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Ru–Arene Complexes

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Arene–Ruthenium(II) Complexes with Bioactive *ortho*-Hydroxydibenzoylmethane Ligands: Synthesis, Structure, and Cytotoxicity

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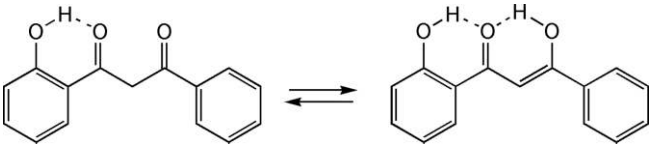
Abstract: The synthesis of a series of neutral arene–ruthenium(II) complexes (arene = *p*-cymene, hexamethylbenzene, and benzene) [(arene)Ru(HDB)Cl] derived from the reaction of the appropriate arene–ruthenium(II) dimers and *ortho*-hydroxydibenzoylmethane (HDBH), a potent inhibitor of cell proliferation, is described. In addition, related ionic complexes [(arene)Ru(HDB)(PTA)](SO_3CF_3) (PTA = 1,3,5-triaza-7-phosphaadamantane) have been prepared. The structure of three complexes has been confirmed by X-ray crystallography. The cytotoxicity of the complexes has been evaluated against human ovarian carcinoma cells (A2780 and A2780cisR), as well as against nontumorigenic human embryonic kidney (HEK293) cells, and compared to the free ligand and cisplatin. Two of the complexes, that is from the first series with *p*-cymene and hexamethylbenzene, display relevant activities against the cisplatin-resistant A2780cisR cancer cell line.

Introduction

Arene–ruthenium(II) complexes have been extensively studied as putative anticancer metallodrugs,[1] with both monofunctional[2] and bifunctional[3] complexes showing promising properties. Half-sandwich ruthenium complexes with O,O′-donor ligands are attracting increasing attention,[4] and among these bidentate ligands β-diketones represent an interesting class of ligands in the synthesis of bioactive complexes.[5]

Recently, arene–ruthenium(II) complexes with biologically active molecules such as 3-hydroxyflavones,[6] lapachol,[7] paullones,[7] ionidamine,[8] and ethacrynic acid[9] have been reported. In some of these compounds the arene–ruthenium fragment and the bioactive organic molecule work together in a synergistic fashion. Dibenzoylmethane is a natural product that is a constituent of the root extract of licorice (*Glycyrrhiza glabra* in the family Leguminosae), recently identified as a promising antimutagenic and anticarcinogenic molecule.[10] Dibenzoylmethane arene–ruthenium(II) complexes possess good activity toward A2780 human ovarian cells[11] and also against A549 lung carcinoma.[12] We recently found a cytotoxic and pro-apoptotic effect of some dibenzoylmethane arene–ruthenium(II) complexes against U266 and RPMI human multiple myeloma cell lines.[13]

In a continuation to these studies, we now report new arene–ruthenium(II) complexes with *ortho*-hydroxydibenzoylmethane (HDBH), which is a β-diketone structurally related to dibenzoylmethane, containing a hydroxyl group bound to one of the aromatic rings (Scheme 1). HDBH is a more potent inhibitor of cell proliferation than dibenzoylmethane and induces apoptosis in carcinoma and adenocarcinoma cell lines.[10g,10h,14] Moreover, previous findings for analogous derivatives such as curcumin indicate that the presence of both the phenolic and the β-diketone moieties is necessary for free-radical-scavenging activity of these type of molecules.[15] We report the synthesis of a series of arene–Ru^{II} complexes [arene = *p*-cymene (cym), hexamethylbenzene (hmb), and benzene (benz)] with HDB, their ionic derivatives with the PTA ligand, and the study of their antiproliferative activity against human ovarian carcinoma cells and nontumorigenic human embryonic kidney cells.



Scheme 1. Tautomeric forms of *ortho*-hydroxydibenzoylmethane (HDBH).

Results and Discussion

HDBH can exist in the tautomeric forms depicted in Scheme 1, which are dependent on the solvent polarity.[16] Complexes **1**–**3** were prepared in high yield by the reaction of $[(arene)RuCl_2]_2$ with deprotonated HDBH in methanol (Scheme 2). Compounds **1**–**3** are air-stable and soluble in most organic solvents. Conduc-

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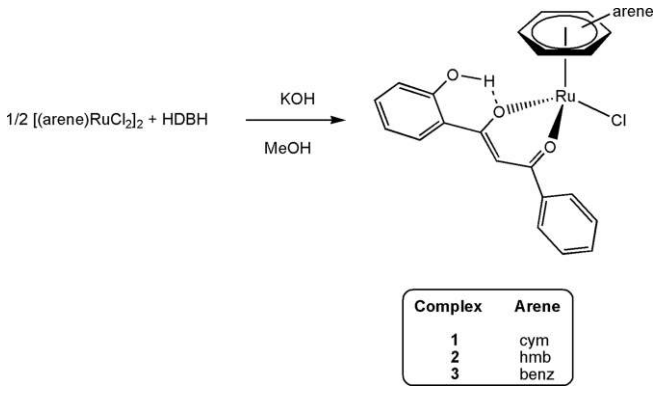
tivity measurements on **1**–**3** indicate a slight dissociation of the chloride ligand in acetonitrile at room temperature.



Scheme 2. Synthesis of **1**–**3**.

