Journal of Organometallic Chemistry 694 (2009) 968–972

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Organometallic complexes that interconvert between trimeric and monomeric structures as a function of pH and their effect on human cancer and fibroblast cells

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ARTICLE INFO

Article history:
Received 1 October 2008
Received in revised form 10 November 2008
Accepted 11 November 2008
Available online 21 November 2008

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

Keywords:
Bioorganometallic
Anticancer drugs
Medicinal chemistry
X-ray crystallography
Ruthenium
Rhodium

ABSTRACT

Organometallic half-sandwich complexes based on ruthenium with aminomethyl-substituted 3-hydroxy-2-pyridone ligands exist in aqueous solution as monomeric O,O′-chelate complexes or trimeric metallamacrocycles depending upon the pH. We hypothesized that administration of the compounds as stable trimers, which subsequently convert to active monomers at the reduced pH of the cancer environment, could facilitate their delivery to cancer cells without undergoing deactivation. Thus, the compounds were evaluated against cancer and fibroblast cell lines *in vitro*. A series of rhodium complexes, which exist mainly as monomers at neutral pH, were also studied for comparative purposes.

1. Introduction

Platinum-based coordination compounds have proven to be extremely important anticancer agents with widespread clinical use [1]. Coordination compounds based on other metal centers have also been evaluated in cancer chemotherapy [2] and organometallic compounds are under intensive investigation [3]. The organometallic compound titanocene dichloride was shown to exhibit antitumor activity in the 1970's [4], and although it entered clinical evaluations it has not gained clinical approval [5]. The ferrocifens, ferrocenyl derivatives of tamoxifen, show considerable promise in hormone-related cancers and paved the way for the rational development of organometallic pharmaceuticals [6,7].

Two coordination compounds based on ruthenium, viz. [ImH][*trans*-$RuCl_4$(DMSO)Im] (NAMI-A) [8] and [ImH][*trans*-$RuCl_4Im_2$] (KP1019) [9], are currently under clinical investigation, which has inspired greater interest in the medicinal properties of this metal, including in part recent studies on organoruthenium compounds [10]. Ruthenium(II)–arene compounds with imidazole [11], alanine and guanine derived co-ligands [12], ethylenediamine [13], disulfoxide [14], and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (pta) and analogous sugar [15] co-ligands have been evaluated. These compounds have been extensively tested *in vitro* and to a limited extent *in vivo* [16], although there is not always a good correlation between *in vitro* and *in vivo* data [17].

Combining the ruthenium(II)–arene fragment with maltolato ligands is an interesting prospect since maltolato systems have found applications in various medicinal applications [18]. Indeed, a series of such compounds has been reported, but it was found that they readily form inactive hydroxo-bridged dimers, following hydrolysis and rapid deprotonation at physiological pH [19]. Dinuclear ruthenium(II)–arene complexes with maltol-derived pyridonato-ligands, on the other hand, were shown to be highly cytotoxic towards human cancer cell lines [20]. In this paper, we describe a series of trinuclear ruthenium(II)–arene complexes with pyridonato-ligands that can fragment to mononuclear complexes according to the pH. We hypothesized that such a mechanism could facilitate their delivery to cancer cells without undergoing deactivation, and in this paper we describe our experiments to test this hypothesis. In addition a series of related rhodium(III)–pentamethylcyclopentadienyl (Cp^*) complexes were also studied.

2. Results and discussion

The half-sandwich complexes based on the (η^6-cymene)Ru (**M1**) and the (η^5-Cp^*)Rh (**M2**) organometallic fragments are

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doi:10.1016/j.jorganchem.2008.11.026

shown in Scheme 1. They were obtained in situ by reaction of the respective $[(\pi\text{-ligand})MCl_2]_2$ precursors with amino-substituted 3-hydroxy-2-pyridone ligands (**L1**–**L3**) in aqueous solution. The spectroscopic data and the behavior of the complexes as a function of pH have been reported previously [21,22]. Interesting differences were observed between the Ru and the Rh complexes: whereas the (η^6-cymene)Ru complexes **1**–**3** are trimers, the (η^5-Cp*)Rh complexes **4**–**6** are predominantly monomers in aqueous solution at neutral pH. It should be noted that the Ru-trimers are remarkably stable compounds. Aqueous solutions of the trimers can be handled in air for several hours without decomposition and they tolerate high salt concentrations (e.g. 100 mM phosphate buffer). Furthermore, it has recently been shown that structurally related trimers remain intact in a complex biological matrix such as reconstituted human serum [23].

