Inorganica Chimica Acta 394 (2013) 723–728

Contents lists available at SciVerse ScienceDirect

Inorganica Chimica Acta

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

Sawhorse-type diruthenium tetracarbonyl complexes containing biologically relevant acids

Justin P. Johnpeter, Bruno Therrien *

Institut de Chimie, Université de Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel, Switzerland

ARTICLE INFO

Article history:
Received 22 June 2012
Received in revised form 25 September 2012
Accepted 26 September 2012
Available online 12 October 2012

Keywords:
Dinuclear complexes
Carbonyl ligands
Carboxylato bridges
Ruthenium
Porphyrin ligands
Biologically active acids

ABSTRACT

The reaction between the biologically active acids probenecid ($HO_2CC_{12}H_{18}NO_2S$), indomethacin ($HO_2CC_{18}H_{15}ClNO_2$) and sulindac ($HO_2CC_{19}H_{16}FOS$) with $Ru_3(CO)_{12}$, followed by addition of axial ligands (L), such as pyridine, triphenylphosphine, or 5-(4-pyridyl)-10,15,20-triphenylporphyrin, generates a series of stable diruthenium tetracarbonyl complexes of the formula $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{12}H_{18}NO_2S)_2L_2$, $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{18}H_{15}ClNO_2)_2L_2$ and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{19}H_{16}FOS)_2L_2$, respectively. The molecular structure of **1a** · C_6H_6 was solved by single-crystal X-ray structure analysis and a typical diruthenium tetracarbonyl backbone bridged by the carboxylato ligands and two axial triphenylphosphine ligands was revealed. The benzene molecule sits between two probenecid units, and is involved in π-stacking interactions with the aromatic part of probenecid. Despite the presence of biologically relevant derivatives and carbonyl groups within the sawhorse-type dinuclear complexes, all systems show no cytotoxicity towards human cancer cells, presumably due to the high lipophilicity of these neutral complexes.

1. Introduction

Carbon monoxide and nitric oxide have now been recognized as two essential signaling agents in the body [1]. Despite the CO ability to bind to hemoglobin and inhibit the respiratory cycle, evidence has been found that CO possesses valuable anti-inflammatory, vasodilatory and anti-apoptotic therapeutic effects [2]. In that respect, complexes able to release CO in biological media have been studied by Mann and his co-workers. For example, the ruthenium complexes $\{Ru(\mu\text{-}Cl)Cl(CO)_3\}_2$ (tricarbonyldichlororuthenium(II) dimer) and $Ru(CO)_3Cl$(glycinate) (tricarbonylchloro(glycinato)ruthenium(II)) (see Chart 1), two known CO-releasing molecules (CORMs), have shown anti-microbial activity on several types of bacteria [3], as well as interesting *in vivo* activity in human [4].

In these CO-releasing complexes, the choice of exploiting ruthenium centers was not accidental. Ruthenium complexes are showing great promise as chemotherapeutic agents [5], and the ability of ruthenium to mimic iron in biological environments gives to ruthenium complexes several interesting properties in designing metal-based drugs [5]. In addition, the chemistry of ruthenium carbonyl complexes is well developed and known for many years [6]. Among ruthenium carbonyl complexes, Lewis and coworkers have reported in 1969 the first sawhorse-type diruthenium tetracarbonyl complexes [7]. Obtained from the reaction of $Ru_3(CO)_{12}$ with carboxylic acids (RCO_2H) in tetrahydrofuran at reflux, followed by addition of two-electron donor ligands (L), sawhorse-type dinuclear tetracarbonyl complexes of the general formula $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CR)_2L_2$ offer versatility and ease of preparation to generate biologically relevant ruthenium carbonyl complexes [8]. Recently, we have shown that porphyrin-derived diruthenium tetracarbonyl complexes possess interesting phototoxicity towards female reproductive cancer cells [9], while sawhorse diruthenium complexes derived from biological active acids such as aspirin, ibuprofen, ethacrynic acid and chlorambucil were not cytotoxic due to their low solubility in water [10] (see Chart 2). Consequently, a new series of sawhorse-type diruthenium tetracarbonyl complexes incorporating other biologically relevant carboxylic acids has been synthesized. Three commercially available carboxylic acids were selected for their therapeutic properties (see Chart 2): Probenecid, an uricosuric drug [11]; indomethacin and sulindac, two anti-inflammatory agents [12]. All $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CR)_2L_2$ complexes were fully characterized with L being pyridine (NC_5H_5), triphenylphosphine (PPh_3) or 5-(4-pyridyl)-10,15,20-triphenylporphyrin ($C_{43}H_{29}N_5$).

2. Results and discussion

Dodecacarbonyltriruthenium ($Ru_3(CO)_{12}$) reacts with an excess of the biologically relevant carboxylic acids, probenecid ($C_{13}H_{19}NO_4S$), indomethacin ($C_{19}H_{16}ClNO_4$), and sulindac ($C_{20}H_{17}FO_3S$) in refluxing tetrahydrofuran (thf) to yield a solution containing the thf intermediates $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{12}H_{18}NO_2S)_2(thf)_2$,

* Corresponding author. Tel.: +41 (0)32 718 24 99; fax: +41 (0)32 718 25 11.
E-mail address: bruno.therrien@unine.ch (B. Therrien).

