Full Paper

Applied Organometallic Chemistry

Received: 18 January 2008 Revised: 19 February 2008 Accepted: 19 February 2008

(www.interscience.com) DOI 10.1002/aoc.1394

Modifying the structure of dinuclear ruthenium complexes with antitumor activity

Maria G. Mendoza-Ferri[a], Christian G. Hartinger[a*], Alexey A. Nazarov[a**], Wolfgang Kandioller[a], Kay Severin[b] and Bernhard K. Keppler[a]

In order to modulate the structure of a recently developed series of antitumor-active, dinuclear Ru(II)–arene compounds, complexes 1c–4c were synthesized. The complexes were modified with respect to their pyridinone moieties and the spacer linking the two metal centers. More particularly, the series of dinuclear ruthenium(II) complexes was extended to compounds with longer spacers, i.e. tetradecane and 3,7,10-trioxotridecane, and the pyridinone ring was modified by replacing the methyl group by an ethyl group and by shifting the position of the methyl group. The organometallic ruthenium compounds were obtained from the reaction between [RuCl$_2$(η^6-*p*-isopropyltoluene)]$_2$ and ligands 1b–4b with yields ranging from 41 to 67%. All compounds were characterized by standard methods: MS, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: anticancer research; dinuclear complexes; lipophilicity; ruthenium compounds; synthesis

Introduction

Ruthenium complexes, such as KP1019 and NAMI-A (Fig. 1), are among the most interesting next-generation anticancer drugs in clinical trials and most importantly, in addition to their tumor-inhibiting properties, the treatment is not accompanied by major drug-related side effects.[1–4] Therefore, there is plenty of space in the therapeutic window and – compared with platinum drugs – compounds with higher cytotoxicity should be still well tolerated. With their mode of action involving probably the concepts of transport via the transferrin cycle[5–9] and activation by reduction to Ru(II) compounds in the cell,[10] low levels of toxic side effects were observed in the chemotherapy of patients.[1] Recently, organometallic Ru(II) complexes, like RAPTA-C (Fig. 1), have gained interest due to their different mode of action, yielding compounds with antimetastatic properties (as also found for NAMI-A).[11–14] With variation of the ligand sphere of Ru(II) species, both low-cytotoxic but antimetastatic compounds,[15] and *in vitro* antineoplastic complexes were obtained.[14,16–18] Ruthenium–arene cluster compounds have also been shown to exhibit interesting *in vitro* effects.[19,20] Recently, dinuclear Ru(II) complexes were introduced and the two Ru centers were found to act synergistically with the dinuclear compound being more active against human tumor cells than the respective mononuclear species. PyrRu$_2$^{12} (Fig. 1) was found to be the most active compound in this series of dinuclear complexes based on pyridinone ligands.[21] The class of hydroxypyrones and *N*-substituted pyridinones, derived from maltol and its analogs, have been widely investigated for the preparation of complexes designed for medicinal applications including treatment of β-thalassemia and diabetes,[22,23] and for radiodiagnostic[22,24] and chemotherapeutic purposes.[25,26] It is well known that these bidentate ligands exhibit high affinity for divalent and trivalent metals ions[22] and are able to form very stable complexes, due to the possible electron delocalization leading to the formation of 'aromatic' zwitterions.[27] Therefore they have been extensively used as chelating moieties in inorganic synthesis.[22,28] The most important examples comprise a VO(maltolato) complex, which is going to enter clinical trials for treatment of diabetes type II, and tris(maltolato)gallium(III), undergoing clinical investigation as an anticancer agent.[29]

One precious advantage of this compound class is the possibility to modulate easily the chemical structure of the pyridinone moiety in order to influence important drug-like parameters such as solubility and hydrophobicity.

Recently, we have reported the preparation of a series of dinuclear ruthenium(II)–arene complexes, including PyrRu$_2$^{12} (Fig. 1), based on 3-hydroxy-2-methyl-pyridinone with the alkyl spacers propane, hexane and dodecane. These complexes exhibit for Ru compounds unusual high anticancer activity in the high nanomolar range against a series of human tumor cell lines. In particular, similar activity to oxaliplatin was found in a colorectal carcinoma cell line, while the mononuclear complexes are inactive.[21] Furthermore, studies into the mode of action of these compounds were performed which revealed low level of covalent binding to DNA or small proteins but affinity to transferrin. A similar approach, i.e. linking more than one metal center, was recently applied for platinum complexes and these compounds even entered clinical trials.[30] Herein, structural analogs of the dinuclear Ru complexes are reported, which were obtained by modification of either the pyridone units (**2c, 3c**) or the spacer

---

* Correspondence to: Christian G. Hartinger, University of Vienna, Institute of Inorganic Chemistry, Waehringer Str. 42, A-1090 Vienna, Austria. E-mail: christian.hartinger@univie.ac.at

** Alexey A. Nazarov, University of Vienna, Institute of Inorganic Chemistry, Austria. E-mail: alex.nazarov@univie.ac.at

a University of Vienna, Institute of Inorganic Chemistry, Austria

b Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland

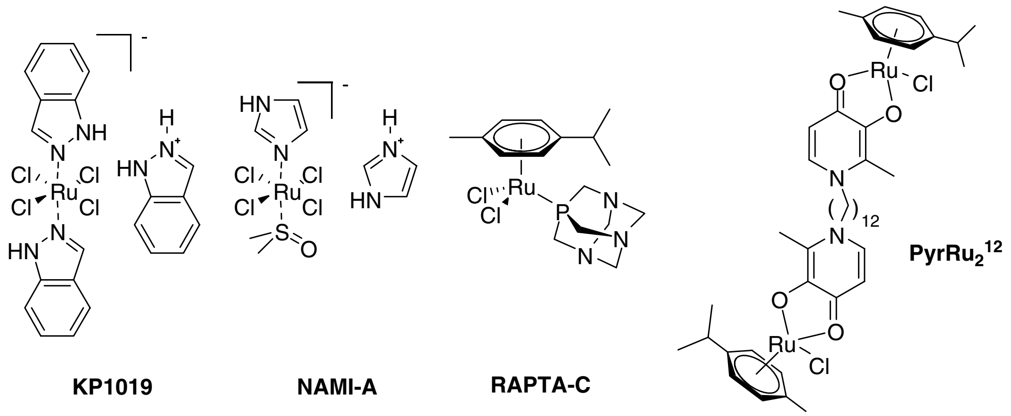


Figure 1. Structural formulae of Ru anticancer drug candidates (from left to right KP1019, NAMI-A, RAPTA-C and PyrRu$_2$^{12}).

(**1c, 4c**), with the intention of modulating the lipophilicity of the complexes.

Experimental Section

All reactions were carried out in dry solvents and under argon atmosphere. 3-Benzyloxy-2-methyl-4-pyrone,[31] 5-benzyloxy-2-methyl-4-pyrone,[32] bis[dichloro(η^6-*p*-isopropyltoluene) ruthenium(II)][33] and 1,14-diaminotetradecane[34] were prepared according to the literature procedures. Purchased chemicals were used without further purification. Melting points were determined with a Büchi B-540 apparatus and are uncorrected. Elemental analyses were carried out with a Perkin Elmer 2400 CHN Elemental Analyzer at the Microanalytical Laboratory of the University of Vienna. NMR spectra were recorded at 25 °C on a Bruker Avance DPX400 spectrometer (Ultrashield™ Magnet) at 400.13 MHz (^{1}H) and 100.63 MHz (^{13}C) in d$_4$-MeOH or D_2O/CF_3COOH (9 : 1). Electrospray ionization mass spectrometry (ESI-MS) was performed on a Bruker *esquire*$_{3000}$ instrument (Bruker Daltonics, Bremen, Germany) and theoretical and experimental isotope distributions were compared.