The aminomethyl-substituted 3-hydroxy-2-pyridone ligands **L1**–**L3** can be obtained by Mannich reactions as described in the literature [24]. The structure of the ligand **L3** in the solid state has now been established by X-ray crystallography and is shown in Fig. 1.

The crystallographic analysis reveals that the ligand is in its preferred pyridone form and not in the tautomeric 2,3-dihydroxypyridine form. As a consequence, the C1–O1 bond (1.281(3) Å) is significantly shorter than the C2–O2 bond (1.371(3) Å). Intermolecular hydrogen bonds between N1–H1 and O1 (1.98 Å) and between O2–H2 and O1 (1.99 Å) result in a ribbon-like connection of the ligands in the solid state (Fig. 1, bottom).

The solid state structures of mononuclear ruthenium(II)–arene complexes containing aminomethyl-substituted 3-hydroxy-2-pyridone ligands have been reported previously [21a], but crystallographic data for analogous Cp*Rh complexes are missing. We managed to obtain single crystals of complex **5** containing the Cp*Rh fragment **M2** and ligand **L2**. This was achieved by dissolving a mixture of $[Cp^*RhCl_2]_2$ and two equivalents of **L2** in chloroform and layering the resulting solution with diethyl ether. The crystallographic analysis revealed that **5** exhibits the expected 'piano-stool' geometry with an O,O′-bound, monoanionic pyridonate ligand (Fig. 2). Since the complex was obtained from an unpolar organic solvent, the third coordination site opposite to the Cp* ligand is occupied by a chloro ligand and not by a water ligand as expected for aqueous solutions of **5** [21a]. The bond lengths of the two Rh–O bonds (Rh1–O1 = 2.1385(18) Å and Rh1–O2 =

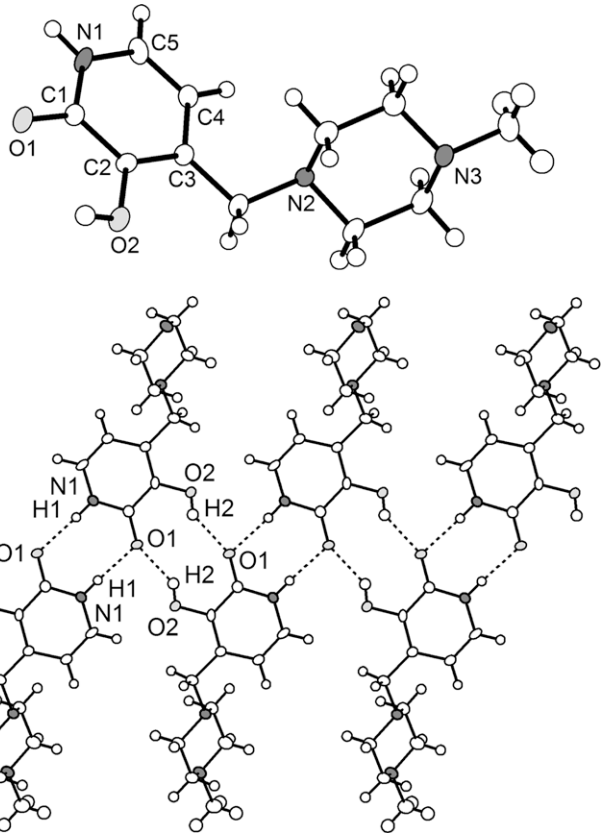
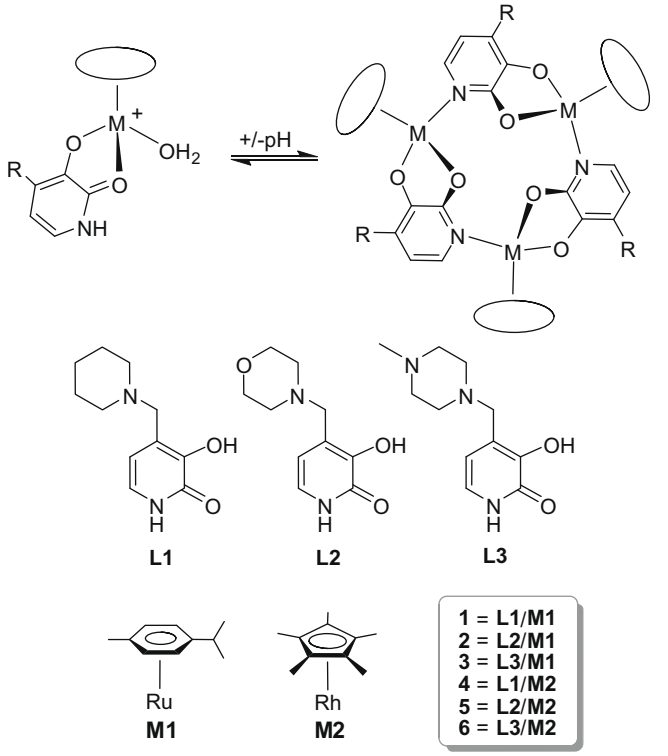