0020-1693/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ica.2012.09.034

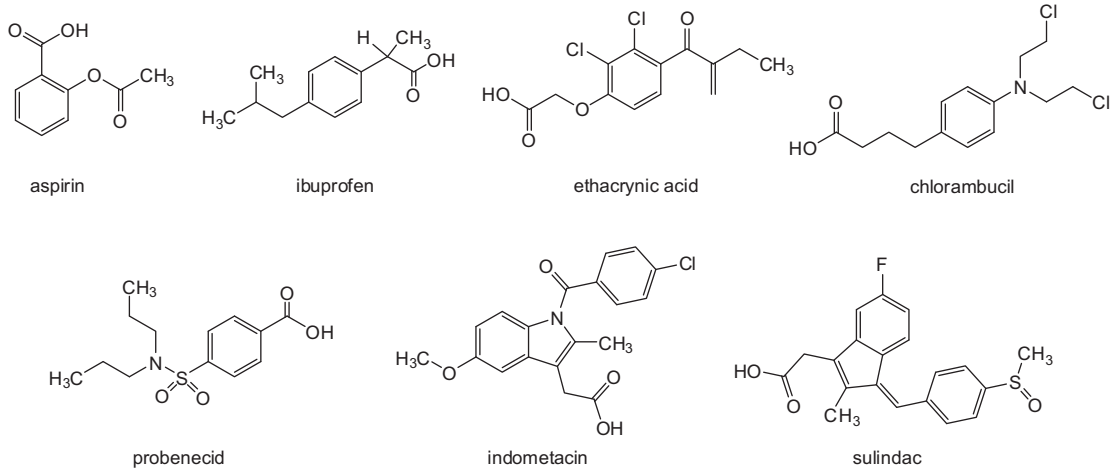
tricarbonyltrichloro ruthenium(II) dimer (CORM-2)

tricarbonylchloro(glycinato)ruthenium(II) (CORM-3)

Chart 1. Examples of CO-releasing ruthenium complexes [2].

$Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{18}H_{15}ClNO_2)_2(thf)_2$ and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{19}H_{16}FOS)_2(thf)_2$, respectively. These labile dinuclear thf intermediates further react with two electron donor ligands (L), such as pyridine (NC_5H_5) (**a**), triphenylphosphine (PPh_3) (**b**) or 5-(4-pyridyl)-10,15,20-triphenylporphyrin ($C_{43}H_{29}N_5$) (**c**), to generate in moderate yields the stable dinuclear complexes $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{12}H_{18}NO_2S)_2L_2$ (L = NC_5H_5, **1a**; PPh_3, **1b**; $C_{43}H_{29}N_5$, **1c**), $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{18}H_{15}ClNO_2)_2L_2$ (L = NC_5H_5, **2a**; PPh_3, **2b**; $C_{43}H_{29}N_5$, **2c**), and $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{19}H_{16}FOS)_2L_2$ (L = PPh_3, **3b**) (Fig. 1). Within the sulindac series, only the complex containing axial triphenylphosphine ligands was isolated in sufficient yield.

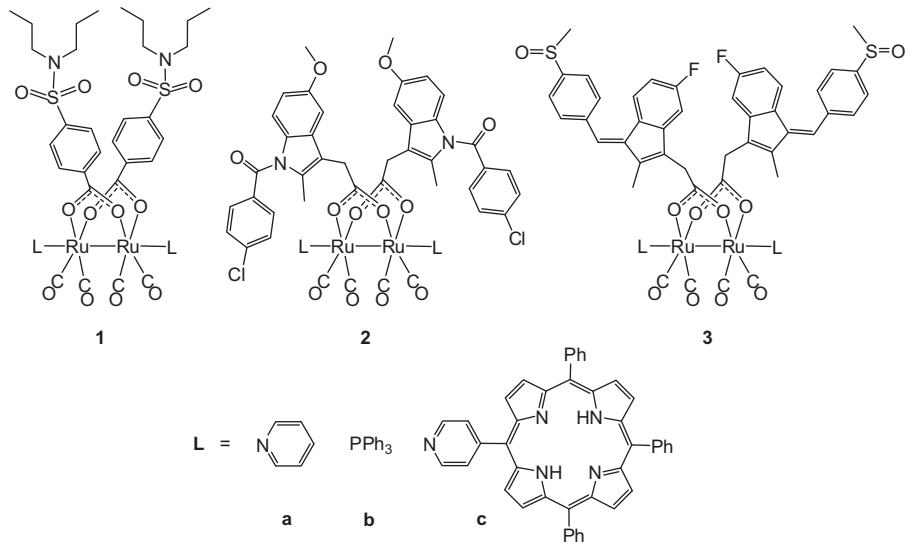
All complexes are air stable, and compounds **1a**, **1b**, **2a**, **2b**, **3b** are yellow crystalline powders, while **1c** and **2c** are purple in color due to the presence of the porphyrin ligands. All complexes have been characterized by IR, NMR, MS, UV–Vis spectroscopy (**1c** and **2c**) as well as by elemental analysis. In the infrared spectra, the $Ru_2(CO)_4$ sawhorse unit exhibits the characteristic three-band pattern for the $\nu_{(CO)}$ absorption at 1950, 1975 and 2020 cm^{-1} [8]. In addition, the two carboxylato bridges show absorption for the $\nu_{(OCO)}$ frequencies around 1550 cm^{-1}, whilst for complexes **1c** and **2c**, a strong absorption centered at 1580 cm^{-1} corresponding to $\nu_{(NCN)}$, along with a strong absorption at 1224 cm^{-1} for N–H deformation and a medium absorption at 3055 cm^{-1} attributed to the $\nu_{(CH)}$ of the porphyrinic axial ligands can be observed. The UV–Vis spectra of complexes **1c** and **2c** display an intense Soret band around 418 nm, and four Q bands between 515 and 645 nm (Table 1). As previously observed with analogous sawhorse-type complexes with porphyrinic ligands [9], the absorption bands of the uncoordinated porphyrinic ligand and those observed after coordination to the diruthenium backbone remain identical,



aspirin ibuprofen ethacrynic acid chlorambucil

probenecid indometacin sulindac

Chart 2. Biologically active carboxylic acids incorporated within sawhorse-type diruthenium tetracarbonyl complexes.



