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Hydroxyquinoline-derived anticancer organometallics: Introduction of amphiphilic PTA as an ancillary ligand increases their aqueous solubility

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ABSTRACT

Organometallic compounds based on bioactive ligand systems have shown promising antiproliferative properties. The use of 8-hydroxyquinoline and its derivatives as bioactive ligands resulted in organometallic complexes with potent anticancer activity, but they lack aqueous solubility for further development. We report here the preparation of a series of $M^{II/III}$(cym/Cp*)Cl complexes (η^6-*p*-cymene (cym): M = Ru, Os; η^5-pentamethylcyclopentadienyl (Cp*): M = Rh, Ir) with hydroxyquinoline-derived co-ligands and in a subsequent step the substitution of the chlorido ligands for amphiphilic 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (PTA). Solubility studies indicated that the introduced PTA ligand significantly improved the aqueous solubility of all complexes. The complexes were shown to be stable in aqueous and DMSO solution over a period of at least 3 d. As would be expected for such modification of complexes, the higher solubility resulted in significantly decreased cytotoxicity in cancer cells. The antiproliferative activity was still more pronounced than that of RAPTA-C [Ru(cym)(PTA)Cl] which, however, has been demonstrated to have antimetastatic and antiangiogenic properties *in vivo*.

1. Introduction

Since the FDA approval of cisplatin for cancer treatment in 1978, drawbacks of resistance, toxicity and selectivity have prompted the development of metal-based compounds with alternative modes of action [1]. Ruthenium complexes have been widely researched as promising anticancer agents. They exhibit novel modes of action, have lower systemic toxicity, usually do not show cross-resistance to Pt drugs, and have been found to exhibit a wide range of activity [2,3]. In recent years, organometallic Ru^{II}(arene) complexes have elicited considerable attention. A significant feature of these complexes is the robust ability for organic compounds with known medicinal importance to be attached to the motif, by either direct coordination to the metal center or functionalization of a ligand in order to improve its therapeutic value [4–10]. Extended arene groups, such as biphenyl or tetrahydroanthracene, can additionally assist in arene-purine base interaction with DNA through π-stacking [2,11–13].

A novel class of organometallic Ru^{II} complexes are the RAPTA compounds, [(η^6-arene)Ru(PTA)Cl_2], which contain a η^6-arene and an amphiphilic monodentate 1,3,5-triaza-7-phospatricyclo-[3.3.1.1]decane (PTA) ligand [14,15]. Generally, complexes containing PTA ligands have low cytotoxic activity. However, RAPTA compounds favorably bind to protein targets, as opposed to DNA, and exhibit selective antimetastatic activity on tumors *in vivo* [15–18]. Various similar complexes incorporating osmium, rhodium and iridium metal centers have also been investigated and some of them have shown promising biological activity [12,13,19–22].

An effective approach that has been useful in drug development and design is to use privileged structures [23–26]. Privileged structures appear often as building blocks of drugs, natural compounds and active biomolecules, displaying promising drug-like properties, which provides the ability for more high-quality leads to be produced and the formation of valuable compound libraries [25,26]. By coordinating these structures to metal centers, the two moieties are able to act in a synergistic manner to improve biological activity [12]. Among the widely studied class of quinoline compounds, 8-hydroxyquinoline (8-HQ) is considered a privileged structure and is one of the most versatile derivatives [25,27]. 8-HQ and its derivatives have been shown to have a wide range of pharmacological applications, such as anticancer and neuroprotective agents, or as iron-chelators, anti-HIV and antifungal compounds, 2-oxoglutarate (2OG)-dependent enzyme and *Mycobacterium tuberculosis* inhibitors, as well as antileishmanial and

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antischistosomal agents [25]. It is also able to form stable metal complexes through bidentate interactions. A derivative of 8-HQ, 5-chloro-7-iodoquinolin-8-ol (clioquinol), is a copper, zinc, and iron metal chelator, which has frequently been used as an antimicrobial agent and shows potential for the treatment of Alzheimer's and Parkinson's diseases [28]. This compound has the ability to readily cross the blood-brain barrier and has exhibited both *in vitro* and *in vivo* anticancer activity by its ability to act as a transition metal ionophore [27,28]. Moreover, it induces apoptosis in blood cancer cells by inhibiting histone deacetylase, as well as reducing the viability, proliferation and metastasis formation of cholangiocarcinoma cells [29,30]. In the presence of Cu^{II} ions, 8-HQ and clioquinol inhibit proteasome activity and cell proliferation, both *in vitro* and *in vivo* [31]. Similar studies have revealed clioquinol to prevent proteasome activity and induce cell death in leukaemia and myeloma cells [32].