The IR spectra of **1**–**3** show the typical shift of the ν(C=O) vibrations to lower frequency upon coordination of the β-diketone ligand to the metal ion in the O,O′-bidentate chelating fashion.[17] Moreover, medium to strong absorption bands in the IR spectra may be assigned to ν(Ru–O) and ν(Ru–Cl) bonds at 438–448 and 269–284 nm, respectively.[18]

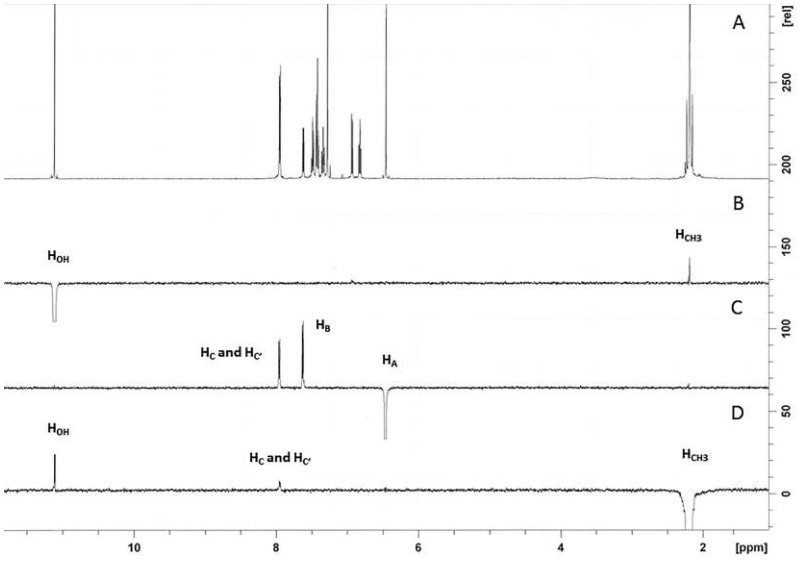
Additional insights about the molecular structure in solution of the ruthenium complexes was obtained by one-dimensional ^{1}H-NOESY NMR experiments carried out on **2**, chosen as a representative complex. After selective irradiation of the H_{OH}, H_A, and H_{CH3} resonances, the presence of strong H_{OH}/H_{CH3} and H_A/H_B dipolar contacts and the absence of H_{OH}/H_D, H_A/H_{OH} and H_{CH3}/H_B dipolar interactions have been observed (Figure 1B–D). All points toward an almost frozen conformation of the phenolic ring in which the OH moiety is steadily oriented toward the vicinal oxygen. This is likely due to the presence of a strong intramolecular H bond between the OH and the vicinal oxygen, as observed in the solid state (see X-ray discussion below).

The chloride ligand in **1**–**3** can be easily removed by reaction with $AgSO_3CF_3$ and replaced by water-soluble phosphine 1,3,5-triaza-7-phosphaadamantane (PTA) in methanol, affording the salts [(arene)Ru(HDB)(PTA)](SO_3CF_3) **4**–**6**, as depicted in Scheme 3.

The IR spectra of these ionic derivatives contain a characteristic absorption pattern, typical of a noncoordinated $^-O_3SCF_3$ anion, centered at 1028 cm^{-1}.[19] Moreover, the substitution of the chloride ligand by PTA and the formation of an ionic compound were confirmed by the disappearance of the ν(Ru–Cl) band. In acetonitrile, complexes **4**–**6** display conductivity values within the range typical of 1:1 electrolytes.[20]

The ^{1}H NMR spectra of **4**–**6** in CD_3CN contain all the expected signals that can be assigned to the coordinated arene ring, HDB, and PTA ligands with two types of methylene protons corresponding to the coordinated PTA ligand. The ^{31}P NMR spectra of **4**–**6** display a singlet in the range from –25 to –35 ppm, typical of related compounds and in accordance with the existence of one species in solution.[21] In the positive ESI mass spectra of **4**–**6** two main peaks were observed, corresponding to the intact cation [(arene)Ru(HDB)(PTA)]$^+$ and the [(arene)Ru(HDB)]$^+$ fragment due to PTA dissociation.

The molecular structures of **1**, **3**, and **4** were confirmed by single-crystal X-ray diffraction analysis (see Exp. Sect. for details of the data collections and Table S1 for structure refinement parameters). The structures of **1** and **3** are shown in Figure 2, and that of **4** is presented in Figure 3. In all complexes, the HDB ligand adopts an O,O′-bidentate coordination mode, in which electronic delocalization is observed within the six-membered metallacyclic ring, that is the two Ru–O, two C–O, and two C–C distances are almost equivalent in each complex.



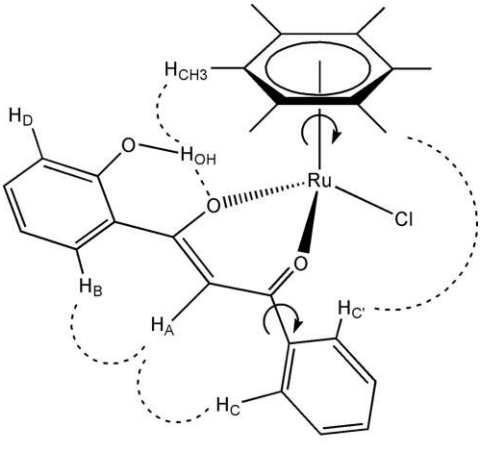
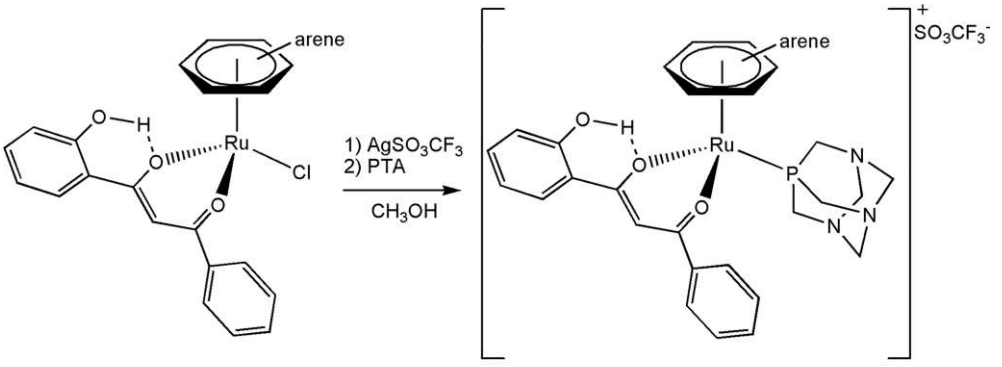