1 **2** **3**

L = **a** **b** **c**

Fig. 1. Sawhorse-type diruthenium tetracarbonyl complexes **1**–**3** containing biologically relevant acids, probenecid (**1**), indomethacin (**2**) and sulindac (**3**).

Table 1
The electronic absorption spectra of complexes **1c**, **2c** and the porphyrinic ligand (**c**) (10^{-6} M concentration) in dichloromethane at room temperature.

Compound	Soret band	Q band IV	Q band III	Q band II	Q band I
1c	418	515	551	590	646
2c	418	515	551	590	645
c	415	514	548	589	645

suggesting no perturbation of the porphyrin π-orbitals upon coordination.

The NMR spectrum of all complexes was measured in $CDCl_3$ at room temperature. All spectra show the signals corresponding to the bridging and axial ligands. For example, the ^1H NMR spectra of **1c** and **2c** display similar patterns for the protons of the coordinated 5-(4-pyridyl)-10,15,20-triphenylporphyrin units. The N–H protons are observed at δ = -2.7 ppm, while two multiplets at 7.8 and 8.2 ppm are found in the aromatic region corresponding to the protons of the phenyl rings of the porphyrin ligands, whereas the pyrrolic protons are found between 8.9 and 9.0 ppm. The $^{13}C\{^1H\}$ NMR spectra of this type of complexes show signals for the terminal carbonyl groups (CO) and the carboxylato bridges (μ_2-η^2-O_2CR) at 176 and 205 ppm, respectively. In addition, for complexes **1b**, **2b** and **3b**, in the $^{31}P\{^1H\}$ NMR spectra, a sharp singlet is observed at ≈15 ppm which corresponds to the PPh_3 axial ligands. Overall, these data are consistent with the proposed structures.

The molecular structure of **1a** was further confirmed by a single-crystal X-ray structure determination. Crystals were obtained by the slow diffusion of benzene in a chloroform solution of **1a**, thus giving rise to a crystalline benzene solvate adduct (**1a** · 0.5 C_6H_6). As expected, the molecular structure shows a normal diruthenium tetracarbonyl core being completed with two pyridine axial ligands and two carboxylato-probenecid ligands in the equatorial positions, see Fig. 2. At 2.6701(7) Å, the Ru–Ru distance is in the range of a single metal–metal bond, while the N–Ru–Ru–N torsion angle is almost linear at 2.8(7)°. These data are comparable to those observed in analogous C_5H_5N–Ru–Ru–NC_5H_5 sawhorse-type diruthenium tetracarbonyl complexes [13]. Similarly, the OCO bond angles of the carboxylato bridges in **1a**, both being 125.4(5)°, differ only slightly from those observed in other $Ru_2(CO)_4(\mu_2$-η^2-$O_2CR)_2L_2$ complexes [10b,13].

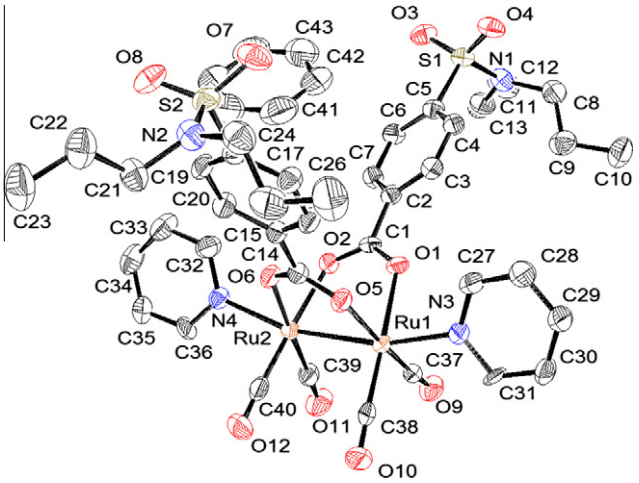


Fig. 2. ORTEP drawing of **1a** · 0.5 C_6H_6 at 50% probability level ellipsoids with hydrogen atoms omitted for clarity. Selected bond lengths (Å) and angles (°): Ru1–Ru2 2.6701(7), Ru1–N3 2.213(5), Ru2–N4 2.216(5), Ru1–O1 2.120(4), Ru1–O5 2.126(4), Ru2–O2 2.143(4), Ru2–O6 2.123(4), O1–C1–O2 125.4(5), O5–C14–O6 125.4(5), O1–Ru1–O5 83.15(16), O2–Ru2–O6 83.55(16), N1–Ru1–Ru2–N2 2.8(7).

The unit cell of **1a** contains a molecule of benzene, which is located between the two probenecid units of **1a**, thus filling some of the voids in the crystals. These benzene molecules form weak slipped-parallel and T-shaped π-stacking interactions with the neighboring phenyl ring of the probenecid moieties. However, more voids remain in the crystal packing, which seem to be empty despite being of approximately 185 $Å^3$: No significant residual densities being observed in those empty spaces. Empty channels are observed along the *a* axis and represent almost 7% of the total volume within the unit cell, see Fig. 3.

The effect of the organometallic complexes **1**–**3** was investigated *in vitro* on human ovarian cancer cells (A2780). The complexes were first dissolved in dimethyl sulfoxide and then diluted in complete medium (RPMI 1640 medium) to the desired concentrations, the dimethyl sulfoxide concentration remaining below 5% v/v. In all cases, after cell exposure at 37 °C to increasing concentrations of complexes, precipitation of the complexes in the culture medium occurred and accordingly no cytotoxicity was observed.

In conclusion, we have synthesized and characterized seven new sawhorse-type diruthenium tetracarbonyl complexes with pyridine, triphenylphosphine, 5-(4-pyridyl)-10,15,20-triphenylporphyrin as axial ligands and containing biologically relevant acids as carboxylato bridging ligands. However, the limited solubility of these complexes in aqueous medium resulted in no cytotoxicity for these systems against human cancer cells.