Numerous studies have reported the synthesis and characterization of various organoruthenium compounds featuring 8-HQ derived ligands [26,33–39]. However, the solubility of the compound class is a major issue for further studies such as in the series of 5,7-dihalido-8-hydroxyquinoline Ru^{II}(cym) (cym = η^6-*p*-cymene) complexes reported by us to have significant *in vitro* anticancer activity [26]. The solubility of metal-arene complexes depends on the metal ion, the type of ligands used and the counteranion [34]. In order for drugs to be able to be administered intravenously, they need to be sufficiently soluble in aqueous medium. However, as cellular membranes are lipophilic, the drug also needs appropriate lipophilicity to cross the membrane to enter into the cell. The balance between solubility and cellular permeability is a constant challenge for drug design and development and we have aimed to address this here for Ru(cym)(8-HQ) complexes by introducing a PTA co-ligand known for its favorable aqueous solubility.

2. Experimental

2.1. Materials and methods

All reactions were carried out under a nitrogen (N_2) flow in darkness using dry solvents and standard Schlenk flasks, unless otherwise stated. Chemicals and solvents purchased from commercial suppliers were used without further purification. All synthesized reagents were dried under vacuum in Schlenk flasks prior to use. Dichloromethane (DCM), diethyl ether (Et_2O) and acetonitrile (MeCN) used in the reactions were first dried through a solvent purification system (LC Technology Solutions Inc., SP-1 solvent purifier) and transferred into Schlenk flasks that were dried under vacuum and purged with N_2 prior to use. Methanol (MeOH) and ethanol (EtOH) were dried for 48 h over activated molecular sieves (3 Å) and under N_2 atmosphere prior to use and stored over molecular sieves.

Celite (Sigma-Aldrich), 5-chloro-7-iodo-8-hydroxyquinoline (OFC Inc., ultrapure), dimethylsulfoxide (Sigma-Aldrich, ≥ 99.5%), hydrazine dihydrochloride (Sigma-Aldrich, ≥ 98%), hydrochloric acid (Merck, 38%), 8-hydroxyquinoline (AK Scientific, 99%), ruthenium, rhodium and iridium chloride hydrate (Precious Metals Online, 99%), osmium tetroxide (Sigma-Aldrich, 99.8%), pentamethylcyclopentadiene (Sigma-Aldrich, 95%), silver triflate (Strem Chemicals, 99%), sodium methoxide (Fluka, ≥ 97%), 1,3,5-triaza-7-phosphaadamantane (Sigma-Aldrich, 97%), α-terpinene (Sigma-Aldrich, ≥ 89%) and triethylamine (Romil Pure Chemistry, ≥ 99.5%) were obtained from commercial sources.

NMR spectra were recorded on Bruker DRX 400 MHz NMR spectrometers at ambient temperature at 399.89 MHz (H^1), 100.61 MHz ($^{13}C\{^1H\}$) and 161.87 MHz ($^{31}P\{^1H\}$). Deuterated chloroform ($CDCl_3$), water (D_2O) and dimethyl sulfoxide (DMSO-d_6) were used as NMR solvents. High resolution mass spectrometry (MS) data were recorded on a Bruker microOTOF-Q II mass spectrometer in positive and negative electrospray ionization (ESI) mode. X-ray diffraction measurements of single crystals were carried out on a Rigaku Oxford Diffraction XtaLAB-Synergy-S single-crystal diffractometer with a PILATUS 200 K hybrid pixel array detector using Cu Kα radiation (λ = 1.54184 Å). The structure solution and refinements were performed with the SHELXS-97, SHELXL-2016 [40] and Olex2 program packages [41,42]. Molecular structures were visualized using Mercury 4.0.0. Elemental analyses were carried out on the vario EL cube CHNOS Elemental Analyzer at the University of Auckland, and at the Campbell Microanalytical Laboratory, the University of Otago.