Syntheses

*1,14-Bis[3-benzyloxy-2-methyl-4(1H)-pyridinon-1-yl]tetradecane (**1a**)*

Sodium hydroxide (1.40 g, 35.0 mmol) was added to a solution of 3-benzyloxy-2-methyl-4-pyrone (4.26 g, 19.7 mmol) and 1,14-diaminotetradecane (1.51 g, 6.6 mmol) in a methanol–water mixture (2 : 1, 210 ml). The reaction mixture was refluxed for 48 h and then allowed to cool to room temperature. The product was extracted with dichloromethane (3 × 50 ml), and the solvents were removed in vacuum to give a brown oil. The pure product (yellow oil) was obtained by silica gel chromatography with methanol as eluent.

Yield: 0.82 g (20%). Elemental analysis, found: C, 74.75; H, 8.06; N, 4.33. Calculated for $C_{40}H_{52}N_2O_4 \cdot H_2O$: C, 74.73; H, 8.47; N, 4.36. MS (ESI$^+$) *m/z* 626 $[M + H]^+$. ^{1}H NMR in d$_4$-MeOH: $\delta = 1.31$ [brs, 20H, CH_2], 1.61–1.68 [m, 4H, $C\underline{H}_2CH_2{-}N$], 2.16 [s, 6H, CH_3], 3.96 [t, 4H, $CH_2{-}N$, $^3J = 7.5$ Hz], 5.10 [s, 4H, $CH_2{-}Ph$], 6.48 [d, 2H, $CH{-}C{=}O$, $^3J = 7.6$ Hz], 7.33–7.41 [m, 10H, CH_{arom}], 7.69 [d, 2H, $N{-}CH$, $^3J = 7.3$ Hz]. ^{13}C NMR in d$_4$-MeOH: $\delta = 11.8$ [CH_3], 26.2 [$\underline{C}H_2(CH_2)_6{-}N$], 29.2 [$\underline{C}H_2(CH_2)_5{-}N$], 29.5 [$\underline{C}H_2(CH_2)_4{-}N$], 29.6 [$\underline{C}H_2(CH_2)_3{-}N$], 29.7 [$\underline{C}H_2(CH_2)_2{-}N$]], 30.6 [$\underline{C}H_2CH_2{-}N$], 54.3 [$CH_2{-}N$], 73.4 [$CH_2{-}Ph$], 116.2 [$CH{-}C{=}O$], 128.4 [$C_{arom}$], 128.4 [$C_{arom}$], 129.4 [$C_{arom}$], 137.4 [$C_{arom}$], 140.2 [$N{-}CH$], 144.1 [$C{-}CH_3$], 145.9 [$C{-}O$], 173.7 [$C{=}O$].

*1,14-Bis[3-hydroxy-2-methyl-4(1H)-pyridinon-1-yl]tetradecane (**1b**)*

Hydrogen was passed through a mixture of **1a** (0.80 g, 1.28 mmol) and palladium on activated carbon (10% Pd, 120 mg) in 100% acetic acid (40 ml). The conversion was monitored by means of TLC and the reaction was finished when the spot of the starting compound had disappeared. The catalyst was filtered off, the solvent was removed and the product was dried in vacuum.

Yield: 0.37 g (65%), m.p. 170–175 °C. Elemental analysis, found: C, 66.72; H, 8.44, N, 5.67. Calculated for $C_{26}H_{40}N_2O_4 \cdot CH_3COOH$: C, 66.64, H, 8.79, N, 5.55. MS (ESI$^+$) *m/z* 446 $[M + H]^+$. ^{1}H NMR in D_2O/CF_3COOH: $\delta = 0.28$ [brs, 10H, CH_2], 0.78 [m, 4H, $C\underline{H}_2CH_2{-}N$], 1.55 [s, 6H, CH_3], 3.21 [t, 4H, $CH_2{-}N$, $^3J = 7.8$ Hz], 6.13 [d, 2H, $CH{-}C{=}O$, $^3J = 7.1$ Hz], 6.84 [d, 2H, CH, $^3J = 7.1$ Hz]. ^{13}C–NMR in D_2O/CF_3COOH: $\delta = 10.8$ [CH_3], 24.9 [$\underline{C}H_2(CH_2)_6{-}N$], 27.7 [$\underline{C}H_2(CH_2)_5{-}N$], 28.0 [$\underline{C}H_2(CH_2)_4{-}N$], 28.2 [$\underline{C}H_2(CH_2)_3{-}N$], 28.3 [$\underline{C}H_2CH_2CH_2{-}N$], 29.2 [$\underline{C}H_2CH_2{-}N$], 56.3 [$CH_2{-}N$], 110.3 [$CH{-}C{=}O$], 136.9 [$N{-}CH$], 141.1 [$C{-}CH_3$], 142.5 [$C{-}O$], 157.3 [$C{=}O$].

*1,14-Bis{chloro[3-(oxo-κO)-2-methyl-4-(1H)-pyridinonato-κO4](η^6-p-isopropyltoluene)ruthenium(II)}tetradecane (**1c**)*

A solution of bis[dichloro(η^6-*p*-isopropyltoluene)ruthenium(II)] (79.1 mg, 0.13 mmol) in methanol (20 ml) was added to a suspension of **1b** (82.0 mg, 0.18 mmol) and sodium methoxide (21.9 mg, 0.41 mmol) in methanol (20 ml). The reaction mixture was stirred for 2 days at room temperature, then the unconverted compounds were removed by filtration and the solvent was removed in vacuum. The complex was purified by extraction with a dichloromethane–diethylether mixture (2 : 1, 2 × 45 ml), the solvent was evaporated and the product was dried in vacuum.

Yield: 52.0 mg (41%), m.p. 118–120 °C (decomp.). Elemental analysis, found: C, 55.25; H, 6.75, N, 2.69. Calculated for $C_{46}H_{66}N_2O_4Ru_2Cl_2 \cdot {}^1\!/\!_4CH_2Cl_2$: C, 55.26, H, 6.67, N, 2.79. MS (ESI$^+$) *m/z* 457 $[M{-}Cl]^+$. ^{1}H NMR in d$_4$-MeOH: $\delta = 1.31$ [m, 32H, CH_2, $(C\underline{H}_3)_2CH$], 1.72 [brs, 4H, $C\underline{H}_2CH_2{-}N$], 2.27 [s, 6H, CH_3], 2.49 [s, 6H, CH_3], 2.84–2.88 [m, 2H, $C\underline{H}(CH_3)_2$], 4.07 [t, 4H, $CH_2{-}N$, $^3J = 7.6$ Hz], 5.44 [d, 4H, CH, $^3J = 5.8$ Hz], 5.66 [d, 4H, CH, $^3J = 5.8$ Hz], 6.50 [d, 2H, $CH{-}C{=}O$, $^3J = 6.6$ Hz], 7.41 [d, 2H, CH, $^3J = 6.8$ Hz]. ^{13}C NMR in d_4-MeOH: $\delta = 10.8$ [CH_3], 17.5 [CH_3], 21.6 [$(\underline{C}H_3)_2CH$], 26.3 [$\underline{C}H_2(CH_2)_6{-}N$], 29.2 [$\underline{C}H_2(CH_2)_5{-}N$], 29.6 [$\underline{C}H_2(CH_2)_4{-}N$, $\underline{C}H_2(CH_2)_3{-}N$], 29.7 [$\underline{C}H_2(CH_2)_2{-}N$], 30.8 [$\underline{C}H_2CH_2{-}N$], 31.4 [$\underline{C}H(CH_3)_2$], 55.0 [$CH_2{-}N$], 77.9 [$C_{arom}$], 79.6 [$C_{arom}$], 96.0 [$C_{arom}$], 98.9 [$C_{arom}$], 109.3 [$CH{-}C{=}O$], 133.6 [$N{-}CH$], 134.3 [$C{-}CH_3$], 159.5 [$C{-}O$], 173.9 [$C{=}O$].