3. Experimental

3.1. General remarks

All manipulations were routinely carried out under nitrogen. Organic solvents were degassed and saturated with nitrogen prior to use. All reagents were purchased either from Aldrich or Fluka and used as received, while $Ru_3(CO)_{12}$ [14] and 5-(4-pyridyl)-10,15,20-triphenylporphyrin [15] were prepared according to published methods. NMR spectra were recorded on a Bruker 400 MHz spectrometer. IR spectra were recorded as KBr pellets on a Perkin–Elmer 1720x FT-IR spectrometer (4000–400 cm^{-1}). Electro-spray mass spectra were obtained in positive-ion mode with an LCQ Finnigan mass spectrometer. Elemental analyses were performed by the Mikroelementarisches Laboratorium, ETH Zürich (Switzerland). UV–Vis optical spectra were measured by an Uvikon 930 spectrophotometer using quartz cell (1 cm). Column chromatography was performed using silica gel 60 (63–200, 60 Å, Brunschwig).

3.2. Preparation of sawhorse-type diruthenium tetracarbonyl complexes *1*–*3*

A solution of $Ru_3(CO)_{12}$ (100 mg, 0.156 mmol) and the carboxylic acid (0.470 mmol) in dry tetrahydrofuran (25 mL), was heated at 120 °C in a pressure Schlenk tube for 18 h. Then, addition of three equivalents of the axial ligand [**1a**, **2a** (L = NC_5H_5); **1b**, **2b**, **3b** (L = PPh_3); **1c**, **2c** (L = $C_{43}H_{29}N_5$)] followed by stirring at room temperature for 3 h, affords the final products. The complexes are isolated from the residue by precipitation from dichloromethane/pentane. In order to improve the purity, the raw products were subjected to chromatography on silica gel using a dichloromethane/pentane mixture as eluent and the solid obtained was dried under vacuum.

3.2.1. $Ru_2(CO)_4(\mu_2$-η^2-$O_2CC_{12}H_{18}NO_2S)_2(NC_5H_5)_2$ (*1a*)

Yield: 130 mg (79%). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, 12 H, ^3J = 7 Hz, H_{CH3}), 1.46–1.53 (m, 8 H, H_{CH2}), 3.01 (t, 8 H, ^3J = 8 Hz, H_{CH2}), 7.56–7.60 (m, 4 H, H_{ar}), 7.72 (d, 4 H, ^3J = 8 Hz, H_{ar}), 7.96–7.98 (m, 6 H,

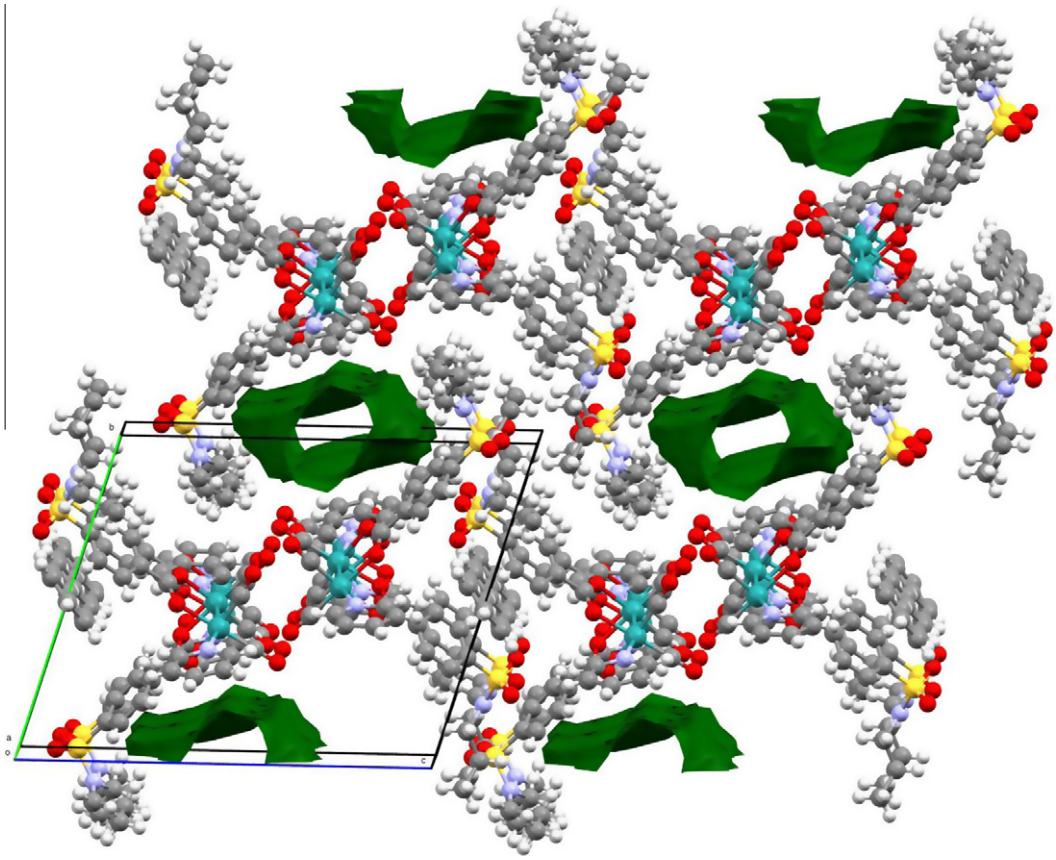


Fig. 3. Crystal packing of **1a** · 0.5 C_6H_6 showing the empty voids of 185 Å^3 along the *a* axis.