Bis[dichlorido(η^6-*p*-cymene)ruthenium(II)], bis[dichlorido(η^6-*p*-cymene)osmium(II)], bis[dichlorido(η^5-pentamethylcyclopenta-dienyl)iridium(II)] and bis[dichlorido(η^5-pentamethylcyclopentadienyl)rhodium(II)] [43–47] as well as [chlorido(8-quinolinolato-κ^{2}N,O)(η^6-p-cymene)ruthenium(II)] **A**, [chlorido(5-chloro-7-iodo-8-quinolinolato-κ^{2}N,O)(η^6-p-cymene)ruthenium (II)] **B** [26], [chlorido(8-quinolinolato-κ^{2}N,O)(η^6-p-cymene)osmium(II)] (**C**) [48], [chlorido(8-quinolinolato-κ^{2}N,O)(η^5-pentamethylcyclo-pentadienyl) rhodium(III)] **E**, and [chlorido(8-quinolinolato-κ^{2}N,O)(η^5-pentamethylcyclopentadienyl)iridium(III)] **G** [49] were prepared as described in the literature.

3. Synthesis

3.1. [Chlorido(5-chloro-7-iodo-8-quinolinolato-κ^{2}N,O)(η^6-p-cymene) osmium(II)] D

$[OsCl_2(cym)]_2$ (0.42 g, 0.53 mmol) in methanol (50 mL) was added to a stirred solution of sodium methoxide (0.07 g, 1.30 mmol) and 5-chloro-7-iodo-8-hydroxyquinoline (0.36 g, 1.18 mmol) in methanol (20 mL). The solution was stirred under at room temperature for 5 h under N_2. The solvent was then evaporated, the residue dissolved in dichloromethane, dried over sodium sulfate, filtered and the complex was precipitated with *n*-hexane. The precipitate was collected by filtration, washed with *n*-hexane and dried *in vacuo* to afford **D** as a dark brown solid (0.49 g, 63%). Anal. Calcd. for $OsC_{19}H_{18}Cl_2NOI{\cdot}0.7\ CH_2Cl_2{\cdot}0.35\ C_6H_{14}$: %C, 34.73; %H, 3.25; %N, 1.86. Found %C, 34.61; %H, 3.37; %N, 2.01. MS (ESI^+): *m/z* 687.9334 $[M - Cl]^+$ (m_{calc} = 687.9298). ^1H NMR (399.89 MHz, $CDCl_3$): δ 8.77 (dd, 1H, ^3J = 5.0, ^4J = 1.3 Hz, H-1), 8.32 (dd, 1H, ^3J = 8.5, ^4J = 1.7 Hz, H-3), 7.85 (s, 1H, H-6), 7.43 (dd, 1H, ^3J = 8.5, ^3J = 5.0 Hz, H-2), 5.99 (d, 1H, ^3J = 5.6 Hz, H-Ar), 5.76 (d, 1H, ^3J = 5.5 Hz, H-Ar), 5.71–5.69 (m, 2H, H-Ar), 2.71 (sept, 1H, ^3J = 6.9 Hz, H-14), 2.39 (s, 3H, H-15), 1.27 (d, 1H, ^3J = 7.0 Hz, H-16), 1.16 (d, 1H, ^3J = 7.0 Hz, H-16) ppm.

3.2. [Chlorido(5-chloro-7-iodo-8-quinolinolato-κ^{2}N,O)(η^5-pentamethylcyclopentadienyl)rhodium(III)] F

Triethylamine (0.23 mL, 1.64 mmol) was added to a stirred solution of $[Rh(Cp^*)Cl_2]_2$ (0.51 g, 0.82 mmol) and 5-chloro-7-iodo-8-hydroxyquinoline (0.50 g, 1.64 mmol) in dichloromethane (30 mL). The solution was stirred for 1 h at room temperature under N_2. The solution was washed with water (2 × 15 mL), the organic phase was collected and rotated to dryness under reduced pressure, and the residue dissolved in dichloromethane. The solution was dried over sodium sulfate, filtered and the complex was precipitated with *n*-hexane. The precipitate was collected by filtration, washed with *n*-hexane and dried *in vacuo* to afford **F** as an orange solid. More orange precipitate was collected from the filtrate and both fractions were shown to be pure **F** (0.82 g, 87%). Anal. Calcd. for $RhC_{19}H_{19}Cl_2NOI{\cdot}0.2\ C_6H_{14}$: %C, 40.76; %H, 3.39; %N, 2.35. Found %C, 40.98; %H, 3.39; %N, 2.30. MS (ESI^+): *m/z* 541.9236 $[M - Cl]^+$ (m_{calc} = 541.9249). ^1H NMR (399.89 MHz, DMSO): δ 8.90 (dd, 1H, ^3J = 5.0, ^4J = 1.0 Hz, H-1), 8.41 (dd, 1H, ^3J = 8.5, ^4J = 1.0 Hz, H-3), 7.82 (s, 1H, H-6), 7.75 (dd, 1H, ^3J = 8.5, ^3J = 5.0 Hz, H-2), 1.64 (s, 15H, H-11) ppm.