1,6-Bis[3-benzyloxy-2-ethyl-4(1H)-pyridinon-1-yl]hexane (**2a**)

Sodium hydroxide (1.40 g, 35.0 mmol) was added to a solution of 3-benzyloxy-2-ethyl-4-pyrone (10.00 g, 43.4 mmol) and 1,6-diaminohexane (1.68 g, 14.5 mmol) in a methanol–water mixture (2 : 1, 210 ml). The reaction mixture was refluxed for 48 h and then allowed to cool to room temperature. The product was extracted with dichloromethane (3 × 80 ml) and the solvents were removed in vacuum to give a brown oil. The pure product (yellow oil) was obtained by silica gel chromatography with methanol as eluent.

Yield: 2.35g (30%). Elemental analysis, found: C, 72.88; H, 7.70; N, 5.34. Calculated for $C_{34}H_{40}N_2O_4 \cdot H_2O$: C, 73.09; H, 7.58; N, 5.01. MS (ESI^+) *m/z* 541 $[M + H]^+$. ^1H NMR in d_4-MeOH: $\delta = 1.08$ [t, 6H, CH_3, $^3J = 7.5$ Hz], 1.32–1.36 [m, 4H, $C\underline{H}_2(CH_2)_2{-}N$], 1.68–1.70 [m, 4H, $C\underline{H}_2CH_2{-}N$], 2.66 [q, 4H, $C\underline{H}_2CH_3$, $^3J = 7.5$ Hz], 3.98 [t, 4H, $CH_2{-}N$, $^3J = 7.5$ Hz], 5.17 [s, 4H, $CH_2{-}Ph$], 6.49 [d, 2H,$CH{-}C{=}O$, $^3J = 7.3$ Hz], 7.30–7.41 [m, 10H, CH_{arom}], 7.69 [d, 2H, CH, $^3J = 7.6$ Hz]. ^{13}C NMR in d_4-MeOH: $\delta = 12.4$ [CH_3], 19.7 [$\underline{C}H_2CH_3$], 25.89 [$\underline{C}H_2(CH_2)_2{-}N$], 31.3 [$\underline{C}H_2CH_2{-}N$], 53.6 [$CH_2{-}N$], 73.3 [$CH_2{-}Ph$], 116.6 [$CH{-}C{=}O$], 128.3 [$C_{arom}$], 128.4 [$C_{arom}$], 129.0 [$C_{arom}$], 140.2 [$N{-}CH$], 141.2 [$C_{arom}$], 145.8 [$C{-}CH_3$], 156.0 [$C{-}O$], 166.3 [$C{=}O$].

1,6-Bis[3-hydroxy-2-ethyl-4(1H)-pyridinon-1-yl]hexane (**2b**)

Hydrogen was passed through a mixture of **2a** (1.51 g, 0.28 mmol) and palladium on activated carbon (10% Pd, 225 mg) in 100% acetic acid (40 ml). The conversion was monitored by means of TLC and the reaction was finished when the spot of the starting compound had disappeared. The catalyst was filtered off, the solvent was removed and the product was dried in vacuum.

Yield: 280.0 mg (28%), m.p. 270–272 °C. Elemental analysis, found: C, 65.66; H, 7.55; N, 7.61. Calculated for $C_{20}H_{28}N_2O_4 \cdot 1/3H_2O$: C, 65.55; H, 7.88; N, 7.64. MS (ESI^+) *m/z* 561 $[M + H]^+$. ^1H NMR in D_2O/CF_3COOH: $\delta = 0.15$ [t, 6H, CH_3, $^3J = 7.5$ Hz], 0.33 [brs, 4H, $C\underline{H}_2(CH_2)_2{-}N$], 0.76 [brs, 4H, $C\underline{H}_2CH_2{-}N$], 1.89 [q, 4H, $C\underline{H}_2CH_3$, $^3J = 7.7$ Hz], 3.16 [t, 4H, $CH_2{-}N$, $^3J = 7.6$ Hz], 6.05 [d, 2H,$CH{-}C{=}O$,$^3J = 7.0$ Hz], 6.73 [d, 2H, CH, $^3J = 7.1$ Hz]. ^{13}C NMR in D_2O/CF_3COOH: $\delta = 9.7$ [CH_3], 18.9 [$\underline{C}H_2CH_3$], 24.5 [$\underline{C}H_2(CH_2)_2{-}N$], 29.8 [$\underline{C}H_2CH_2{-}N$], 53.3 [$CH_2{-}N$], 110.4 [$CH{-}C{=}O$], 136.7 [$N{-}CH$], 142.2 [$C{-}CH_3$], 145.9 [$C{-}O$], 157.5 [$C{=}O$].

1,6-Bis{chloro[3-(oxo-κO)-2-ethyl-4-(1H)-pyridinonato-κO4](η^6-p-isopropyltoluene)ruthenium(II)}hexane (**2c**)

A solution of bis[dichloro(η^6-*p*-isopropyltoluene)ruthenium(II)] (142.7 mg, 0.23 mmol) in methanol (20 ml) was added to a suspension of **2b** (120.0 mg, 0.33 mmol) and sodium methoxide (39.6 mg, 0.73 mmol) in methanol (20 ml). The reaction mixture was stirred at room temperature and under argon atmosphere for 2 days. The unconverted compounds were removed by filtration and the solvent was evaporated in vacuum. The complex was purified by extraction with a dichloromethane/diethylether mixture (2 : 1, 45 ml). Afterwards the solvent was removed and the purification was performed by precipitation from dichloromethane with *n*-hexane.