Figure 1. ^{1}H NMR spectrum of **2** in $CDCl_3$ (A). One-dimensional ^{1}H-NOESY spectra of **2** after irradiation of H_{OH} (δ = 11.12 ppm, B), H_A (δ = 6.44 ppm, C) and H_{CH3} (δ = 2.17 ppm, D). The ESI mass spectra of **1**–**3** in positive ion mode display parent peaks corresponding to the cationic fragment [(arene)Ru (HDB)]$^+$ generated by the loss of the chloride ligand. The ^{1}H NMR and ^{13}C NMR spectra recorded in $CDCl_3$ of **1**–**3** display the expected resonances corresponding to the coordinated HDB ligand.



Complex	Arene
1	cym
2	hmb
3	benz

Complex	Arene
4	cym
5	hmb
6	benz

Scheme 3. Synthesis of **4**–**6**.

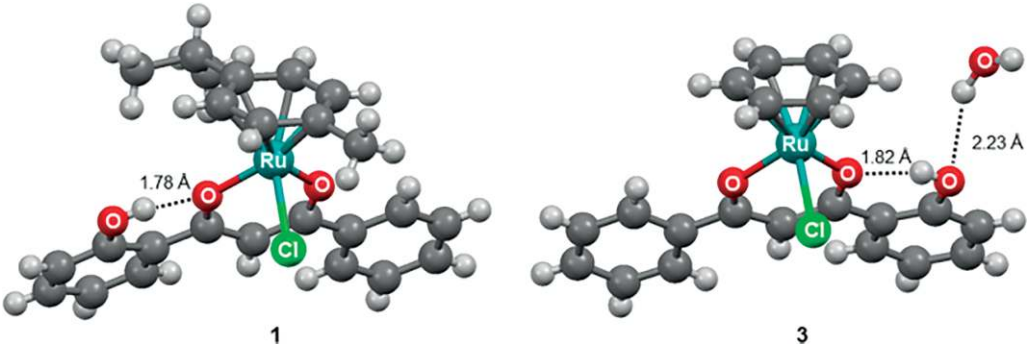


Figure 2. Molecular structures of **1** and **3**·H_2O.

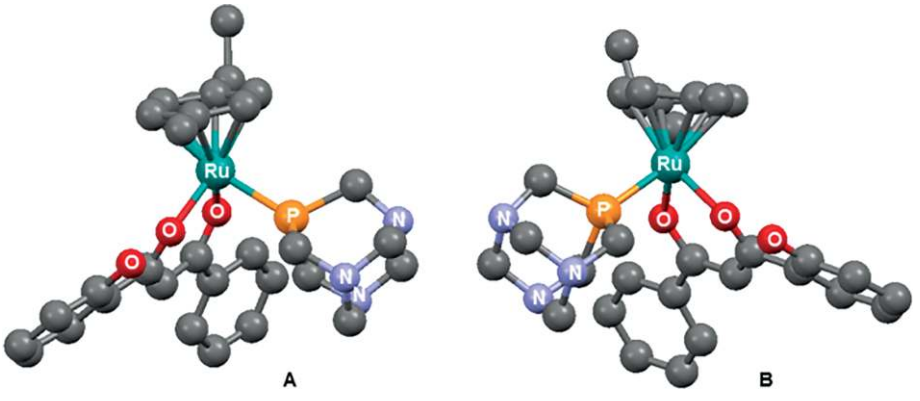


Figure 3. Molecular structure of complex **4** showing the two independent cations (**A** and **B**) observed in the crystal. Triflate anions and hydrogen atoms are omitted for clarity.

Moreover, all complexes show an intramolecular hydrogen bond involving the hydroxyl group and its neighboring oxygen atom. In **1**, the O···O separation is 2.496(3) Å (O–H···O angle of 145.8°), whereas the O···O separation is slightly longer in **3** [2.539(4) Å and 145.2°] and **4** [**A** 2.58(1) Å, 141.8° and **B** 2.53(1) Å, 143.2°]. The presence of water molecules in the crystal packing of **3** generates additional hydrogen bonds as shown in Figure 2.

In **4**, two crystallographically nonequivalent complexes are observed in the crystal. As emphasized in Figure 3, these two complexes are enantiomers, and their geometrical parameters are almost identical. Despite the replacement of the chloride (complex **1**) with PTA (complex **4**), the (*p*-cym)Ru(HDB) unit is geometrically unchanged, and even the Cl–Ru–O and P–Ru–O angles remain equivalent (see Table S2). The stability of **4** was investigated in water (D_2O containing 10 % of [D_6]DMSO) at

37 °C and monitored for 96 h by ^{1}H and ^{31}P NMR spectroscopy. Compound **4** was stable during the entire period, that is the ^{1}H and ^{31}P NMR spectra of **4** remained unchanged over the 96 h (Figure 4).

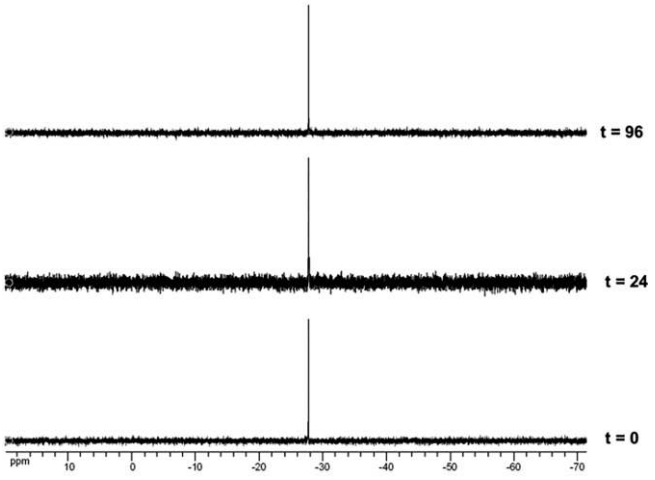


Figure 4. ^{31}P NMR spectra of **4** in aqueous solution.