3.3. [Chlorido(5-chloro-7-iodo-8-quinolinolato-κ^{2}N,O)(η^5-pentamethylcyclopentadienyl)iridium(III)] H

Triethylamine (0.23 mL, 1.64 mmol) was added to a stirred solution

of $[Ir(Cp^*)Cl_2]_2$ (0.65 g, 0.82 mmol) and 5-chloro-7-iodo-8-hydroxyquinoline (0.50 g, 1.64 mmol) in dichloromethane (30 mL). The solution was stirred for 1 h at room temperature under N_2. The solution was washed with water (2 × 15 mL), the organic phase was collected and rotated to dryness under reduced pressure, and the residue dissolved in dichloromethane. The solution was dried over sodium sulfate, filtered and the complex was precipitated with *n*-hexane. The precipitate was collected by filtration, washed with *n*-hexane and dried *in vacuo* to afford **H** as a yellowish brown solid. More yellowish brown precipitate was collected from the filtrate and both fractions were shown to be pure **H** (0.66 g, 60%). Anal. Calcd. for $IrC_{19}H_{19}Cl_2NOI{\cdot}0.25\ C_6H_{14}$: %C, 35.74; %H, 3.29; %N, 2.03. Found %C, 36.14; %H, 2.93; %N, 2.02. HRMS (ESI^+): *m/z* 631.9809 $[M - Cl]^+$ (m_{calc} = 631.9816). ^1H NMR (399.89 MHz, $CDCl_3$): δ 8.57 (dd, 1H, ^3J = 4.9, ^4J = 1.1 Hz, H-1), 8.33 (dd, 1H, ^3J = 8.6, ^4J = 1.3 Hz, H-3), 7.86 (s, 1H, H-6), 7.46 (dd, 1H, ^3J = 8.6, ^3J = 4.9 Hz, H-2), 1.72 (s, 15H, H-11) ppm.

3.4. General procedure for the synthesis of complexes **1a–4b**

Silver triflate (1.05 equiv.) was added to a solution of **A–H** (1 equiv.) in acetonitrile and stirred for 1 h at room temperature. The mixture was filtered through celite to remove silver chloride. 1,3,5-Triaza-7-phosphaadamantane (1.05 equiv.) was added to the filtrate and the reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated, the residue dissolved in dichloromethane, filtered and the complex was precipitated with *n*-hexane. The precipitate was collected by filtration, washed with *n*-hexane and dried *in vacuo*.

3.5. [(1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane)(8-quinolinolato-κ^2N,O)(η^6-p-cymene)ruthenium(II)]triflate **1a**