Yield: 100.2 mg (48%), m.p. 258–260 °C. Elemental analysis, found: C, 52.88; H, 6.06, N, 3.46. Calculated for $C_{40}H_{54}N_2O_4Ru_2Cl_2 \cdot 1/7CH_2Cl_2$: C, 52.86, H, 6.00, N, 3.07. MS (ESI^+) *m/z* 415 $[M - 2Cl]^{2+}$. ^1H NMR in d_4-MeOH: $\delta = 1.23$ [t, 6H, CH_3, $^3J = 7.4$ Hz], 1.31–1.33 [m, 16H, $C\underline{H}_2(CH_2)_2{-}N$, $(C\underline{H}_3)_2CH$], 1.72 [brs, 4H, $C\underline{H}_2CH_2{-}N$], 2.28 [s, 6H, CH_3], 2.81–2.88 [m, 2H, CH_3], 2.93 [q, 4H, $C\underline{H}_2CH_3$, $^3J = 7.4$ Hz], 4.04 [t, 4H, $CH_2{-}N$, $^3J = 7.4$ Hz], 5.44 [d, 4H, CH, $^3J = 5.8$ Hz], 5.66 [d, 4H, CH, $^3J = 6.0$ Hz], 6.49 [d, 2H, $CH{-}C{=}O$, $^3J = 6.8$ Hz], 7.37 [d, 2H,CH, $^3J = 6.8$ Hz]. ^{13}C NMR in d_4-MeOH: $\delta = 11.9$ [CH_3], 17.6 [CH_3], 19.0 [$\underline{C}H_2CH_3$], 21.6 [$(\underline{C}H_3)_2CH$], 25.9 [$\underline{C}H_2(CH_2)_2{-}N$], 31.4 [$\underline{C}H_2CH_2{-}N$], 31.4 [$\underline{C}H(CH_3)_2$], 54.3 [$CH_2{-}N$], 77.8 [$C_{arom}$], 79.7 [$C_{arom}$], 96.2 [$C_{arom}$], 98.7 [$C_{arom}$], 109.4 [$CH{-}C{=}O$], 133.4 [$N{-}CH$], 139.4 [$C{-}CH_3$], 159.4 [$C{-}O$], 174.5 [$C{=}O$].

1,8-Bis[5-benzyloxy-2-methyl-4(1H)-pyridinon-1-yl]octane (**3a**)

Sodium hydroxide (0.30 g, 7.5 mmol) was added to a solution of 5-benzyloxy-2-methyl-4-pyrone (2.16 g, 9.99 mmol) and 1,8-diaminooctane (0.48 g, 3.33 mmol) in a methanol–water mixture (2 : 1, 210 ml). The reaction mixture was refluxed for 48 h and then allowed to cool to room temperature. The pure product was slowly crystallized (usually within 3–4 days) from the oil, washed with ethyl acetate (3 × 30 ml) and dried in vacuum.

Yield: 1.03 g (57%). m.p. 190–195 °C. Elemental analysis, found: C, 74.63; H, 7.40; N, 5.06. Calculated for $C_{34}H_{40}N_2O_4 \cdot ½H_2O$: C, 74.28; H, 7.52; N, 5.10. MS (ESI^+) *m/z* 542 $[M + H]^+$. ^1H NMR in d_4-MeOH: $\delta = 1.27$ [brs, 8H, CH_2], 1.62–1.69 [m, 4H, $C\underline{H}_2CH_2{-}N$], 2.37 [s, 6H, CH_3], 3.94 [t, 4H, $CH_2{-}N$, $^3J = 7.6$ Hz], 5.11 [s, 4H, $CH_2{-}Ph$], 6.38 [s, 2H, $CH{-}C{=}O$], 7.29–7.47 [m, 10H, CH_{arom}], 7.50 [s, 2H, CH]. ^{13}C NMR in d_4-MeOH: $\delta = 17.9$ [CH_3], 26.1 [CH_2], 29.1 [$\underline{C}H_2CH_2{-}N$], 30.4 [$\underline{C}H_2{-}(CH_2)_2{-}N$], 53.7 [$CH_2{-}N$], 71.2 [$CH_2{-}Ph$], 116.7 [$CH{-}C{=}O$], 127.8 [$C_{arom}$], 128.1–128.5 [$N{-}CH$, C_{arom}], 136.9 [C_{arom}], 147.2 [$C{-}CH_3$], 147.7 [$C{-}O$], 172.7 [$C{=}O$].

1,8-Bis[5-hydroxy-2-methyl-4(1H)-pyridinon-1-yl]octane (**3b**)

Hydrogen was passed through a mixture of **3a** (1.25 g, 2.31 mmol) and palladium on activated carbon (10% Pd, 200 mg) in 100% acetic acid (40 ml). The conversion was monitored by means of TLC and the reaction was finished when the spot of the starting compound had disappeared. The catalyst was filtered off, the solvent was removed and the product was dried in vacuum.

Yield: 0.61 g (72%), m.p. 250–252 °C (decomp.). Elemental analysis, found: C, 64.47; H, 7.68, N, 7.03. Calculated for $C_{20}H_{28}N_2O_4 \cdot ½CH_3COOH$: C, 64.59, H, 7.74, N, 7.17. MS (ESI^+) *m/z* 462 $[M + H]^+$. ^1H NMR in D_2O/CF_3COOH: $\delta = 0.16$ [brs, 8H, CH_2], 0.61 [brs, 4H, $C\underline{H}_2CH_2{-}N$], 1.33 [s, 6H, CH_3], 2.96 [t, 4H, $CH_2{-}N$, $^3J = 7.7$ Hz], 5.89 [s, 2H, $CH{-}C{=}O$], 6.74 [s, 2H, CH]. ^{13}C NMR in D_2O/CF_3COOH: $\delta = 16.9$ [CH_3], 24.6 [$\underline{C}H_2(CH_2)_3{-}N$], 27.3 [$\underline{C}H_2(CH_2)_2{-}N$], 28.8 [$\underline{C}H_2CH_2{-}N$], 55.4 [$CH_2{-}N$], 113.6 [$CH{-}C{=}O$], 129.8 [$N{-}CH$], 142.8 [$C{-}CH_3$], 147.2 [$C{-}O$], 158.9 [$C{=}O$].

1,8-Bis{chloro[5-(oxo-κO)-2-methyl-4-(1H)-pyridinonato-κO4](η^6-p-isopropyltoluene)ruthenium(II)}octane (**3c**)

A solution of bis[dichloro(η^6-*p*-isopropyltoluene)ruthenium(II)] (178.4 mg, 0.29 mmol) in methanol (20 ml) was added to a suspension of **3b** (150.0 mg, 0.42 mmol) and sodium methoxide (49.2 mg, 0.91 mmol) in methanol (20 ml). The reaction mixture was stirred at room temperature and under argon atmosphere for 3 days. The unconverted compounds were removed by filtration and the solvent was evaporated in vacuum. The complex was purified by extraction with a dichloromethane–diethylether mixture (2 : 1, 45 ml). The solvent was removed and the purification was performed by precipitation from dichloromethane with *n*-hexane.

Yield: 176.0 mg (67%), m.p. 256–260 °C (decomp.). Elemental analysis, found: C, 52.00; H, 5.70, N, 3.23. Calculated for $C_{40}H_{54}N_2O_4Ru_2Cl_2 \cdot 1/3CH_2Cl_2$: C, 52.19, H, 5.94, N, 3.02. MS (ESI$^+$) *m/z* 462 [M + H]$^+$. ^{1}H NMR in d_4-MeOH: $\delta = 1.32-1.34$ [m, 20H, $C\underline{H}_2(CH_2)_3-N$, $C\underline{H}_2(CH_2)_2-N$, $(C\underline{H}_3)_2CH$], 1.71 [brs, 4H, $C\underline{H}_2CH_2-N$], 2.26 [s, 6H, CH_3], 2.36 [s, 6H, CH_3], 2.82–2.89 [m, 2H, $C\underline{H}(CH_3)_2$], 3.97 [t, 4H, CH_2-N, $^3J = 7.6$ Hz], 5.44 [d, 4H, CH, $^3J = 3.8$ Hz], 5.66 [d, 4H, CH, $^3J = 5.3$ Hz], 6.45 [s, 2H, CH–C=O], 7.24 [s, 2H, CH]. ^{13}C NMR in d_4-MeOH: $\delta = 17.5$ [CH_3], 17.8 [CH_3], 21.6 [$(\underline{C}H_3)_2CH$], 26.2 [$\underline{C}H_2(CH_2)_3-N$], 29.0 [$\underline{C}H_2(CH_2)_2-N$], 30.4 [$\underline{C}H_2CH_2N$], 31.4 [$\underline{C}H(CH_3)_2$], 54.4 [$CH_2-N$], 77.7 [$C_{arom}$], 79.7 [$C_{arom}$], 84.9 [$C_{arom}$], 95.2 [$C_{arom}$], 112.0 [CH–C=O], 125.1 [N–CH], 142.4 [$C-CH_3$], 160.0 [C–O], 167.4 [C=O].