Fig. 1. Graphic representation of the molecular structure of ligand **L3** (top). The 3-hydroxy-2-pyridone groups form a hydrogen bond network with intermolecular NH···O and OH···O interactions (bottom). The thermal ellipsoids are at the 50% probability level.



Scheme 1. Structures of the complexes employed in this study; at pH 7 compounds **1**–**3** are trimeric, whereas **4**–**6** are predominantly monomeric.

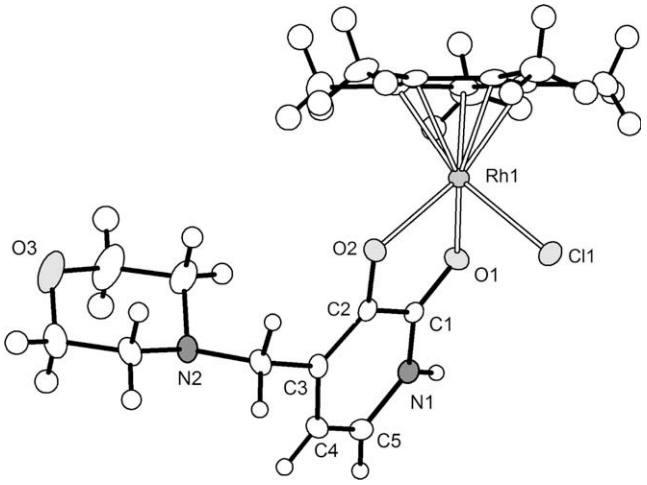


Fig. 2. Graphic representation of the molecular structure of complex **5**. The thermal ellipsoids are at the 50% probability level. Key bond lengths (Å) and angles (°) for **5** include: Rh1–O1 = 2.1385(18), Rh2–O2 = 2.1349(17), Rh1–Cl1 = 2.4208(7), C2–O2 = 1.335(3), C1–O1 = 1.285(3); Cl1–Rh1–O1 = 86.89(5), Cl1–Rh1-O2 = 89.33(5), O1–Rh1–O2 = 78.31(7).

2.1349(17) Å) are similar to the average Ru–O bond lengths of analogous (η^6-C_6Me_6)Ru complexes ($Ru–O_{av.}$ = 2.12 Å) [21a], but slightly longer than those observed for ruthenium(II)–arene complexes with deprotonated 3-hydroxy-4-pyridone [20a,25] or maltolato ligands [19].