H_{ar}), 8.90–8.92 (m, 4 H, H_{ar}). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 11.12 (4 C, CH_3), 21.95 (4 C, CH_2), 50.00 (4 C, CH_2), 125.12 (4 C, C_{ar}), 126.56 (4 C, C_{ar}), 130.19 (4 C, C_{ar}), 136.42 (2 C, C_{ar}), 137.72 (2 C, C_{ar}), 142.44 (4 C, C_{ar}), 151.81 (2 C, C_{ar}), 177.36 (2 C, C_{COO}), 203.74 (4 C, C_{CO}). IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1558.17, $\nu_{(CO)}$ 1946.64 vs, (ν_{CO}) 1976.27 m, (ν_{CO}) 2026.98 vs. ESI-MS (positive mode): *m*/*z* = 935.58 $[M–NC_5H_5–CO+H]^+$. $C_{40}H_{46}N_4O_{12}Ru_2S_2$ (1041.08) C 46.15, H 4.45, N 5.38. Found: C 46.27, H 4.42, N 5.31%.

3.2.2. $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{12}H_{18}NO_2S)_2(PPh_3)_2$ (**1b**)

Yield: 159 mg (72%). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, 12 H, ^3J = 7 Hz, H_{CH3}), 1.46–1.52 (m, 8 H, H_{CH2}), 3.01 (t, 8 H, ^3J = 7 Hz, H_{CH2}), 7.10 (d, 4 H, ^3J = 8 Hz, H_{ar}), 7.39–7.49 (m, 22 H, H_{ar}), 7.60–7.65 (m, 12 H, H_{ar}). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 11.14 (4 C, C_{CH3}), 21.92 (4 C, C_{CH2}), 49.89 (4 C, C_{CH2}), 126.20 (4 C, C_{ar}), 128.57 (12 C, C_{ar}), 129.90 (6 C, C_{ar}), 130.44 (4 C, C_{ar}), 133.13 (12 C, C_{ar}), 133.71 (6 C, C_{ar}), 136.41 (2 C, C_{ar}), 142.46 (2 C, C_{ar}), 179.16 (2 C, C_{COO}), 205.08 (4 C, C_{CO}). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 18.20 ppm. IR (KBr, cm^{-1}) $\nu_{(OCO)}$ 1558.06, $\nu_{(CO)}$ 1957.11 vs, (ν_{CO}) 1983.87 m, (ν_{CO}) 2026.80 vs. ESI-MS (positive mode): *m*/*z* = 1431.13 $[M+Na]^+$. *Anal.* Calc. for $C_{66}H_{66}N_2O_{12}P_2Ru_2S_2$ (1407.45) C 56.32, H 4.73, N 1.99. Found: C 56.60, H, 4.90, N 2.00%.

3.2.3. $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{12}H_{18}NO_2S)_2(C_{43}H_{29}N_5)_2$ (**1c**) [16]

Yield: 40 mg (57%) ^1H NMR (400 MHz, $CDCl_3$): δ = −2.72 (s, 4 H, NH), 0.80 (t, 12 H, ^3J = 7 Hz, H_{CH3}), 1.47–1.54 (m, 8 H, H_{CH2}), 3.02 (t, 8 H, ^3J = 8 Hz, H_{CH2}), 7.78–7.86 (m, 22 H, H_{porph} and H_{ar}), 8.23–8.25 (m, 12 H, ^3J = 8 Hz, H_{porph}), 8.31 (d, 4 H, ^3J = 8 Hz, H_{ar}), 8.51 (d, 4 H, ^3J = 6 Hz, H_{ar}), 8.90 (s, 8 H, H_{porph}), 9.02 (s, 8 H, H_{porph}), 9.40 (d, 4 H, ^3J = 6 Hz, H_{porph}). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 11.10 (4 C, C_{CH3}), 21.95 (4 C, C_{CH2}), 50.02 (4 C, C_{CH2}), 114.67 (8 C, C_{ar}), 120.92 (6 C, C_{ar}), 126.74 (4 C, C_{ar}), 126.83 (4 C, C_{ar}), 127.90 (12 C, C_{ar}), 127.98 (16 C, C_{ar}), 130.43 (4 C, C_{ar}), 130.83 (12 C, C_{ar}), 130.94 (12 C, C_{ar}), 134.52 (6 C, C_{ar}), 136.62 (2 C, C_{ar}), 141.76 (4 C, C_{ar}), 150.00 (2 C, C_{ar}), 177.96 (2 C, C_{COO}), 204.01 (4 C, C_{CO}). UV–Vis [1.0×10^{-6} M, CH_2Cl_2] λ_{max}/nm ($\varepsilon \times 10^6$ M^{-1} cm^{-1}) = 418 (3.251), 515 (0.230), 551 (0.121), 590 (0.074), 646 (0.055). IR (KBr, cm^{-1}): $\nu_{(porph\ N–H)}$ 1214.92, $\nu_{(OCO)}$ 1557.00, (ν_{CO}) 1979.01 vs, (ν_{CO}) 1976.27 m, (ν_{CO}) 2028.45 vs, ($\nu_{C–H\ aro}$) 3056.83 m. ESI-MS (positive mode): *m*/*z* = 1501.23 $[M–C_{43}H_{29}N_5+H]^+$. $C_{116}H_{94}N_{12}O_{12}Ru_2S_2 \cdot 2\ H_2O$ (2150.36) C 64.79, H 4.59, N 7.82. Found: C 64.70, H 4.64, N 7.65%.