The stability of **4** was also determined under pseudopharmacological conditions in aqueous solutions containing two different concentrations of NaCl: 5 mM, which corresponds to the low intracellular NaCl concentration in cells, and 100 mM, which approximates the higher chloride levels in blood. Solutions of **4** (c = 2.0 mM) in aqueous NaCl (c = 5 mM or 100 mM in D_2O containing 10 % of [D_6]DMSO) were prepared, maintained at 37 °C for 7 d, and monitored by ^{1}H and ^{31}P NMR spectroscopy. Again, the complex did not undergo hydrolysis during the incubation time, that is the ^{31}P NMR spectra of **4** remained unchanged after 7 d (Figure 5).

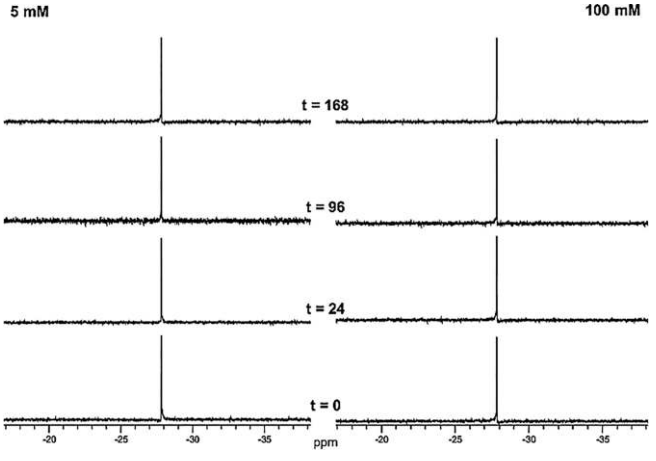


Figure 5. ^{31}P NMR spectra of **4** in 5 mM (left) and in 100 mM (right) aqueous NaCl solution.

The HDBH ligand and **1**–**6** were tested for their cytotoxicity to human ovarian A2780 carcinoma cells and the A2780cisR variant with acquired resistance to cisplatin as well as against nontumorigenic human embryonic kidney (HEK293) cells. IC_{50} values of the compounds were determined after exposure of the cells to the compounds for 72 h with use of the MTT assay and are listed in Table 1.

Table 1. Cytotoxicity [IC_{50} (μM)] of HDBH, **1**–**6**, and cisplatin. Following exposure for 72 h to the nontumorigenic Human Embryonic Kidney HEK293 cells and Human Ovarian A2780 and A2780cisR (cisplatin-resistant) cancer cell lines.

Compound	HEK293	A2780	A2780cisR
HDBH	11.6 ± 1.4	57.5 ± 4.1	74.0 ± 1.0
1	9.1 ± 1.5	13.9 ± 5.0	7.0 ± 2.1
2	9.5 ± 0.2	13.4 ± 0.5	8.0 ± 1.1
3	25.0 ± 6.9	61.0 ± 8.0	47.0 ± 6.0
4	30.0 ± 4.0	46.0 ± 5.0	22.9 ± 2.1
5	22.3 ± 2.7	48.0 ± 3.0	56.0 ± 6.0
6	131.0 ± 41.0	182.0 ± 42.0	90.0 ± 9.0
cisplatin	7.3 ± 0.6	1.0 ± 0.2	25.0 ± 0.2

The HDBH ligand is cytotoxic to the nontumorigenic HEK293 cell line (11.6 ± 1.4 μM) and several times less active on the two cancer cell lines (> 50 μM). In comparison, the six HDB-containing complexes show similar activities on cancer and non-cancer cells, none of them being cancer cell selective. Among the complexes evaluated, [(arene)Ru(HDB)Cl] derivatives **1** (with cym) and **2** (with hmb) are the most promising when compared to cisplatin. These two complexes have essentially an equivalent cytotoxicity to the model healthy HEK293 cell line (9.1 ± 1.5 and 9.5 ± 0.2 μM for **1** and **2**, respectively, vs. 7.3 ± 0.6 μM for cisplatin). However, in the cisplatin-resistant A2780cisR cancer cell line they are about 3-fold more cytotoxic (7.0 ± 2.1 and 8.0 ± 1.1 μM for **1** and **2**, respectively, vs. 25.0 ± 0.2 μM for cisplatin) compared to cisplatin. However, the difference in cytotoxicity between HDBH and **3**–**6** is much less striking and, in the case of **6**, the cytotoxicity is less than that of the free ligand in all three cell lines. The cytotoxicities of the complexes are correlated to the hydrophobicity of the arene ligands cym, hmb, and benz, that is the more hydrophobic complexes with the cym and hmb ligands are more cytotoxic than the complexes with the benz ligand. On the basis of calculated values for the arene ligands, the log P values of cym, hmb, and benz are 3.19, 3.72, and 1.66, respectively. The most cytotoxic compounds in each series correspond to those with the cym and hmb ligands, that is **1** and **2**, **4** and **5**. The difference in hydrophobicity of the cym and hmb arene ligands is comparatively small and thus leads to very similar IC_{50} values. Exchanging the chloride by the PTA ligand decreases the cytotoxicity by factor 3, highlighting the importance of the "fine-tuned" hydrophobic nature of these complexes. Nevertheless, such structure-activity relationships must be taken with caution as in other arene–ruthenium(II) systems, ligands such as benz and PTA can lead to improved activity.[22]

Conclusions

We describe the synthesis and structural characterization of six arene–ruthenium(II) complexes incorporating the bioactive ligand derived from *ortho*-hydroxydibenzoylmethane (HDBH). The complexes showed no selectivity towards ovarian cancer cells compared to non-cancer cells. A trend in structure-activity

was observed on the basis of the lipophilicity of the complexes, whereby the more hydrophobic compounds bearing the cym and hmb arene ligands were more cytotoxic, but the presence of the amphiphilic PTA ligand did not enhance cytotoxicity or cancer-cell selectivity.