As mentioned above, complexes **1**–**6** interconvert between trimeric and monomeric structures as a function of pH. The ruthenium(II)–arene complexes **1**–**3** are nearly completely trimerized at pH 7.0, but form monomeric complexes at pH $\leqslant$ 4.0. Between pH 4.5–6.5 the monomers and the trimers coexist in solution. The Cp^*Rh complexes **4**–**6** show a similar behavior but at a different pH. At pH 7.0, they exist mainly in their monomeric form and complete trimerization requires a pH of $\geqslant$8.5. We hypothesized that delivery of compounds **1**–**3** as stable trimers, which subsequently convert to active monomers at the reduced pH of the cancer environment, or potentially upon reaction with biomolecules once inside a cell, could overcome problems of deactivation and their effect on cancer cells and model healthy cells has therefore been studied. The monomeric Cp^*Rh complexes **4**–**6** as well as RAPTA-C, (η^6-cymene)$RuCl_2$(pta) [15], were included for comparative purpose.

Table 1
Inhibition of cell viability (IC_{50}, μM) of **1**–**6** and RAPTA-C on A2780/A2780cisR ovarian carcinoma and VS79/GS78 fibroblast cell lines. Cell viability was determined using the MTT assay after 72 h of exposure.

Complex	A2780	A2780cisR	VS79	GS78
1	436	620	634	681
2	410	619	744	640
3	442	639	670	710
4	341	371	678	718
5	344	365	676	654
6	379	361	676	730
RAPTA-C	353	252	>1000	>1000

The cytotoxicities of compounds **1**–**6** were evaluated against A2780 and A2780cisR ovarian carcinoma cell lines, the latter exhibiting a 6-fold increase in cisplatin resistance. Two model healthy cell lines, i.e. VS79 and GS78 fibroblast cell lines were also used in order to determine any compound selectivity. For comparative purposes RAPTA-C was also evaluated since its pharmacological properties has been well characterized *in vitro* and *in vivo* [17]. All the cells were grown at pH 7.2 such that the ruthenium compounds **1**–**3** are in the trimeric form and the rhodium compounds **4**–**6** are present as mononuclear species. The IC_{50} values of **1**–**6** after 72 h incubation in the four cell lines are listed in Table 1 and representative dose–response curves are shown in Fig. 3.

In general, all the compounds are more cytotoxic towards the cancer cells lines in comparison to the non-tumorigenic fibroblast cells. It is also noteworthy that while the ruthenium complexes are less active on the cisplatin-resistant ovarian cancer cell line the rhodium complexes exhibit essentially the same activities on both strains, suggesting that a different mechanism is in operation. However, complexes **1**–**6** do not appear to offer any advantages over RAPTA-C which has the greatest difference in cytotoxicity between the tumorigenic and non-tumorigenic cell lines. It is also worth noting that these cytotoxicites are all considerably lower compared to drugs such as cisplatin. However, despite the low activity *in vitro*, *in vivo* RAPTA-C has been shown to be both highly selective and active on metastatic tumors [17] which make it, and potentially related compounds, particularly interesting as mortality usually results from metastatic tumors and not primary tumors which tend to be treated by surgical removal.

In conclusion, the compounds reported herein are only slightly cytotoxic towards the screened cancer cells lines. It was not possi-