3.2.4. $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{18}H_{15}ClNO_2)_2(NC_5H_5)_2$ (**2a**)

Yield: 60 mg (32%) ^1H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 6 H, H_{CH3}), 3.47 (s, 4 H, H_{CH2}), 3.67 (s, 6 H, H_{CH3}), 6.64 (dd, 2 H, ^3J = 9 Hz, ^4J = 2 Hz, H_{ar}), 6.83 (d, 2 H, ^4J = 2 Hz, H_{ar}), 6.93 (d, 2 H, ^3J = 9 Hz, H_{ar}), 7.19 (dd, 4 H, ^3J = 7 Hz, ^4J = 2 Hz H_{ar}), 7.43 (d, 4 H, ^3J = 8 Hz, H_{ar}), 7.57 (d, 4 H, ^3J = 8 Hz, H_{ar}), 7.73 (t, 2 H, ^3J = 8 Hz, H_{ar}), 8.42 (d, 4 H, ^3J = 5 Hz, H_{ar}). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 13.21 (2 C, C_{CH3}), 32.25 (2 C, C_{CH2}), 55.44 (2 C,C_{CH3}), 101.95 (2 C, C_{ar}), 111.14 (2 C, C_{ar}), 114.66 (2 C, C_{ar}), 115.13 (2 C, C_{ar}), 124.57 (4 C, C_{ar}), 129.01 (2 C, C_{ar}), 130.77 (4 C, C_{ar}), 131.03 (4 C, C_{ar}), 131.16 (2 C, C_{ar}), 134.00 (2 C, C_{ar}), 134.79 (2 C, C_{ar}), 137.11 (2 C, C_{ar}), 139.06 (2 C, C_{ar}), 151.63 (4 C, C_{ar}), 155.84 (2 C, C_{ar}), 168.23 (2 C, C_{CON}), 183.66 (2 C, C_{COO}), 203.93 (4 C, C_{CO}). IR (KBr, cm^{-1}): $\nu_{(OCO)}$ 1581.79, (ν_{CO}) 1936.73 vs, (ν_{CO}) 1970.86 m, (ν_{CO}) 2022.40 vs. ESI-MS (positive mode): *m*/*z* = 1187.02 $[M+H]^+$. *Anal.* Calc. for $C_{52}H_{40}Cl_2N_4O_{12}Ru_2$ (1185.94) C 52.66, H 3.40, N 4.72. Found: C 52.39, H 3.59, N 4.60%.

3.2.5. $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{18}H_{15}ClNO_2)_2(PPh_3)_2$ (**2b**)

Yield: 277 mg (83%) ^1H NMR (400 MHz, $CDCl_3$): δ = 1.76 (s, 6 H, H_{CH3}), 3.31 (s, 4 H, H_{CH2}), 3.63 (s, 6 H, H_{CH3}), 6.68- (br-s, 2 H,

^3J = 9 Hz, H_{ar}), 6.9 (d, 2 H, ^4J = 2 Hz, H_{ar}), 7.01 (d, 2 H, ^3J = 9 Hz H_{ar}), 7.14–7.19 (m, 18 H, H_{ar}), 7.21 (d, 2 H, ^3J = 7 Hz, H_{ar}), 7.32 (t, 6 H, ^3J = 7 Hz, H_{ar}), 7.38–7.42 (m, 12 H, H_{ar}). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 12.95 (2 C, C_{CH3}), 32.32 (2 C, C_{CH2}), 55.48 (2 C, C_{CH3}), 101.19 (2 C, C_{ar}), 111.35 (2 C, C_{ar}), 114.54 (2 C, C_{ar}), 114.92 (2 C, C_{ar}), 128.2 (12 + 6 C, C_{ar}), 128.78 (4 C, C_{ar}), 129.65 (2 C, C_{ar}), 130.89 (12 C, C_{ar}), 133.34 (4 C, C_{ar}), 133.49 (6 C, C_{ar}), 133.66 (2 C, C_{ar}), 133.84 (2 C, C_{ar}), 134.86 (2 C, C_{ar}), 138.68 (2 C, C_{ar}), 156.06 (2 C, C_{ar}), 167.98 (2 C, C_{CON}), 185.77 (2 C, C_{COO}), 204.95 (4 C, C_{CO}). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 12.99 ppm. IR (KBr, cm^{-1}): $\nu_{(OCO)}$ 1578.77, (ν_{CO}) 1950.87 vs, (ν_{CO}) 1980.63 m, (ν_{CO}) 2023.55 vs. ESI-MS (positive mode): m/z = 1575.12 $[M+Na]^+$. *Anal.* Calc. for $C_{78}H_{60}Cl_2N_2O_{12}P_2Ru_2$ (1552.31) C 60.35, H 3.90, N 1.80. Found: C 60.08, H 4.08, N 1.81%.

3.2.6. $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{18}H_{15}ClNO_2)_2(C_{43}H_{29}N_5)_2$ (**2c**) [16]