However, compared to the free ligand, which has proven anticancer effects,[10g,10h,14] complexes [(arene)Ru(HDB)Cl] **1** (with cym) and **2** (with hmb) are considerably superior, notably against the cisplatin-resistant A2780cisR cell line, while displaying similar cytotoxicity to cisplatin against the nontumorigenic cell line.

Experimental Section

Materials and Methods: The dimers $[(arene)RuCl_2]_2$ (arene = *p*-cymene, hexamethylbenzene, and benzene) and *ortho*-hydroxydibenzoylmethane were purchased from Aldrich. All other materials were obtained from commercial sources and were used as received. IR spectra were recorded from 4000 to 30 cm^{-1} with a Perkin–Elmer Frontier Spectrometer FTIR/FIR Instrument. ^1H and ^{13}C NMR spectra were recorded with a 400 Mercury Plus Varian instrument operating at room temperature (400 MHz for ^1H, 100 MHz for ^{13}C) relative to TMS. ^1H-NOESY-1D spectra were recorded with a 500 Bruker Ascend™ instrument operating at room temperature (500 MHz for ^1H) relative to TMS. ^{31}P NMR spectra were recorded with a 400 Mercury Plus Varian instrument operating at room temperature, 162 MHz relative to 85 % H_3PO_4. Positive ion electrospray ionization mass spectra (ESI-MS) were obtained with a Series 1100 MSI detector HP spectrometer with use of methanol as the mobile phase. Solutions for analysis (3 mg mL^{-1}) were prepared by using reagent-grade methanol. Masses and intensities were compared to those calculated with use of IsoPro Isotopic Abundance Simulator, version 2.1.28. Melting points are uncorrected and were measured with a STMP3 Stuart scientific instrument and with a capillary apparatus. Samples for microanalysis were dried in vacuo to constant weight (20 °C, ca. 0.1 Torr) and analyzed with a Fisons Instruments 1108 CHNS-O elemental analyzer. Electrical conductivity measurements (Λ_M, reported as S cm^2 mol^{-1}) of acetonitrile solutions of the complexes were recorded with a Eutech Instruments CON2700 at room temperature.

X-ray Crystallography: Crystals of **1**, **3**·H_2O, and **4** were mounted with a Stoe Mark II-Image Plate Diffraction System, and analyzed by using Mo-K_α graphite monochromated radiation, image plate distance 135 mm, 2θ range from 2.4–51.3°, $D_{max} - D_{min}$ = 16.029–0.836 Å. The structures were solved by direct methods with use of the program SHELXS-97.[23] Refinement and all further calculations were carried out by using SHELXL-97. The H atoms were included in calculated positions, except for the OH groups, and treated as riding atoms by using the SHELXL default parameters. The non-H atoms were refined anisotropically by using weighted full-matrix least-square on F^2. In complex **1** the hydroxyl group was disordered over two positions (65:35 occupation factors). In complex **4**, the triflate anions were highly disordered, thus giving rise to a relatively low resolution. These triflate anions were idealized, with use of the highest electronic density as the S atoms and as pivots. Nevertheless, the data collection was resolved, and the structure is presented here, thus confirming the expected structure of **4**. Crystallographic details of complexes **1**, **3**·H_2O, and **4** are summarized in Table S1. Figures 1 2 were drawn with Mercury.[24]

CCDC 1499523 (for **1**), 1499524 (for **2**), and 1499525 (for **3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Cell Culture and Inhibition of Cell Growth: Human A2780 and A2780cisR ovarian carcinoma and HEK (human embryonic kidney) cells were obtained from the European Collection of Cell Cultures (Salisbury, U.K.). A2780 and A2780R cells were grown routinely in RPMI-1640 medium, while HEK cells were grown with DMEM medium, with 10 % fetal calf serum (FCS) and antibiotics at 37 °C and 5 % CO_2. Cytotoxicity was determined by using the MTT assay [MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium tetrazolium bromide]. Cells were seeded in 96-well plates as monolayers with cell solution (100 µL, approximately 20 000 cells) per well and preincubated for 24 h in medium supplemented with 10 % FCS. Compounds were prepared as DMSO solutions and then dissolved in the culture medium and serially diluted to the appropriate concentration, to give a final DMSO concentration of 0.5 %. A portion of the drug solution (100 µL) was added to each well, and the plates were incubated for another 72 h. Subsequently, MTT solution (5 mg mL^{-1}) was added to the cells, and the plates were incubated for a further 2 h. The culture medium was aspirated, and the purple formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in DMSO. The optical density, directly proportional to the number of surviving cells, was quantified at 590 nm by using a multiwell plate reader, and the fraction of surviving cells was calculated from the absorbance of untreated control cells. Evaluation is based on means from two independent experiments, each comprising three microcultures per concentration level.