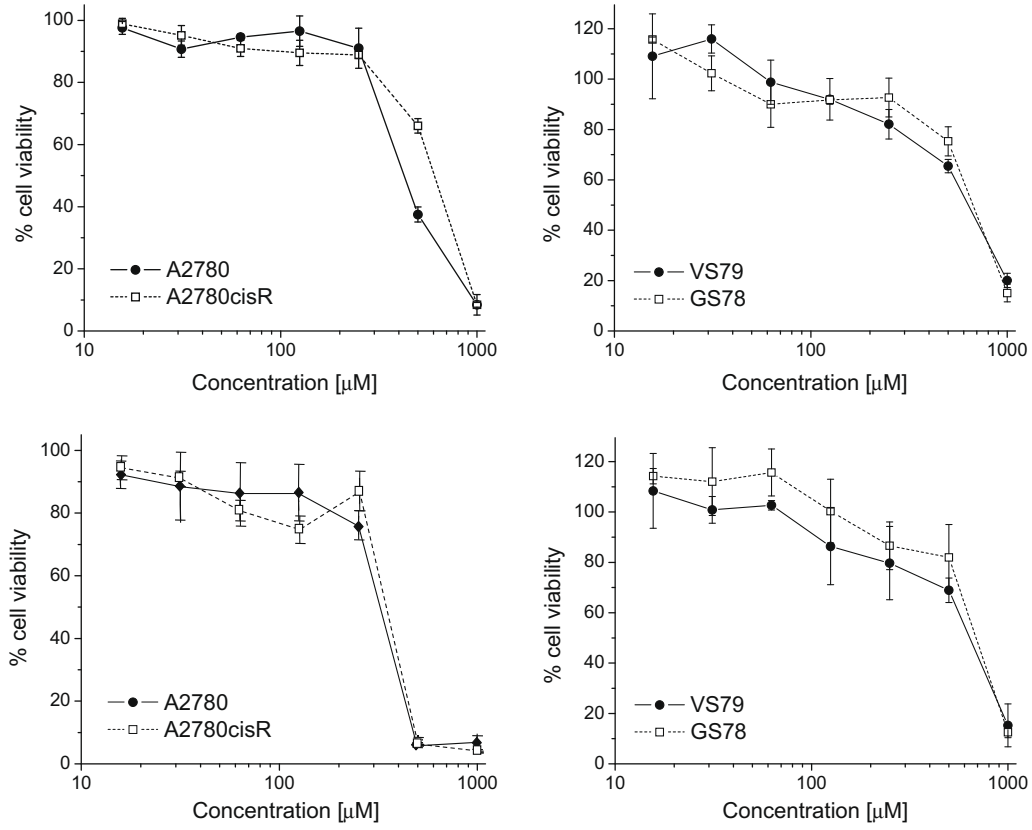


Fig. 3. Dose–response curves of **3** (top) and **5** (bottom) to A2780/A2780cisR ovarian carcinoma and VS79/GS78 fibroblast cell lines after 72 h exposure. Cell viability was determined using the MTT assay.

ble to directly (or indirectly based on a comparison of the ruthenium and rhodium compounds) ascertain whether a pH-dependent activation process involving a structural change takes place. Nevertheless, the compounds show a reasonable selectivity towards tumorigenic cells although less than that observed for the benchmark compound RAPTA-C.

3. Experimental

3.1. General

The complexes $[(\eta^6\text{-cymene})RuCl_2]_2$ [26], $[\eta^5\text{-Cp}^*RhCl_2]_2$ [27], RAPTA-C [15a] and the ligands **L1**–**L3** [24] were prepared according to literature procedures. Complexes **1**–**6** were prepared in situ by reacting the $[(\pi\text{-ligand})MCl_2]_2$ precursors with two equivalents of respective ligand in aqueous solution, resulting in the formation of monomeric complexes. At the pH of the *in vitro* cell assays, however, the ruthenium(II)–arene complexes **1**–**3** are expected to exist as trimers, whereas the Cp^*Rh complexes **4**–**6** form predominantly monomers [21a].

3.2. Spectroscopic characterization

Below the ^1H NMR data of selected metal–ligand combinations are listed. A mixture of the respective half-sandwich complex $[(\pi\text{-ligand})MCl_2]_2$ (37.5 μmol) and the respective ligand (75.0 μmol) was stirred in D_2O (5.00 mL) until a clear solution (15 mM) was obtained. The ^1H NMR spectra of the resulting monomeric complexes were obtained from these solutions. For additional analytical data (^1H NMR spectra of the trimers, elemental analyses, pH-titrations) see Ref. [21a].