Yield: 107 mg (86%) ^1H NMR (400 MHz, $CDCl_3$): δ = −2.74 (s, 4 H, H_{NH}), 2.41 (s, 6 H, H_{CH3}), 3.67 (s, 6 H, H_{CH2}), 3.84 (s, 4 H, H_{CH3}), 6.64 (dd, 2 H, ^3J = 9 Hz, ^4J = 2 Hz, H_{ar}), 6.71 (d, 2 H, ^3J = 9 Hz, H_{ar}), 6.98 (d, 4 H, ^3J = 8 Hz, H_{ar}), 7.15 (d, 2 H, ^4J = 2 Hz, H_{ar}), 7.35 (d, 4 H, ^3J = 8 Hz, H_{ar}), 7.79–7.85 (m, 18 H, H_{porph}), 8.11 (d, 4 H, ^3J = 6 Hz, H_{porph}), 8.25–8.27 (m, 12 H, H_{porph}), 8.84–8.90 (m, 16 H, H_{porph}), 8.96 (d, 4 H, ^3J = 5 Hz, H_{porph}). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 13.47 (2 C,C_{CH3}), 32.53 (2 C, C_{CH2}), 55.56 (2 C, C_{CH3}), 102.56 (2 C, C_{ar}), 110.79 (2 C, C_{ar}), 110.82 (2 C, C_{ar}), 114.67 (2 C, C_{ar}), 120.77 (8 C, C_{ar}), 126.72 (12 C, C_{ar}), 126.79 (4 C, C_{ar}), 128.73 (2 C, C_{ar}), 130.41 (4 C, C_{ar}), 130.87 (4 C, C_{ar}), 131.40 (2 C, C_{ar}), 133.70 (16 C, C_{ar}), 134.54 (2 C, C_{ar}), 135.29 (2 C, C_{ar}), 141.84 (2 C, C_{ar}), 149.90 (4 C, C_{ar}), 152.00 (16 C, C_{ar}), 155.88 (2 C, C_{ar}), 168.12 (2 C, C_{CON}), 184.43 (2 C, C_{COO}), 204.25 (4 C, C_{CO}). UV–Vis [1.0×10^{-6} M, CH_2Cl_2] λ_{max}/nm ($\varepsilon \times 10^6$ M^{-1} cm^{-1}) = 418 (3.343), 515 (0.355), 551 (0.171), 590 (0.109), 645 (0.083). IR (KBr, cm^{-1}): $\nu_{(porph\ N-H)}$ 1224.17, $\nu_{(OCO)}$ 1580.28, (ν_{CO}) 1942.78 vs, (ν_{CO}) 1975.35 m, (ν_{CO}) 2025.14 vs, ($\nu_{C-H\ aro}$) 3056.41 m. ESI-MS (positive mode): m/z = 616.25 $[C_{43}H_{29}N_5+H]^+$. *Anal.* Calc. for $C_{128}H_{88}Cl_2N_{12}O_{12}Ru_2 \cdot 3\ H_2O$ (2313.23) C 66.46, H 4.10, N 7.27. Found: C 66.55, H 4.03, N 7.19%.

3.2.7. $Ru_2(CO)_4(\mu_2\text{-}\eta^2\text{-}O_2CC_{19}H_{16}FOS)_2(PPh_3)_2$ (**3b**)

Yield 54 mg (23%) ^1H NMR (400 MHz, DMSO): δ = 1.68 (s, 6 H, H_{CH3}), 2.80 (s, 6 H, H_{CH3}), 3.18 (s, 4 H, H_{CH2}), 6.35 (dd, 2 H, ^3J = 9 Hz, ^4J = 2 Hz, H_{CH2}), 6.65–6.70 (m, 2 H, H_{ar}), 7.10–7.14 (m, 2 H, H_{ar}), 7.15 (s, 2 H, H_{ar}), 7.35–7.36 (m, 22 H, H_{ar}), 7.41–7.45 (m, 8 H, H_{ar}), 7.61 (d, 4 H, ^3J = 8 Hz, H_{ar}), 7.77 (d, 4 H, ^3J = 8 Hz, H_{ar}). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 9.87 (2 C, C_{CH3}), 32.32 (2 C, C_{CH2}), 43.86 (2 C,C_{CH3}), 105.95 (2 C, C_{ar}), 110.41 (2 C, C_{ar}), 123.28 (2 C, C_{ar}) 123.74 (4 C, C_{ar}), 127.01 (4 C, C_{ar}), 128.13 (12 + 6 C, C_{ar}), 129.57 (2 C, C_{ar}), 130.14 (2 C, C_{ar}), 133.09 (12 C, C_{ar}), 133.65 (6 C, C_{ar}), 133.77 (2 C, C_{ar}), 137.05 (2 C, C_{ar}), 139.87 (2 C, C_{ar}), 141.87 (2 C, C_{ar}), 145.22 (2 C, C_{ar}), 147.33 (2 C, C_{ar}), 164.39 (2 C, C_{ar}), 184.93 (2 C, C_{COO}), 205.05 (4 C, C_{CO}). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ = 14.57 ppm. IR (KBr, cm^{-1}): $\nu_{(OCO)}$ 1580.41, (ν_{CO}) 1954.58 vs, (ν_{CO}) 1980.41 m, (ν_{CO}) 2025.10 vs. ESI-MS (positive mode): m/z = 997.56 $[M\text{-}2\ PPh_3\text{-}CO+H]^+$. *Anal.* Calc. for $C_{80}H_{62}F_2O_{10}P_2Ru_2S_2$ (1549.56) C 62.01, H 4.03. Found: C 61.60, H 4.15%.

3.3. Single-crystal X-ray structure analysis

A crystal of compound **1a** · 0.5 C_6H_6 was mounted on a Stoe Image Plate Diffraction system equipped with a Φ circle goniometer, using Mo Kα graphite monochromated radiation (λ = 0.71073 Å) with Φ range 0–200°. The structure was solved by direct methods using the program SHELXS-97, while the refinement and all further calculations were carried out using SHELXL-97 [17]. The H-atoms were included in calculated positions and treated as riding atoms using the SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-square on F^2. Crystallographic details are summarized in Table 2. Fig. 2 was drawn with ORTEP [18] and Fig. 3 with MERCURY [19].

Table 2
Crystallographic and structure refinement parameters for complex **1a** · 0.5 C_6H_6.

	1a · 0.5 C_6H_6
Chemical formula	$C_{43}H_{49}N_4O_{12}Ru_2S_2$
Formula weight	1080.12
Crystal system	triclinic
Space group	$P\bar{1}$ (No. 2)
Crystal color and shape	yellow block
Crystal size	0.23 × 0.19 × 0.16
a (Å)	10.4848(6)
b (Å)	15.3189(11)
c (Å)	18.2466(12)
α (°)	72.648(5)
β (°)	84.706(5)
γ (°)	73.398(5)
V (Å^3)	2680.6(3)
Z	2
T (K)	173(2)
D_c (g·cm^{-3})	1.338
μ (mm^{-1})	0.697
Scan range (°)	1.58 < θ < 29.26
Unique reflections	14483
Observed reflections [$I > 2\sigma(I)$]	9716
R_{int}	0.1231
Final R indices [$I > 2\sigma(I)$]*	0.0910, wR_2 0.1523
R indices (all data)	0.1472, wR_2 0.1734
Goodness-of-fit (GOF)	1.131
Maximum, Minimum, Δρ/e (Å^{-3})	0.847 and 1.939

* Structure was refined on F_0^2: $wR_2 = [\Sigma[w\ (F_0^2 - F_c^2)^2]/\Sigma w\ (F_0^2)^2]^{1/2}$, where $w^{-1} = [\Sigma(F_0^2) + (aP)^2 + bP]$ and $P = [\max(F_0^2, 0) + 2F_c^2]/3$.