Synthesis and Characterization

[(cym)Ru(HDB)Cl] (**1**). *ortho*-Hydroxydibenzoylmethane (HDBH, 120 mg, 0.5 mmol) was dissolved in methanol (20 mL). KOH (30 mg, 0.53 mmol) was added, and the resulting mixture was stirred for 1 h at room temperature. Next, $[(cym)RuCl_2]_2$ (123 mg, 0.2 mmol) was added, and the mixture was stirred for 24 h at room temperature. A red-orange precipitate formed that was removed by filtration and washed with *n*-hexane. The material was dissolved in methanol (ca. 2 mL) and stored at 4 °C. Red crystals formed over several days. Compound **1** is soluble in alcohols, acetone, acetonitrile, chlorinated solvents, DMF, and DMSO and slightly soluble in diethyl ether and water. Yield: 78 % (158 mg, 0.31 mmol). M.p.: 197–198 °C. $C_{25}H_{25}ClO_3Ru$ (509.99): calcd. C 58.88, H 4.94; found C 59.23, H 4.87. IR: $\tilde{\nu}$ = 3061–2970 [w ν(C–H)], 1617 (w), 1589 [m ν(C=C)], 1539 (s), 1513 [vs ν(C=O)], 1457 (s), 1437 (s), 1297 (m), 1242 (m), 1205 (m), 1023 (m), 781 (vs), 686 (s), 654 (s), 573 (m), 549 (m), 455 (w), 438 [m ν(Ru–O)], 284 [vs ν(Ru–Cl)] cm^{-1}. ^1H NMR ($CDCl_3$, 293 K): δ = 1.40 [d, ^3J = 6.8 Hz, 6 H, $CH_3C_6H_4CH(CH_3)_2$], 2.33 [s, 3 H, $CH_3C_6H_4CH(CH_3)_2$], 3.01 [sept, ^3J = 6.8 Hz, 1 H, $CH_3C_6H_4CH(CH_3)_2$], 5.33–5.39 [m, 2 H, $CH_3C_6H_4CH(CH_3)_2$], 5.60–5.64 [m, 2 H, $CH_3C_6H_4CH(CH_3)_2$], 6.47 (s, 1 H, *CH* of HDB), 6.82 (t, ^3J = 7.6 Hz, 1 H, Ph of HDB), 6.92 (d, ^3J = 8.4 Hz, 1 H, Ph of HDB), 7.32–7.48 (m, 4 H, Ph of HDB), 7.60 (d, ^3J = 8.8 Hz, 1 H, Ph of HDB), 7.90 (d, ^3J = 7.2 Hz, 2 H, Ph of HDB), 10.92 (s, 1 H, O*H* of HDB) ppm. ^{13}C NMR ($CDCl_3$, 293 K): δ = 18.3 [$CH_3C_6H_4CH(CH_3)_2$], 22.5 [$CH_3C_6H_4CH(CH_3)_2$], 31.1 [$CH_3C_6H_4CH(CH_3)_2$], 80.8, 81.5, 82.4, 82.9 [$CH_3C_6H_4CH(CH_3)_2$], 94.1 (CH of HDB), 97.5, 100.9 [$CH_3C_6H_4CH(CH_3)_2$], 118.2, 119.1, 121.7, 127.5, 128.0, 128.8, 131.5, 133.6, 139.2 (Ph of HDB), 160.1 (*C*-OH of HDB) 182.8 and 183.0 (*C*=O of HDB) ppm. MS (ESI+, CH_3OH): *m/z* (%) = 475 (100) $[(cym)Ru(HDB)]^+$. Λ_m ($CDCN_3$, 293 K, 10^{-4} mol L^{-1}): 20 S cm^2 mol^{-1}.

[(hmb)Ru(HDB)Cl] (2): The synthesis was performed as for **1** by using $[(hmb)RuCl_2]_2$. Compound **2** precipitated directly from the reaction solution. Compound **2** is soluble in alcohols, acetone, aceto-

nitrile, chlorinated solvents, DMF, and DMSO and slightly soluble in diethyl ether and water. Yield: 84 %. M.p.: 244–246 °C. $C_{27}H_{29}ClO_3Ru$ (538.05): calcd. C 60.27, H 5.43; found C 60.12, H 5.41. IR: $\tilde{\nu}$ = 3060–2920 [w ν(C–H)], 1618 (m), 1590 [m ν(C=C)], 1542 (vs), 1514 [vs ν(C=O)], 1485 (m), 1460 (m), 1396 (m), 1296 (vs), 1241 (m), 1140 (m), 1022 (m), 846 (m), 768 (vs), 714 (s), 691 (m), 651 (m), 573 (w), 545 (w), 531 (w), 459 (w), 437 [m ν(Ru–O)], 275 [m ν(Ru–Cl)] cm^{-1}. ^1H NMR ($CDCl_3$, 293 K): δ = 2.17 [s, 18 H, CH_3(hmb)], 6.44 (s, 1 H, C*H* of HDB), 6.80 (t, ^3J = 7.6 Hz, 1 H, Ph of HDB), 6.91 (d, ^3J = 8.4 Hz, 1 H, Ph of HDB), 7.26–7.47 (m, 4 H, Ph of HDB), 7.60 (d, ^3J = 8.0 Hz, 1 H, Ph of HDB), 7.93 (d, ^3J = 7.6 Hz, 2 H, Ph of HDB), 11.12 (s, 1 H, OH of HDB) ppm. ^{13}C NMR ($CDCl_3$, 293 K): δ = 15.7 [CH_3(hmb)], 90.6 [C_6(hmb)], 93.7 (*C*H of HDB), 118.2, 119.0, 121.9, 127.3, 127.5, 128.4, 131.3, 133.4, 139.4 (Ph of HDB), 160.3 (*C*-OH of HDB) 182.5 and 182.7 (*C*=O of HDB) ppm. MS (ESI+, CH_3OH): *m/z* (%) = 503 (100) [(hmb)Ru(HDB)]$^+$. Λ_m ($CDCN_3$, 293 K, 10^{-4} mol L^{-1}): 32 S cm^2 mol^{-1}.