3.3. $[(\eta^6\text{-cymene})RuCl_2]_2$ + *L1*

^1H NMR (400 MHz, D_2O): δ (ppm) = 1.28 (d, ^3J = 7 Hz, 6H, $CH(CH_3)_2$), 1.35–2.05 (m, 6H, CH_2, piperidine), 2.23 (s, 2H, $CH_3C_6H_4^iPr$), 2.82 (sept, ^3J = 7 Hz, 1H, $CH(CH_3)_2$), 2.00 (m_c, 2H, CH_2, piperidine), 3.48 (m_c, 2H, CH_2, piperidine), 4.21 (s, 2H, NCH_2), 5.56 (d, ^3J = 6 Hz, 2H, $MeC_6H_4^iPr$), 5.81 (d, ^3J = 6 Hz, 2H, $MeC_6H_4^iPr$), 6.50 (d, ^3J = 7 Hz, 1H, pyridone), 6.88 (d, ^3J = 7 Hz, 1H, pyridone).

3.4. $[(\eta^6\text{-cymene})RuCl_2]_2$ + *L2*

^1H NMR (400 MHz, D_2O): δ (ppm) = 1.30 (d, ^3J = 7 Hz, 6H, $CH(CH_3)_2$), 2.25 (s, 2H, $CH_3C_6H_4^iPr$), 2.84 (sept, ^3J = 7 Hz, 1H, $CH(CH_3)_2$), 3.29 (m, br, 2H, CH_2, morpholine), 3.47 (m, br, 2H, CH_2, morpholine), 3.80 (m, br, 2H, CH_2, morpholine), 4.12 (m, br, 2H, CH_2, morpholine), 4.33 (s, 2H, NCH_2), 5.59 (d, ^3J = 6 Hz, 2H, $MeC_6H_4^iPr$), 5.83 (d, ^3J = 6 Hz, 2H, $MeC_6H_4^iPr$), 6.53 (d, ^3J = 7 Hz, 1H, pyridone), 6.90 (d, ^3J = 6 Hz, 1H, pyridone).

3.5. $[(\eta^6\text{-cymene})RuCl_2]_2$ + *L3*

^1H NMR (400 MHz, D_2O): δ (ppm) = 1.25 (d, ^3J = 7 Hz, 6H, $CH(CH_3)_2$), 2.23 (s, 2H, $CH_3C_6H_4^iPr$), 2.65 (m, br, 2H, CH_2, piperazine), 2.80 (sept, ^3J = 7 Hz, 1H, $CH(CH_3)_2$), 2.84 (s, 3H, NCH_3), 3.10 (m, br, 4H, CH_2, piperazine), 3.45 (m, br, 2H, CH_2, piperazine), 3.70 (s, 2H, NCH_2), 5.56 (d, ^3J = 6 Hz, 2H, $MeC_6H_4^iPr$), 5.79 (d, ^3J = 6 Hz, 2H, $MeC_6H_4^iPr$), 6.53 (d, ^3J = 7 Hz, 1H, pyridone), 6.88 (d, ^3J = 7 Hz, 1H, pyridone).

3.6. $[\eta^5\text{-Cp}^*RhCl_2]_2$ + *L1*

^1H NMR (400 MHz, D_2O): δ (ppm) = 1.35–2.05 (m, 6H, CH_2, piperidine), 1.67 (s, 15H, Cp^*), 3.00 (m_c, 2H, NCH_2, piperidine), 3.50 (m, br, 2H, NCH_2, piperidine), 4.18 (s, 2H, NCH_2), 6.45 (d, ^3J = 7 Hz, 1H, pyridone), 6.81 (d, ^3J = 7 Hz, 1H, pyridone).

3.7. $[\eta^5\text{-Cp}^*RhCl_2]_2$ + *L3*

^1H NMR (400 MHz, D_2O): δ (ppm) = 1.66 (s, 15 H, Cp^*), 2.35–3.60 (m, br, 8H, CH_2, piperazine), 2.79 (s, 3H, NCH_3), 3.72 (s, 2H, NCH_2), 6.49 (d, ^3J = 7 Hz, 1H, pyridone), 6.82 (d, ^3J = 7 Hz, 1H, pyridone).