*1,13-Bis[3-benzyloxy-2-methyl-4(1H)-pyridinon-1-yl]-4,7,10-trioxatridecane (**4a**)*

Sodium hydroxide (1.40 g, 35.0 mmol) was added to a solution of 3-benzyloxy-2-methyl-4-pyrone (10.00 g, 46.2 mmol) and 4,7,10-trioxa-1,13-tridecanediamine (3.43 g, 15.4 mmol) in a methanol–water mixture (2 : 1, 210 ml). The reaction mixture was refluxed for 48 h and then allowed to cool to room temperature. The product was extracted with dichloromethane (3 × 50 ml), the solvents were removed in vacuum to give a brown oil. The pure product (yellow oil) was obtained by silica gel chromatography in pure methanol.

Yield: 4.75 g (50%). Elemental analysis, found: C, 65.64; H, 7.20; N, 4.16. Calculated for $C_{36}H_{44}N_2O_7 \cdot 5/2H_2O$: C, 65.34; H, 7.46; N, 4.23. MS (ESI$^+$) *m/z* 618 [M + H]$^+$. ^{1}H NMR in d_4-MeOH: $\delta = 1.87-1.93$ [m, 4H, $C\underline{H}_2CH_2-N$], 2.18 [s, 6H, CH_3], 3.37–3.40 [m, 4H, $C\underline{H}_2(CH_2)_2-N$], 3.55–3.58 [m, 4H, $C\underline{H}_2OCH_2(CH_2)_2-N$], 3.62–3.64 [m, 4H, $C\underline{H}_2CH_2OCH_2(CH_2)_2-N$], 4.08 [t, 4H, CH_2-N, $^3J = 6.8$ Hz], 5.10 [s, 4H, CH_2-Ph], 6.47 [d, 2H, CH–C=O, $^3J = 7.3$ Hz], 7.33–7.41 [m, 10H, CH_{arom}], 7.72 [d, 2H, CH, $^3J = 7.3$ Hz]. ^{13}C NMR in d_4-MeOH: $\delta = 11.78$ [CH_3], 30.18 [$\underline{C}H_2CH_2-N$], 51.19 [CH_2-N], 66.7 [$\underline{C}H_2(CH_2)_2-N$], 70.3 [$\underline{C}H_2OCH_2(CH_2)_2-N$], 70.5 [$\underline{C}H_2CH_2OCH_2(CH_2)_2-N$], 73.4 [$CH_2-Ph$], 116.2 [CH–C=O], 128.4 [C_{arom}], 129.4 [C_{arom}], 137.5 [C_{arom}], 140.7 [N–CH], 144.2 [$C-CH_3$], 146.0 [C–O], 173.8 [C=O].

*1,13-Bis[3-hydroxy-2-methyl-4(1H)-pyridinon-1-yl]-4,7,10-trioxatridecane (**4b**)*

Hydrogen was passed through a mixture of **4a** (1.45 g, 2.35 mmol) and palladium on activated carbon (10% Pd, 145 mg) in 100% acetic acid (40 ml). The conversion was monitored by means of TLC and the reaction was finished when the spot of the starting compound had disappeared. The catalyst was filtered off, the solvent was removed and the product was dried in vacuum.

Yield: 0.73 g (69%), m.p. 142–146 °C. Elemental analysis, found: C, 59.66; H, 7.24, N, 6.15. Calculated for $C_{22}H_{32}N_2O_7 \cdot 1/3H_2O$: C, 59.71, H, 7.44, N, 6.33. MS (ESI$^+$) *m/z* 438 [M + H]$^+$. ^{1}H NMR in d_4-MeOH: $\delta = 2.01$ [m, 4H, $C\underline{H}_2CH_2-N$], 2.45 [s, 6H, CH_3], 3.47 [t, 4H, $C\underline{H}_2(CH_2)_2-N$, $^3J = 5.7$ Hz], 3.60–3.62 [m, 4H, $C\underline{H}_2OCH_2(CH_2)_2-N$], 3.65–3.67 [m, 4H, $C\underline{H}_2CH_2OCH_2(CH_2)_2-N$], 4.18 [t, 4H, CH_2-N, $^3J = 6.9$ Hz], 6.41 [d, 2H, CH–C=O, $^3J = 7.4$ Hz], 7.66 [d, 2H, N–CH, $^3J = 7.1$ Hz]. ^{13}C NMR in d_4-MeOH: $\delta = 10.9$ [CH_3], 30.4 [$\underline{C}H_2CH_2-N$], 51.2 [CH_2-N], 66.8 [$\underline{C}H_2(CH_2)_2-N$], 70.3 [$\underline{C}H_2OCH_2(CH_2)_2-N$], 70.6 [$\underline{C}H_2CH_2OCH_2(CH_2)_2-N$], 111.5 [CH–C=O], 132.1 [$C-CH_3$], 138.3 [N–CH], 146.2 [C–O], 169.4 [C=O].

*1,13-Bis{chloro[3-(oxo-κO)-2-methyl-4-(1H)-pyridinonato-κO4](η^6-p-isopropyltoluene)ruthenium(II)}-4,7,10-trioxatridecane (**4c**)*

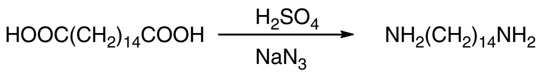
A solution of bis[dichloro(η^6-*p*-isopropyltoluene)ruthenium] (162.0 mg, 0.26 mmol) in methanol (20 ml) was added to a suspension of **4b** (154.0 mg, 0.35 mmol) and sodium methoxide (41.9 mg, 0.78 mmol) in methanol (20 ml). The reaction mixture was stirred at room temperature and under argon atmosphere for 2 days. The unconverted compounds were removed by filtration and the solvent was evaporated in vacuum. The complex was purified by extraction with a dichloromethane–diethylether mixture (2 : 1, 45 ml). Afterwards the solvent was removed and the purification was performed by precipitation from dichloromethane with *n*-hexane.