The synthesis was performed according to the general procedure using **A** (0.20 g, 0.48 mmol), silver triflate (0.13 g, 0.51 mmol) and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (0.08 g, 0.51 mmol) to afford **1a** as a yellow powder (0.20 g, 72%). Single crystals suitable for X-ray diffraction analysis were grown by slow diffusion of diethyl ether into a solution of the complex in dichloromethane. Anal. Calcd. for $(RuC_{25}H_{32}N_4OP)(SO_3CF_3){\cdot}1.25\ H_2O$: %C, 44.10; %H, 4.91; %N, 7.91. Found %C, 44.35; %H, 4.67; %N, 7.56. MS (ESI^+): *m/z* 537.1360 $[M - CF_3SO_3]^+$ (m_{calc} = 537.1358). MS (ESI^-): *m/z* 148.9523 $[CF_3SO_3]^-$ (m_{calc} = 148.9526). ^1H NMR (399.89 MHz, $CDCl_3$): δ 8.99 (d, 1H, ^3J = 5.2 Hz, H-1), 8.19 (d, 1H, ^3J = 8.0 Hz, H-3), 7.52 (dd, 1H, ^3J = 8.4, ^3J = 5.0 Hz, H-2), 7.39 (t, 1H, ^3J = 8.0 Hz, H-6), 6.97 (d, 1H, ^3J = 7.9 Hz, H-7), 6.93 (d, 1H, ^3J = 7.9 Hz, H-5), 5.95 (d, 1H, ^3J = 5.9 Hz, H-14), 5.88–5.84 (m, 2H, H-15/H-12), 5.78 (d, 1H, ^3J = 5.9 Hz, H-11), 4.34 (s, 6H, H-21), 3.95–3.78 (m, 6H, H-20), 2.71 (sept, 1H, ^3J = 6.8 Hz, H-17), 2.32 (s, 3H, H-16), 1.26 (d, 3H, ^3J = 6.9 Hz, H-18/H-19), 1.07 (d, 3H, ^3J = 6.9 Hz, H-18/H-19) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 168.4 (C-8), 153.0 (C-1), 144.6 (C-9), 138.6 (C-3), 130.5 (C-6), 130.1 (C-4), 123.4 (C-2), 115.4 (C-7), 115.0 (C-13), 112.0 (C-5), 102.0 (C-10), 89.1 (C-15), 87.3 (C-12), 86.6 (C-14), 85.4 (C-11), 72.7 (C-21), 50.5 (C-20), 31.3 (C-17), 22.3 (C-18/C-19), 18.7 (C-16) ppm. $^{31}P\{^1H\}$ NMR (161.87 MHz, $CDCl_3$): δ −34.7 (s) ppm.

3.6. [(1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane)(5-chloro-7-iodo-8-quinolinolato-κ^2N,O)(η^6-p-cymene)ruthenium(II)]triflate **1b**

The synthesis was performed according to the general procedure using **B** (0.45 g, 0.78 mmol), silver triflate (0.21 g, 0.82 mmol) and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (0.13 g, 0.82 mmol) to afford **1b** as an orange powder (0.64 g, 97%). Anal. Calcd. for $(RuC_{25}H_{30}N_4OPICl)(SO_3CF_3){\cdot}1.15\ CH_2Cl_2$: %C, 34.56; %H, 3.45; %N, 5.94. Found %C, 34.40; %H, 3.54; %N, 6.13. MS (ESI^+): *m/z* 696.9949 $[M - CF_3SO_3]^+$ (m_{calc} = 696.9932). MS (ESI^-): *m/z* 148.9517 $[CF_3SO_3]^-$ (m_{calc} = 148.9526). ^1H NMR (399.89 MHz, DMSO-d_6): δ 8.79 (d, 1H, ^3J = 4.8 Hz, H-1), 8.52 (d, 1H, ^3J = 8.6 Hz, H-3), 7.94 (s, 1H, H-6), 7.74 (dd, 1H, ^3J = 8.8, ^3J = 5.0 Hz, H-2), 6.26–6.25 (m, 1H, H-14), 6.19–6.14 (m, 2H, H-12/H-15), 5.98 (d, 1H, ^3J = 5.8 Hz, H-11), 4.35–4.28 (m, 6H, H-21), 3.86–3.71 (m, 6H, Hz, H-20), 2.73 (sept, 1H, ^3J = 6.8 Hz, H-17), 2.22 (s, 3H, H-16), 1.28 (d, 3H, ^3J = 6.9 Hz, H-18/H-19), 1.20 (d, 3H, ^3J = 6.9 Hz, H-18/H-19) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, DMSO-d_6): δ 166.7 (C-8), 153.9 (C-1), 141.9 (C-9), 136.0 (C-6), 135.3 (C-3), 127.0 (C-4), 124.5 (C-2), 113.9 (C-13), 112.4 (C-5), 97.6 (C-10), 91.9 (C-15), 89.1 (C-12), 88.8 (C-14), 81.4 (C-7), 81.1 (C-11), 71.4 (C-21), 49.5 (C-20), 30.7 (C-17), 21.8 (C-18/C-19), 17.4 (C-16) ppm. $^{31}P\{^1H\}$ NMR (161.87 MHz, DMSO-d_6): δ −33.4 (s) ppm.