[(benz)Ru(HDB)Cl] (3): The synthesis was performed as for **1** by using [(benz)$RuCl_2]_2$. Compound **3** is soluble in acetone, acetonitrile, alcohols, chlorinated solvents, DMF, and DMSO and slightly soluble in diethyl ether and water. The powder was recrystallized from methanol. Yield: 72 %. M.p.: 224–225 °C. $C_{21}H_{17}ClO_3Ru$ (453.89): calcd. C 55.57, H 3.78; found C 55.53, H 3.71. IR: $\tilde{\nu}$ = 3066 [wb ν(C–H)], 1616 (m), 1586 [m ν(C=C)], 1536 (s), 1514 [vs ν(C=O)], 1485 (s), 1459 (m), 1386 (m), 1299 (vs), 1238 (m), 1196 (m), 1136 (m), 837 (m), 757 (vs), 711 (s), 688 (m), 657 (m), 448 [m ν(Ru–O)], 376 (m), 269 [vs ν(Ru–Cl)] cm^{-1}. ^1H NMR ($CDCl_3$, 293 K): δ = 5.77 (s, C_6H_6 benz), 6.47 (s, 1 H, C*H* of HDB), 6.82 (t, ^3J = 7.6 Hz, 1 H, Ph of HDB), 6.94 (d, ^3J = 8.4 Hz, 1 H, Ph of HDB), 7.35–7.48 (m, 4 H, Ph of HDB), 7.58 (d, ^3J = 8.0 Hz, 1 H, Ph of HDB), 7.88 (d, ^3J = 8.0 Hz, 2 H, Ph of HDB), 10.82 (s, 1 H, OH of HDB) ppm. ^{13}C NMR ($CDCl_3$, 293 K): δ = 82.7 (C_6H_6 benz), 94.3 (*C*H of HDB), 118.3, 119.3, 121.5, 127.0, 127.7, 128.4, 131.6, 133.8, 139.0 (Ph of HDB), 160.0 (*C*-OH of HDB) 182.8 and 183.2 (*C*=O of HDB) ppm. MS (ESI+, CH_3OH): *m/z* (%) = 419 (100) [(benz)Ru(HDB)]$^+$. Λ_m ($CDCN_3$, 293 K, 10^{-4} mol L^{-1}): 20 S cm^2 mol^{-1}.

[(cym)Ru(HDB)(PTA)](CF_3SO_3) (4): Compound **1** (95 mg, 0.19 mmol) was dissolved in methanol (15 mL) and $AgSO_3CF_3$ (48 mg, 0.19 mmol) was added. The mixture was stirred for 1 h at room temperature and filtered to remove AgCl. PTA (PTA = 1,3,5-triaza-7-phosphaadamantane; 29 mg, 0.19 mmol) was then added to the filtrate, and the resulting mixture was stirred for 24 h at room temperature. Then the solution was dried by rotary evaporation, and the crude product was obtained by precipitation with use of a mixture of dichloromethane and *n*-hexane. The yellow powder obtained was identified as **4**. It is soluble in alcohols, acetonitrile, acetone, chlorinated solvents, DMF, DMSO, and ethyl acetate and slightly soluble in water and diethyl ether. The powder was recrystallized from methanol. Yield: 70 % (102.4 mg, 0.131 mmol). M.p.: 220–222 °C. $C_{32}H_{37}F_3N_3O_6PRuS$ (780.76): calcd. C 49.23, H 4.78, N 5.38; found C 49.39, H 4.82, N 5.35. IR: $\tilde{\nu}$ = 3069–2936 [w ν(C–H)], 1588 [m ν(C=C)], 1535 (s), 1515 (vs) ν(C=O), 1484 (m), 1461 (m), 1373 (m), 1256 (vs), 1241 (vs), 1156 (s), 1028 [vs ν(SO_3CF_3)], 946 (vs), 637 (vs), 573 (s), 478 [m ν(Ru–O)], 451 (w), 389 (m) cm^{-1}. ^1H NMR (CD_3CN, 293 K): δ = 1.29 [d, ^3J = 7.2 Hz, 6 H, $CH_3C_6H_4CH(CH_3)_2$], 2.08 [s, 3 H, $CH_3C_6H_4CH(CH_3)_2$], 2.69 [sept, ^3J = 7.2 Hz, 1 H, $CH_3C_6H_4CH(CH_3)_2$], 4.21 (s, 6 H, PTA), 4.49 (s, 6 H, PTA), 5.94 [d, ^3J = 6.4 Hz, 2 H, $CH_3C_6H_4CH(CH_3)_2$], 6.04 [d, ^3J = 6.4 Hz, 2 H, $CH_3C_6H_4CH(CH_3)_2$], 6.92 (s, 1 H, C*H* of HDB), 6.96–7.00 (m, 2 H, Ph of HDB), 7.49–7.64 (m, 4 H, Ph of HDB), 7.90 (d, ^3J = 8.0 Hz, 1 H, Ph of HDB), 7.99 (d, ^3J = 7.2 Hz, 2 H, Ph of HDB) ppm. ^{13}C NMR (CD_3CN, 293 K): δ = 17.8 [$CH_3C_6H_4CH(CH_3)_2$], 22.5 [$CH_3C_6H_4CH(CH_3)_2$], 31.5 [$CH_3C_6H_4CH(CH_3)_2$], 52.4 ($J_{C,P}$ = 12.9 Hz, PCH_2N, PTA), 73.3 ($J_{C,P}$ = 7.6 Hz, NCH_2N, PTA), 87.7, 89.7, 90.3, 90.8 [$CH_3C_6H_4CH(CH_3)_2$], 94.1, 95.3 (*C*H of HDB), 97.7, 106.3 [$CH_3C_6H_4CH(CH_3)_2$], 120.4, 120.8, 127.3, 128.0, 128.5, 129.9, 133.5, 135.6, 138.5 (Ph of HDB), 160.3 (*C*-OH of HDB), 185.1 and 185.4 (*C*=O of HDB) ppm. ^{31}P NMR (CD_3CN, 293 K): δ = –28.7 (s, PTA) ppm. MS (ESI+, CH_3OH): *m/z* (%) = 632 (100) [(cym)Ru(HDB)(PTA)]$^+$, 475 (5) [(cym)Ru(HDB)]$^+$. Λ_m ($CDCN_3$, 293 K, 10^{-4} mol L^{-1}): 134 S cm^2 mol^{-1}.