Acknowledgements

Financial support of this work by the Swiss National Science Foundation and a generous loan of ruthenium chloride hydrate from the Johnson Matthey Research Centre are gratefully acknowledged.

Appendix A. Supplementary material

CCDC 887790 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2012.09.034.

References

[1] B.E. Mann, R. Motterlini, Chem. Commun. (2007) 4197.
[2] B.E. Mann, Top. Organomet. Chem. 32 (2010) 247.
[3] (a) T.R. Johnson, B.E. Mann, I.P. Teasdale, H. Adams, R. Foresti, C.J. Green, R. Motterlini, Dalton Trans. (2007) 1500;
(b) H. Smith, B.E. Mann, R. Motterlini, R.K. Poole, IUBMB Life 63 (2011) 363.
[4] E. Bathoorn, D.-J. Slebos, D.S. Postma, G.H. Koeter, A.J.M. van Oosterhout, M. van der Toorn, H.M. Boezen, H.A.M. Kerstjens, Eur. Respir. J. 30 (2007) 1131.
[5] (a) N.J. Farrer, P.J. Sadler, Medicinal inorganic chemistry: state of the art, new trends, and a vision of the future, in: E. Alessio (Ed.), Bioinorganic Medicinal Chemistry, Wiley-VCH, Weinheim, Germany, 2011, pp. 1–47;
(b) I. Bratsos, T. Gianferrara, E. Alessio, C.G. Hartinger, M.A. Jakupec, B.K. Keppler, Ruthenium and other non-platinum anticancer compounds, in: E. Alessio (Ed.), Bioinorganic Medicinal Chemistry, Wiley-VCH, Weinheim, Germany, 2011, pp. 151–174;
(c) G. Süss-Fink, Dalton Trans. 39 (2010) 1673;
(d) G.S. Smith, B. Therrien, Dalton Trans. 40 (2011) 10793;
(e) W.H. Ang, A. Casini, G. Sava, P.J. Dyson, J. Organomet. Chem. 696 (2011) 989.
[6] (a) G. Lavigne, Eur. J. Inorg. Chem. (1999) 917;
(b) M.I. Bruce, Coord. Chem. Rev. 76 (1987) 1.

[7] G.R. Crooks, B.F.G. Johnson, J. Lewis, I.G. Williams, G. Gamlen, J. Chem. Soc. A (1969) 2761.
[8] B. Therrien, G. Süss-Fink, Coord. Chem. Rev. 253 (2009) 2639.
[9] (a) F. Schmitt, M. Auzias, P. Štěpnička, Y. Sei, K. Yamaguchi, G. Süss-Fink, B. Therrien, L. Juillerat-Jeanneret, J. Biol. Inorg. Chem. 14 (2009) 693;
(b) J.P. Johnpeter, F. Schmitt, E. Denoyelle-Di-Muro, G. Wagnières, L. Juillerat-Jeanneret, B. Therrien, Inorg. Chim. Acta http://dx.doi.org/10.1016/j.ica.2012.05.026.
[10] (a) M. Auzias, B. Therrien, G. Süss-Fink, Inorg. Chim. Acta 359 (2006) 3412;
(b) M. Auzias, J. Mattsson, B. Therrien, G. Süss-Fink, Z. Anorg, Allg. Chem. 635 (2009) 115.
[11] A. Enomoto, H. Kimura, A. Chairoungdua, Y. Shigeta, P. Jutabha, S.H. Cha, M. Hosoyamada, M. Takeda, T. Sekine, T. Igarashi, H. Matsuo, Y. Kikuchi, T. Oda, K. Ichida, T. Hosoya, K. Shimokata, T. Niwa, Y. Kanai, H. Endou, Nature 417 (2002) 447.
[12] (a) C.P. Duffy, C.J. Elliott, R.A. O'Connor, M.M. Heenan, S. Coyle, I.M. Cleary, K. Kavanagh, S. Verhaegen, C.M. O'Loughlin, R. NicAmhlaoibh, M. Clynes, Eur. J. Cancer 34 (1998) 1250;
(b) E.R. Rayburn, S.J. Ezell, R. Zhang, Mol. Cell Pharmacol. 1 (2009) 29;
(c) K.M. Detjen, M. Welzel, B. Wiedenmann, S. Rosewicz, Int. J. Cancer 107 (2003) 844.
[13] J.P. Johnpeter, B. Therrien, J. Struct. Chem. 52 (2011) 151.
[14] M.I. Bruce, C.M. Jensen, N.L. Jones, Inorg. Synth. 26 (1989) 259.
[15] E.B. Fleischer, A.M. Shachter, Inorg. Chem. 30 (1991) 3763.
[16] The limited solubility of complexes **1c** and **2c** did not allow a complete assignment of their ^{13}C NMR spectral data.
[17] G.M. Sheldrick, Acta Cryst. A64 (2008) 112.
[18] L.J. Farrugia, J. Appl. Cryst. 30 (1997) 565.
[19] I.J. Bruno, J.C. Cole, P.R. Edgington, M. Kessler, C.F. Macrae, P. McCabe, J. Pearson, R. Taylor, Acta Cryst. B58 (2002) 389.