3.7. [(1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane)(8-quinolinolato-κ^2N,O)(η^6-p-cymene)osmium(II)]triflate **2a**

The synthesis was performed according to the general procedure using **C** (0.50 g, 0.10 mmol), silver triflate (0.27 g, 1.04 mmol) and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (0.16 g, 1.04 mmol) to afford **2a** as orange crystalline needles (0.57 g, 74%). Single crystals suitable for X-ray diffraction analysis were grown by slow diffusion of diethyl ether into a solution of the complex in dichloromethane. Anal. Calcd. for $(OsC_{25}H_{32}N_4OP)(SO_3CF_3){\cdot}1.45H_2O{\cdot}0.3CH_3CN$: %C, 39.28; %H, 4.44; %N, 7.41. Found %C, 38.92; %H, 4.15; %N 7.81. MS (ESI^+): *m/z* 627.1919 $[M - CF_3SO_3]^+$ (m_{calc} = 627.1924). MS (ESI^-): *m/z* 148.9531 $[CF_3SO_3]^-$ (m_{calc} = 148.9526). ^1H NMR (399.89 MHz, $CDCl_3$): δ 9.13 (d, 1H, ^3J = 5.0 Hz, H-1), 8.17 (d, 1H, ^3J = 8.5 Hz, H-3), 7.52 (dd, 1H, ^3J = 8.4, ^3J = 5.0 Hz, H-2), 7.42 (t, 1H, ^3J = 8.0 Hz, H-6), 6.96 (d, 1H, ^3J = 7.8 Hz, H-7), 6.92 (d, 1H, ^3J = 8.0 Hz, H-5), 6.07 (d, 1H, ^3J = 5.7 Hz, H-14), 5.94–5.88 (m, 2H, H-15/H-12), 5.83 (d, 1H, ^3J = 5.7 Hz, H-11), 4.37–4.34 (m, 6H, H-21), 3.89–3.67 (m, 6H, H-20), 2.63 (sept, 1H, ^3J = 6.9 Hz, H-17), 2.40 (s, 3H, H-16), 1.26 (d, 3H, ^3J = 6.9 Hz, H-18/H-19), 1.05 (d, 3H, ^3J = 6.9 Hz, H-18/H-19) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 170.1 (C-8), 153.2 (C-1), 145.2 (C-9), 138.9 (C-3), 130.5 (C-6), 130.0 (C-4), 123.6 (C-2), 115.4 (C-7), 113.0 (C-5), 107.8 (C-13), 96.0 (C-10), 80.1 (C-15), 78.3 (C-12), 77.4 (C-14), 76.8 (C-11), 72.7 (C-21), 49.6 (C-20), 31.3 (C-17), 22.5 (C-18/C-19), 22.5 (C-18/C-19), 18.7 (C-16) ppm. $^{31}P\{^1H\}$ NMR (161.87 MHz, $CDCl_3$): δ −72.7 (s) ppm.

3.8. [(1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane)(5-chloro-7-iodo-8-quinolinolato-κ^2N,O)(η^6-p-cymene)osmium(II)]triflate **2b**

The synthesis was performed according to the general procedure using **D** (0.100 g, 0.15 mmol), silver triflate (0.041 g, 0.16 mmol) and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (0.025 g, 0.16 mmol) to afford the title compound as an orange powder (0.097 g, 69%). Anal. Calcd. for $(OsC_{25}H_{30}N_4OPICl)(SO_3CF_3){\cdot}0.25\ H_2O$: %C, 33.23; %H, 3.27; %N, 5.96. Found %C, 33.36; %H, 3.67; %N, 6.25. MS (ESI^+): *m/z* 787.0509 $[M - CF_3SO_3]^+$ (m_{calc} = 787.0490). MS (ESI^-): *m/z* 146.9626 $[CF_3SO_3]^-$ (m_{calc} = 148.9526). ^1H NMR (399.89 MHz, DMSO-d_6): δ 8.90 (d, 1H, ^3J = 5.1 Hz, H-1), 8.49 (d, 1H, ^3J = 8.6 Hz, H-3), 8.01 (s, 1H, H-6), 7.73 (dd, 1H, ^3J = 8.9, ^3J = 5.3 Hz, H-2), 6.28–6.27 (m, 1H, H-14), 6.25 (d, 1H, ^3J = 6.0 Hz, H-12), 6.15 (d, 1H, ^3J = 5.6 Hz, H-15), 6.08 (d, 1H, ^3J = 5.8 Hz, H-11), 4.34–4.20 (m, 6H, H-21), 3.79–3.62 (m, 6H, H-20), 2.68 (sept, 1H, ^3J = 6.9 Hz, H-17), 2.36 (s, 3H, H-16), 1.31 (d, 3H, ^3J = 6.9 Hz, H-18/H-19), 1.18 (d, 3H, ^3J = 6.9 Hz, H-18/H-19) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, DMSO-d_6): δ 168.4 (C-8), 154.1 (C-1), 145.0 (C-9), 136.0 (C-6), 135.8 (C-3), 125.5 (C-4), 124.7 (C-2), 106.5 (C-13), 101.4 (C-5), 97.7 (C-10), 87.2 (C-11), 81.0 (C-15), 80.7 (C-12), 72.3 (C-14), 71.5 (C-21), 48.6 (C-20), 30.6 (C-17), 22.0 (C-18/C-19), 17.5 (C-16) ppm. $^{31}P\{^1H\}$ NMR (161.87 MHz, DMSO-d_6): δ −72.2 (s) ppm.