Yield: 91.1 mg (36%), m.p. 88–90 °C. Elemental analysis, found: C, 49.42; H, 5.78, N, 2.46. Calculated for $C_{42}H_{58}N_2O_7Ru_2Cl_2 \cdot 2/3CH_2Cl_2$: C, 49.63, H, 5.79, N, 2.71. MS (ESI$^+$) *m/z* 453 [M − 2Cl]$^{2+}$. ^{1}H NMR in d_4-MeOH: $\delta = 1.34$ [d, 12H, $(C\underline{H}_3)_2CH$, $^3J = 7.1$ Hz], 1.94–1.97 [m, 4H, $C\underline{H}_2CH_2-N$], 2.28 [s, 6H, CH_3], 2.49 [s, 6H, CH_3], 2.81–2.89 [m, 2H, $C\underline{H}(CH_3)_2$], 3.40–3.43 [t, 4H, $C\underline{H}_2(CH_2)_2-N$, $^3J = 5.6$ Hz], 3.57–3.60 [m, 4H, $C\underline{H}_2OCH_2(CH_2)_2-N$], 3.63–3.66 [m, 4H, $C\underline{H}_2CH_2OCH_2(CH_2)_2-N$], 4.18 [t, 4H, $C\underline{H}_2-N$, $^3J = 7.1$ Hz], 5.44 [d, 4H, CH, $^3J = 6.0$ Hz], 5.66 [d, 4H, CH, $^3J = 6.1$ Hz], 6.51 [d, 2H, CH–C=O, $^3J = 6.8$ Hz], 7.44 [d, 2H, CH, $^3J = 6.8$ Hz]. ^{13}C NMR in d_4-MeOH: $\delta = 10.8$ [CH_3], 17.6 [CH_3], 21.6 [$(\underline{C}H_3)_2CH$], 30.4 [$\underline{C}H_2CH_2N$], 31.4 [$\underline{C}H(CH_3)_2$], 51.9 [CH_2-N], 66.7 [$\underline{C}H_2(CH_2)_2-N$], 70.3 [$\underline{C}H_2OCH_2(CH_2)_2-N$], 70.5 [$\underline{C}H_2CH_2OCH_2(CH_2)_2-N$], 78.0 [$C_{arom}$], 79.6 [$C_{arom}$], 95.9 [$C_{arom}$], 99.0 [$C_{arom}$], 109.3 [CH–C=O], 134.1 [N–CH], 134.2 [$C-CH_3$], 159.6 [C–O], 174.1 [C=O].

Results and Discussion

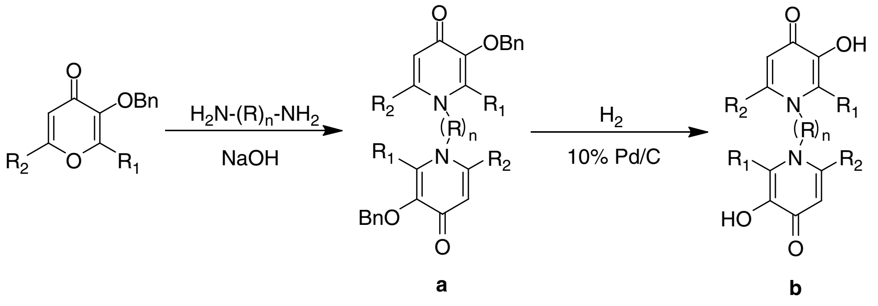
With the intention to make the reported dinuclear anticancer complexes[21] more lipophilic and thereby increasing the cellular uptake of the Ru species, complex **1c** with a tetradecane spacer was synthesized. 1,14-Diaminotetradecane was prepared from commercially available 1,16-hexadecanedioic acid by converting it in a one step reaction into 1,14-diaminotetradecane following a literature procedure (Fig. 2).[34]

In a second step 1,14-diaminotetradecane was refluxed with benzyl-protected maltol in methanol–water solution in the presence of NaOH for 48 h (Fig. 3), yielding the ligand **1b** containing linked pyridinone moieties which is a HCl-free compound (in contrast to the method described by Harris[31]). Similar procedures were applied for the synthesis of **2b**–**4b**. The derivatives **2b** and **3b** were chosen for synthesis in order to obtain information on the influence of structural changes in the pyridinone moiety, i.e. maltol[21] vs ethylmaltol vs allomaltol (with hexane or octane alkyl chains as linkers, respectively), on the anticancer activity of the compound class, whereas another modification of the bridge between the two coordinating moieties



$$HOOC(CH_2)_{14}COOH \xrightarrow[NaN_3]{H_2SO_4} NH_2(CH_2)_{14}NH_2$$

Figure 2. Synthesis of 1,14-diaminotetradecane from 1,16-hexadecanedioic acid.



$R = CH_2$ n = 14 $R_1 = CH_3$ $R_2 = H$ **(1)**
n = 6 $R_1 = CH_2CH_3$ $R_2 = H$ **(2)**
n = 8 $R_1 = H$ $R_2 = CH_3$ **(3)**

R = 4,7,10-trioxatridecane, n = 1
and $R_1 = CH_3$ $R_2 = H$ **(4)**

Figure 3. Synthetic pathway from benzyl-protected maltol to ligands with varying spacers and modifications in the pyridinone moiety.

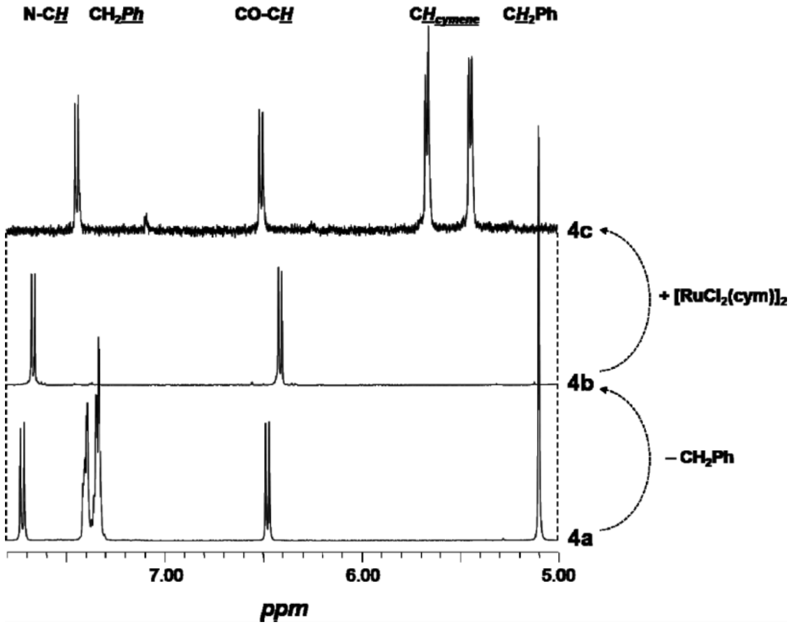


Figure 4. Following the conversion of **4a** to **4b** and **4c** by ^{1}H NMR spectroscopy.

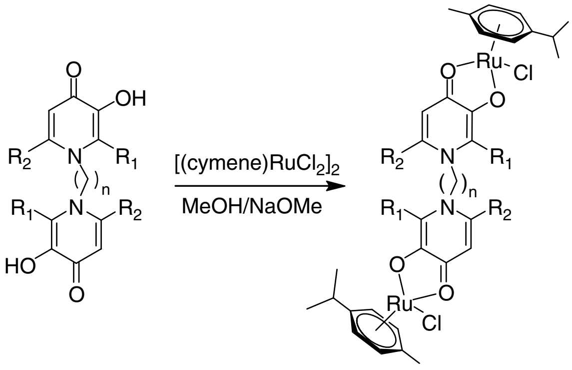
ended in the synthesis of a complex based on the polyether 4,7,10-trioxa-1,13-tridecanediamine (**4b**), which was also thought to overcome solubility problems in aqueous solutions of **1c** (or $PyrRu_2$[14], Fig. 5), but still maintaining the distance between the metal centers.

