F. Schmitt, M. Auzias, P. Štěpnička, S. Sei, K. Yamaguchi, G. Süss-Fink, B. Therrien and L. Juillerat-Jeanneret, *JBIC, J. Biol. Inorg. Chem.*, 2009, **14**, 693; (*e*) C. Sanchez-Cano and M. J. Hannon, *Dalton Trans.*, 2009, 10702; (*f*) T. Gianferrara, I. Bratsos, E. Iengo, B. Milani, A. Oštrić, C. Spagnul, E. Zangrando and E. Alessio, *Dalton Trans.*, 2009, 10742.

14 (*a*) W. H. Ang and P. J. Dyson, *Eur. J. Inorg. Chem.*, 2006, 4003; (*b*) F. Linares, M. A. Galindo, S. Galli, M. A. Romero, J. A. R. Navarro and E. Barea, *Inorg. Chem.*, 2009, **48**, 7413; (*c*) G. Süss-Fink, *Dalton Trans.*, 2010, **39**, 1673.

15 (*a*) M.-G. Mendoza-Ferri, C. G. Hartinger, R. E. Eichinger, N. Stolyarova, K. Severin, M. A. Jakupec, A. A. Nazarov and B. K. Keppler, *Organometallics*, 2008, **27**, 2405; (*b*) M. G. Mendoza-Ferri, C. G. Hartinger, M. A. Mendoza, M. Groessl, A. E. Egger, R. E. Eichinger, J. B. Mangrum, N. P. Farrell, M. Maruszak, P. J. Bednarski, F. Klein, M. A. Jakupec, A. A. Nazarov, K. Severin and B. K. Keppler, *J. Med. Chem.*, 2009, **52**, 916; (*c*) M. G. Mendoza-Ferri, C. G. Hartinger, A. A. Nazarov, R. E. Eichinger, M. A. Jakupec, K. Severin and B. K. Keppler, *Organometallics*, 2009, **28**, 6260; (*d*) O. Novakova, A. A. Nazarov, C. G. Hartinger, B. K. Keppler and V. Brabec, *Biochem. Pharmacol.*, 2009, **77**, 364.

16 M. Auzias, B. Therrien, G. Süss-Fink, P. Štěpnička, W. H. Ang and P. J. Dyson, *Inorg. Chem.*, 2008, **47**, 578.

17 S. W. Magennis, A. Habtemariam, O. Novakova, J. B. Henry, S. Meier, S. Parsons, I. D. H. Oswald, V. Brabec and P. J. Sadler, *Inorg. Chem.*, 2007, **46**, 5059.

18 B. Therrien, W. H. Ang, F. Chérioux, L. Vieille-Petit, L. Juillerat-Jeanneret, G. Süss-Fink and P. J. Dyson, *J. Cluster Sci.*, 2007, **18**, 741.

19 (*a*) F. Schmitt, P. Govindaswamy, G. Süss-Fink, W. H. Ang, P. J. Dyson, L. Juillerat-Jeanneret and B. Therrien, *J. Med. Chem.*, 2008, **51**, 1811; (*b*) F. Schmitt, P. Govindaswamy, O. Zava, G. Süss-Fink, L. Juillerat-Jeanneret and B. Therrien, *JBIC, J. Biol. Inorg. Chem.*, 2009, **14**, 101.

20 P. Govender, N. C. Antonels, J. Mattsson, A. K. Renfrew, P. J. Dyson, J. R. Moss, B. Therrien and G. S. Smith, *J. Organomet. Chem.*, 2009, **694**, 3470.

21 (*a*) B. Therrien, *Eur. J. Inorg. Chem.*, 2009, 2445; (*b*) N. P. E. Barry, N. H. Abd Karim, R. Vilar and B. Therrien, *Dalton Trans.*, 2009, 10717.

22 J. Mattsson, P. Govindaswamy, A. K. Renfrew, P. J. Dyson, P. Štěpnička, G. Süss-Fink and B. Therrien, *Organometallics*, 2009, **28**, 4350.

23 (*a*) B. Therrien, G. Süss-Fink, P. Govindaswamy, A. K. Renfrew and P. J. Dyson, *Angew. Chem., Int. Ed.*, 2008, **47**, 3773; (*b*) J. Mattsson, P. Govindaswamy, J. Furrer, Y. Sei, K. Yamaguchi, G. Süss-Fink and B. Therrien, *Organometallics*, 2008, **27**, 4346; (*c*) O. Zava, J. Mattsson, B. Therrien and P. J. Dyson, *Chem.–Eur. J.*, 2010, **16**, 1428.

24 H. Yan, G. Süss-Fink, A. Neels and H. Stoeckli-Evans, *J. Chem. Soc., Dalton Trans.*, 1997, 4345.

25 L. L. Gladkov and K. N. Solovyov, *Spectrochim. Acta.*, 1986, **42A**, 1.

26 X.-Y. Li, R. S. Czernuszewicz, J. R. Kincaid, P. Stein and T. G. Spiro, *J. Phys. Chem.*, 1990, **94**, 47.

27 N. P. E. Barry, M. Austeri, J. Lacour and B. Therrien, *Organometallics*, 2009, **28**, 4894.

28 P. Govindaswamy, D. Linder, J. Lacour, G. Süss-Fink and B. Therrien, *Chem. Commun.*, 2006, 4691.

29 Y.-F. Han, Y.-J. Lin, L.-H. Weng, H. Berke and G.-X. Jin, *Chem. Commun.*, 2008, 350.

30 B. Vitorge, S. Bieri, M. Humam, P. Christen, K. Hostettmann, O. Muñoz, S. Loss and D. Jeannerat, *Chem. Commun.*, 2009, 950.

31 (*a*) F. Ricchelli, *J. Photochem. Photobiol., B*, 1995, **29**, 109; (*b*) K. D. Benkstein, C. L. Stern, K. E. Splan, R. C. Johnson, K. A. Walters, F. W. M. Vanhelmont and J. T. Hupp, *Eur. J. Inorg. Chem.*, 2002, 2818; (*c*) K. Ono, M. Yoshizawa, T. Kato, K. Watanabe and M. Fujita, *Angew. Chem. Int. Ed.*, 2007, **46**, 1803.

32 (*a*) A. L. Harris, X. Yang, A. Hegmans, L. Povirk, J. L. Ryan, L. Kelland and N. P. Farrell, *Inorg. Chem.*, 2005, **44**, 9598; (*b*) Z. Ma, J. Roy Choudhury, M. W. Wright, C. S. Day, G. Saluta, G. L. Kucera and U. Bierbach, *J. Med. Chem.*, 2008, **51**, 7574; (*c*) A. V. Klein and T. W. Hambley, *Chem. Rev.*, 2009, **109**, 4911.

33 Some ^{13}C NMR signals are missing probably due to dynamic phenomena in solution.