3.8. Crystallography

The relevant details of the crystals, data collection and structure refinement are listed in Table 2. Diffraction data were collected using Mo Kα radiation on a 4-circle kappa goniometer equipped with an Oxford Diffraction KM4 Sapphire CCD. Data reduction was performed with CrysAlis RED [28]. Absorption correction was applied to all data sets using a semi-empirical method [29]. All structures were refined using the full-matrix least-squares on F^2 with all non-H atoms anisotropically defined. The hydrogen atoms were placed in calculated positions using the "riding model" with U_{iso} = a* U_{eq} (where *a* is 1.5 for methyl hydrogen atoms and 1.2 for others). Structure refinement and geometrical calculations were carried out on all structures with SHELXTL [30].

3.9. In vitro assays

Human A2780 and A2780cisR ovarian carcinoma cell lines were obtained from the European Collection of Cell Culture (ECACC, Porton Down, Wiltshire, UK). The cells were routinely grown in RPMI 1640 medium containing 10% foetal calf serum (FCS) and antibiotics at 37 °C and 6% CO_2 until 70–80% confluence. For A2780cisR cells, cisplatin solution (1 μM) was added every 2–3 passages, 24 h after seeding. Human VS79 and GS78 vaginal myofibroblasts were obtained from surgical biopsy samples of posterior/anterior vaginal wall from patients according to a protocol approved by patients and the ethics committee of the CHUV. The cells were routinely grown in DMEM medium containing 4.5 g/l glucose,

Table 2
Crystallographic data for L3 and 5.

	L3	**5**
Empirical formula	$C_{11}H_{17}N_3O_2$	$C_{20}H_{28}ClN_2O_3Rh$
Molecular weight (g mol^{-1})	223.28	482.80
Crystal size (mm^3)	0.21 × 0.06 × 0.05	0.23 × 0.12 × 0.07
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$
a (Å)	4.704(2))	7.4799(5)
b (Å)	6.049(2)	22.9529(14)
c (Å)	20.849(9)	12.0712(6)
α (°)	97.79(3)	90
β (°)	94.58(5)	93.000(5)
γ (°)	98.06(4)	90
Volume (Å^3)	579.0(4)	2069.6(2)
Z	2	4
Density (g cm^{-3})	1.281	1.550
Temperature (K)	140(2)	140(2)
Absorption coefficient (mm^{-1})	0.090	0.976
θ Range (°)	3.44–25.02	3.15–25.02
Index ranges	−5 → 5, −6 → 7, −24 → 24	−8 → 8, −27 → 27, −12 → 12
Reflections collected	3501	12027
Data/restraints/parameters	1801/0/146	3421/0/245
Goodness-of-fit on F^2	0.826	1.072
Final *R* indices [$I > 2s(I)$]	R_1 = 0.0486, wR_2 = 0.0819	R_1 = 0.0282, wR_2 = 0.0676
R indices (all data)	R_1 = 0.1237, wR_2 = 0.0991	R_1 = 0.0331, wR_2 = 0.0698
Largest difference in peak and hole (e Å^3)	0.213 and −0.227	0.657 and −0.845

10% foetal calf serum (FCS) and antibiotics at 37 °C and 6% CO_2 until confluence. The cells were harvested by trypsin/EDTA, diluted and grown over a period of 14–21 days to reach confluence.

For the MTT assay, the cells are plated into 48-well plates (VS79/ GS78) or 96-well plates (A2780/A2780cisR) in accordance with established protocols. The compounds were dissolved directly in culture medium and exposed to the cells for 72 h in triplicates. MTT (final concentration 0.2 mg/mL) was added and the cells were incubated for 2 h at 37 °C. The culture medium was aspirated and the purple formazan precipitate was dissolved in 0.1 N HCl/isopropanol. The absorbance was quantified at 540 nm using a multiwell plate reader (iEMS Reader MF, Labsystems, US) and the fraction of surviving cells was calculated as a percentage of untreated control cells.

Acknowledgement

This work was supported by the EPFL and by the Swiss National Science Foundation.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.11.026.

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