The benzylidene protection groups of **1a**–**4a** were removed by hydrogenolysis, catalyzed by Pd on activated charcoal. The progress of the reactions was monitored by means of TLC, ^{1}H NMR and ESI-MS.

The condensations of the diamines with maltol were accompanied by the appearance of the signals of alkyl moieties in the proton NMR spectra. The cleavage of the benzylidene group, i.e. unprotection of the maltol hydroxy group, could be monitored by decreasing resonances at approximately 7.4 and 5.1 ppm corresponding to aromatic and CH_2 protons of the protection group, respectively, and the heterocycle CH protons were shifted slightly to higher field. Typical changes in the ^{1}H NMR spectra upon linking the maltol moieties and unprotection of the pyridinone hydroxy group can be seen in Fig. 4.

The complexation reaction between the $RuCl_2(\eta^6$-*p*-cymene)-dimer and the corresponding deprotonated ligand (activated by sodium methoxide) in absolute methanol resulted in the formation of compounds **1c**–**4c** (Fig. 5). The complexes were purified by extraction with dichloromethane–diethylether and were isolated as dark-red solids; **4c** was found to decompose within approximately 1–2 days to a black oil.

The complexes were characterized by ^{1}H and ^{13}C NMR, ESI-MS and elemental analysis. The coordination of the metal center to the ligand resulted in the ^{1}H NMR spectra in an upfield shift of approximately 0.2 ppm for the N–CH proton (at about 7.4 ppm; C^2–H in the allomaltol derivative and C^6–H in the maltol complexes), whereas the CH signal at about 6.5 ppm, assigned to the CO–CH proton, shifted slightly downfield. In general, high purity compounds and good yields were obtained, which was



b **c**

n = 14 $R_1 = CH_3$ $R_2 = H$ **(1)**
n = 6 $R_1 = CH_2CH_3$ $R_2 = H$ **(2)**
n = 8 $R_1 = H$ $R_2 = CH_3$ **(3)**

or spacer: 4,7,10-trioxa-1,13-tridecanediamine
and $R_1 = CH_3$ $R_2 = H$ **(4)**

Figure 5. Synthesis of the dinuclear ruthenium(II)–arene complexes.

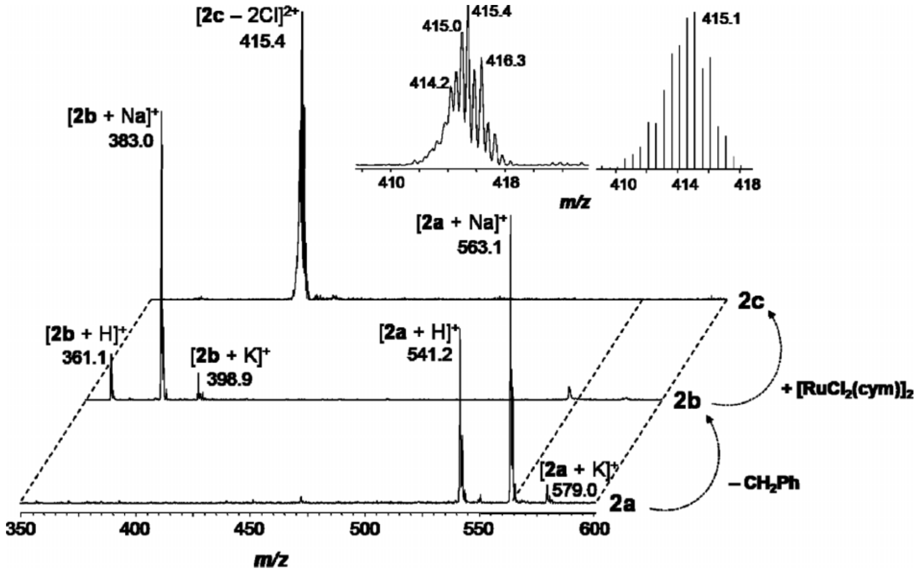


Figure 6. Mass spectrometric characterization of compounds **2a**–**c**; the inset shows the measured (left) and calculated (right) isotope pattern of the doubly charged complex ion.

also expressed by the clean NMR spectra of the complexes, which contained exclusively one set of aromatic protons assigned to the cymene ligand.

In ^{13}C NMR spectra of the maltol-type compounds **1, 2** and **4** similar upfield shifts were observed when going from **a** to **b** and **c** from approximately 140 via 137 to 134 ppm and from 117 via 111 to 109 ppm for the N–CH and CH–CO carbon atoms, respectively. In contrast, for **3** significantly different chemical shifts were observed: unprotecting **3a** to **3b** resulted in a minor downfield shift from 128 to 130 ppm whereas the coordination gave an upfield shifted resonance at 125 ppm for the N–CH carbons. However, for the CH–CO carbon, similar behavior as for the maltol-derived compounds was seen. Elemental analyses of both ligands and complexes were found to contain rests of solvents, i.e. water, acetic acid or dichloromethane, which could not be removed under vacuum (less than 1×10^{-2} mbar) for a few days. However, drying at elevated temperature is not an option due to decomposition of the compounds.

The soft ionization technique electrospray ionization mass spectrometry was found particularly useful for characterizing labile metal complexes, and studying interactions of metal complexes with biomolecules.[35–38] In the mass spectra of the neutral molecules **1a**–**4a** and **1b**–**4b** the $[M + Na]^+$ pseudomolecular ions were the most abundant signals in the mass spectra followed by $[M+H]^+$ and $[M+K]^+$ (Fig. 6 for **2**). For the complexes **1c**–**4c** the doubly charged $[M - 2Cl]^{2+}$ peak was the only significant signal in the mass spectrum. All the complexes were analyzed in methanol and the observed isotope pattern was in good correlation to the theoretical one (Fig. 6; inset).

Complex **1c** shows generally poor solubility in water (<0.1 mg ml^{-1}) and in organic solvents compatible for administration into biological systems, and for this reason **1c** was excluded from further studies. The less lipophilic analogue of **1c**, i.e. **4c**, was found to decompose rapidly after synthesis, although both the ligands **4a** and **4b** were stable. However, attempts at characterization of decomposition products were unsuccessful. Hence, further investigations were abandoned. In contrast, compounds **2c** and **3c** were found to be stable upon exposure to air. In accordance with the structural similarity to the maltol analog,[21] similar lipophilicity was expected, though the position and size of the alkyl group on the pyridinone moiety possibly had an influence on the potential *in vitro* anticancer activity, which is currently under investigation.

Conclusions

Herein, it was shown that the mode of synthesis applied for obtaining dinuclear complexes with high anticancer activity is also suitable for preparing compounds with even longer spacers between the metal centers, and also for replacing maltol with similar derivatives, i.e. allomaltol and ethylmaltol. However, low stability of **4c** and high lipophilicity of **1c** did not support further investigation of these compounds' biological activities. For compounds **2c** and **3c** *in vitro* anticancer activity is under investigation.

Acknowledgment

We thank the University of Vienna, the Hochschuljubiläumsstiftung Vienna, the Theodor-Körner-Fonds, the Austrian Council for Research and Technology Development, the FFG, Austrian Research Promotion Agency (Project FA 526003), the FWF, Austrian Science Fund (Schrödinger Fellowship J2613-N19 [C.G.H.] and project P18123-N11), and COST D20 and D39, for financial support. We gratefully acknowledge Dr Markus Galanski for recording the NMR spectra.