[(hmb)Ru(HDB)(PTA)](CF_3SO_3) (5): The synthesis was performed as for **4** by using precursor **2**. Compound **5** is soluble in alcohols, acetonitrile, acetone, chlorinated solvents, DMF, and DMSO. Yield: 70 %. M.p.: 223–225 °C. $C_{34}H_{41}F_3N_3O_6PRuS$ (808.81): calcd. C 50.49, H 5.11, N 5.20; found C 50.41, H 5.19, N 5.10. IR: $\tilde{\nu}$ = 3059–2941 [w ν(C–H)], 1588 [m ν(C=C)], 1515 [vs ν(C=O)], 1482 (s), 1454 (s), 1374 (s), 1263 (vs), 1241 (vs), 1223 (vs), 1154 (s), 1029 [vs ν(SO_3CF_3)], 1013 (s), 947 (vs), 636 (vs), 572 (s), 516 (m), 475 [m ν(Ru–O)], 454 (w), 433 (w), 392 (w), 278 (w) cm^{-1}. ^1H NMR (CD_3CN, 293 K): δ = 2.13 [s, 18 H, CH_3(hmb)], 4.13 (s, 6 H, PTA), 4.43 (s, 6 H, PTA), 6.93 (s, 1 H, C*H* of HDB), 6.99–7.01 (m, 2 H, Ph of HDB), 7.54–7.66 (m, 4 H, Ph of HDB), 7.90 (d, ^3J = 8.4 Hz, 1 H, Ph of HDB), 8.04 (d, ^3J = 7.6 Hz, 2 H, Ph of HDB), 10.25 (s, 1 H, OH of HDB) ppm. ^{13}C NMR (CD_3CN, 293 K): δ = 16.5 [CH_3(hmb)], 50.4 ($J_{C,P}$ = 12.1 Hz, PCH_2N, PTA), 73.3 ($J_{C,P}$ = 6.9 Hz, NCH_2N, PTA), 96.9 [C_6(hmb)], 99.4 (*C*H of HDB), 119.3, 120.9, 122.3, 128.3, 129.6, 130.0, 133.5, 135.6, 139.1 (Ph of HDB), 160.5 (*C*-OH of HDB), 184.7 and 185.2 (*C*=O of HDB) ppm. ^{31}P NMR (CD_3CN, 293 K): δ = –35.9 (s, PTA) ppm. MS (ESI+, CH_3OH): *m/z* (%) = 660 (100) [(hmb)Ru(HDB)(PTA)]$^+$, 503 (5) [(hmb)Ru(HDB)]$^+$. Λ_m ($CDCN_3$, 293 K, 10^{-4} mol L^{-1}): 109 S cm^2 mol^{-1}.

[(benz)Ru(HDB)(PTA)](CF_3SO_3) (6): The synthesis was performed as for **4** by using precursor **3** and with a reaction time of 6 h. Compound **6** is soluble in alcohols, acetonitrile, acetone, chlorinated solvents, DMF, and DMSO. Yield: 62 %. M.p.: 283–284 °C. $C_{28}H_{29}F_3N_3O_6PRuS$ (724.65): calcd. C 46.41, H 4.03, N 5.80; found C 46.20, H 4.03, N 5.74. IR: $\tilde{\nu}$ = 3081–2937 [bw ν(C–H)], 1616 (w), 1588 [m ν(C=C)], 1513 [vs ν(C=O)], 1484 (s), 1461 (s), 1438 (m), 1376 (m), 1240 (vs), 1157 (s), 1100 (m), 1028 [vs ν(SO_3CF_3)], 971 (vs), 946 (vs), 757 (s), 692 (w), 637 (vs), 573 (s), 516 (m), 480 [m ν(Ru–O)], 451 (w), 390 (w), 360 (mw) cm^{-1}. ^1H NMR (CD_3CN, 293 K): δ = 4.23 (s, 6 H, PTA), 4.47 (s, 6 H, PTA), 5.96 (s, C_6H_6 benz), 6.92 (s, 1 H, C*H* of HDB), 6.97–7.00 (m, 2 H, Ph of HDB), 7.49–7.64 (m, 4 H, Ph of HDB), 7.91 (d, ^3J = 8.0 Hz, 1 H, Ph of HDB), 8.00 (d, ^3J = 7.6 Hz, 2 H, Ph of HDB), 10.17 (s, 1 H, OH of HDB) ppm. ^{13}C NMR (CD_3CN, 293 K): δ = 48.9 (J_{CP} = 16.7 Hz, PCH_2N, PTA), 71.5 ($J_{C,P}$ = 6.8 Hz, NCH_2N, PTA), 93.1 (C_6H_6 benz), 99.4 (*C*H of HDB), 117.0, 118.2, 119.7, 125.8, 126.3, 127.3, 130.1, 132.4, 137.9 (Ph of HDB), 158.8 (*C*-OH of HDB), 181.9 and 182.1 (*C*=O of HDB) ppm. ^{31}P NMR (CD_3CN, 293 K): δ = –25.8 (s, PTA) ppm. MS (ESI+, CH_3OH): *m/z* (%) = 576 (100) [(benz)Ru(HDB)(PTA)]$^+$, 419 (5) [(benz)Ru(HDB)]$^+$. Λ_m ($CDCN_3$, 293 K, 10^{-4} mol L^{-1}): 148 S cm^2 mol^{-1}.

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