References

[1] C. G. Hartinger, S. Zorbas-Seifried, M. A. Jakupec, B. Kynast, H. Zorbas, B. K. Keppler, *J. Inorg. Biochem.* **2006**, *100*, 891.
[2] P. J. Dyson, G. Sava, *Dalton Trans.* **2006**, 1929.
[3] J. M. Rademaker-Lakhai, D. van den Bongard, D. Pluim, J. H. Beijnen, J. H. Schellens, *Clin. Cancer Res.* **2004**, *10*, 3717.
[4] I. Bratsos, S. Jedner, T. Gianferrara, E. Alessio, *Chimia* **2007**, *61*, 692.
[5] M. Pongratz, P. Schluga, M. A. Jakupec, V. B. Arion, C. G. Hartinger, G. Allmaier, B. K. Keppler, *J. Anal. At. Spectrom.* **2004**, *19*, 46.
[6] A. R. Timerbaev, S. S. Aleksenko, K. Polec-Pawlak, R. Ruzik, O. Semenova, C. G. Hartinger, S. Oszwaldowski, M. Galanski, M. Jarosz, B. K. Keppler, *Electrophoresis* **2004**, *25*, 1988.
[7] F. Piccioli, S. Sabatini, L. Messori, P. Orioli, C. G. Hartinger, B. K. Keppler, *J. Inorg. Biochem.* **2004**, *98*, 1135.
[8] M. Sulyok, S. Hann, C. G. Hartinger, B. K. Keppler, G. Stingeder, G. Koellensperger, *J. Anal. Atom. Spectrom.* **2005**, *20*, 856.
[9] A. R. Timerbaev, C. G. Hartinger, S. S. Aleksenko, B. K. Keppler, *Chem. Rev.* **2006**, *106*, 2224.
[10] P. Schluga, C. G. Hartinger, A. Egger, E. Reisner, M. Galanski, M. A. Jakupec, B. K. Keppler, *Dalton Trans.* **2006**, 1796.
[11] C. S. Allardyce, P. J. Dyson, D. J. Ellis, S. L. Heath, *Chem. Commun. (Cambridge)* **2001**, 1396.
[12] W. H. Ang, E. Daldini, C. Scolaro, R. Scopelliti, L. Juillerat-Jeannerat, P. J. Dyson, *Inorg. Chem.* **2006**, *45*, 9006.
[13] C. Scolaro, T. J. Geldbach, S. Rochat, A. Dorcier, C. Gossens, A. Bergamo, M. Cocchietto, I. Tavernelli, G. Sava, U. Rothlisberger, P. J. Dyson, *Organometallics* **2006**, *25*, 756.
[14] W. H. Ang, P. J. Dyson, *Eur. J. Inorg. Chem.* **2006**, 4003.
[15] C. Scolaro, A. Bergamo, L. Brescacin, R. Delfino, M. Cocchietto, G. Laurenczy, T. J. Geldbach, G. Sava, P. J. Dyson, *J. Med. Chem.* **2005**, *48*, 4161.
[16] A. F. A. Peacock, A. Habtemariam, R. Fernandez, V. Walland, F. P. A. Fabbiani, S. Parsons, R. E. Aird, D. I. Jodrell, P. J. Sadler, *J. Am. Chem. Soc.* **2006**, *128*, 1739.
[17] Y. K. Yan, M. Melchart, A. Habtemariam, P. J. Sadler, *Chem. Commun. (Cambridge)* **2005**, 4764.
[18] C. A. Vock, W. H. Ang, C. Scolaro, A. D. Phillips, L. Lagopoulos, L. Juillerat-Jeanneret, G. Sava, R. Scopelliti, P. J. Dyson, *J. Med. Chem.* **2007**, *50*, 2166.
[19] C. S. Allardyce, P. J. Dyson, D. J. Ellis, P. A. Salter, R. Scopelliti, *J. Organomet. Chem.* **2003**, *668*, 35.
[20] B. Therrien, W. H. Ang, F. Cherioux, L. Vieille-Petit, L. Juillerat-Jeanneret, G. Suess-Fink, P. J. Dyson, *J. Cluster Sci.* **2007**, *18*, 741.
[21] M. G. Mendoza-Ferri, C. G. Hartinger, M. A. Mendoza, A. Egger, M. Groessl, R. E. Eichinger, N. Stolyarova, F. Klein, M. A. Jakupec, A. A. Nazarov, K. Severin, B. K. Keppler, submitted.
[22] K. H. Thompson, C. A. Barta, C. Orvig, *Chem. Soc. Rev.* **2006**, *35*, 545.
[23] K. H. Thompson, C. Orvig, *Dalton Trans.* **2006**, 761.
[24] M. A. Santos, R. Grazina, A. Q. Neto, G. Cantinho, L. Gano, L. Patricio, *J. Inorg. Biochem.* **2000**, *78*, 303.
[25] L. R. Bernstein, T. Tanner, C. Godfrey, B. Noll, *Metal-Based Drugs* **2000**, *7*, 33.
[26] A. F. A. Peacock, M. Melchart, R. J. Deeth, A. Habtemariam, S. Parsons, P. J. Sadler, *Chem. Eur. J.* **2007**, *13*, 2601.
[27] R. Lang, A. Schorwerth, K. Polborn, W. Ponikwar, W. Beck, T. Severin, K. Severin, *Z. Anorg. Allg. Chem.* **1999**, *625*, 1384.
[28] R. Lang, K. Polborn, T. Severin, K. Severin, *Inorg. Chim. Acta* **1999**, *294*, 62.
[29] M. A. Jakupec, B. K. Keppler, *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)* **2004**, *4*, 1575.
[30] N. Farrell, *Comprehensive Coordination Chemistry II*, Vol. 9, Elsevier, Oxford **2004**, 809.
[31] R. L. N. Harris, *Aust. J. Chem.* **1976**, *29*, 1329.
[32] G. Öztürk, D. D. Erol, M. D. Aytemir, T. Uzbay, *Eur. J. Med. Chem.* **2002**, *37*, 829.
[33] M. A. Bennett, T. N. Huang, T. W. Matheson, A. K. Smith, *Inorg. Synth.* **1982**, *21*, 74.
[34] P. T. Tanev, Y. Liang, T. J. Pinnavaia, *J. Am. Chem. Soc.* **1997**, *119*, 8616.
[35] C. G. Hartinger, A. A. Nazarov, V. Chevchenko, V. B. Arion, M. Galanski, B. K. Keppler, *Dalton Trans.* **2003**, 3098.
[36] U. Warnke, C. Rappel, H. Meier, C. Kloft, M. Galanski, C. G. Hartinger, B. K. Keppler, U. Jaehde, *ChemBioChem* **2004**, *5*, 1543.
[37] C. G. Hartinger, A. A. Nazarov, V. B. Arion, G. Giester, M. L. Kuznetsov, M. Galanski, B. K. Keppler, *Eur. J. Inorg. Chem.* **2005**, 1589.
[38] C. G. Hartinger, M. G. Ferri-Mendoza, A. A. Nazarov, B. K. Keppler, *Polyhedron* **2006**, *25*, 1971.