3.9. [(1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane)(8-quinolinolato-κ^2N,O)(η^5-pentamethylcyclopentadienyl)rhodium(III)]triflate **3a**

The synthesis was performed according to the general procedure

using **E** (0.40 g, 0.96 mmol), silver triflate (0.26 g, 1.01 mmol) and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (0.16 g, 1.01 mmol) to afford **3a** as an orange powder (0.65 g, 98%). Single crystals suitable for X-ray diffraction analysis were grown by slow diffusion of diethyl ether into a solution of the complex in dichloromethane. Anal. Calcd for $(RhC_{25}H_{33}N_4OP)(SO_3CF_3)\cdot 0.5H_2O$: %C, 44.77; %H, 4.91; %N, 8.03. Found %C, 44.49; %H, 4.69; %N, 8.36. MS (ESI^+): *m/z* 539.1421 $[M - CF_3SO_3]^+$ (m_{calc} = 539.1442). MS (ESI^-): *m/z* 148.9529 $[CF_3SO_3]^-$ (m_{calc} = 148.9526). ^1H NMR (399.89 MHz, $CDCl_3$): δ 8.88 (d, 1H, ^3J = 5.0 Hz, H-1), 8.22 (d, 1H, ^3J = 8.3 Hz, H-3), 7.65 (dd, 1H, ^3J = 8.3, ^3J = 5.0 Hz, H-2), 7.39 (t, 1H, ^3J = 8.0 Hz, H-6), 7.00 (d, 1H, ^3J = 7.3 Hz, H-7), 6.93 (d, 1H, ^3J = 8.0 Hz, H-5), 4.39–4.35 (m, 6H, H-21), 4.00–3.91 (m, 6H, H-20), 1.75–1.74 (m, 15H, H-11) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 167.0 (C-8), 151.3 (C-1), 144.7 (C-9), 139.0 (C-3), 130.7 (C-4), 130.6 (C-6), 123.9 (C-2), 115.5 (C-7), 112.1 (C-5), 99.9 (C-10), 72.8 (C-21), 49.2 (C-20), 9.3 (C-11) ppm. $^{31}P\{^1H\}$ NMR (161.87 MHz, $CDCl_3$): δ −39.6 (d, ^1J = 148 Hz) ppm.

*3.10. [(1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane)(5-chloro-7-iodo-8-quinolinolato-κ^2N,O)(η^5-pentamethylcyclopentadienyl)rhodium(III)] triflate **3b***

The synthesis was performed according to the general procedure using **F** (0.40 g, 0.69 mmol), silver triflate (0.19 g, 0.72 mmol) and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (0.11 g, 0.72 mmol) to afford **3b** as an orange powder (0.49 g, 83%). Anal. Calcd. for $(RhC_{25}H_{31}N_4OPICl)(SO_3CF_3)$: %C, 36.79; %H, 3.68; %N, 6.60. Found %C, 36.50; %H, 4.07; %N, 6.97. MS (ESI^+): *m/z* 699.0018 $[M - CF_3SO_3]^+$ (m_{calc} = 699.0018). MS (ESI^-): *m/z* 148.9538 $[CF_3SO_3]^-$ (m_{calc} = 148.9526). ^1H NMR (399.89 MHz, $CDCl_3$): δ 9.06 (d, 1H, ^3J = 4.9 Hz, H-1), 8.52 (d, 1H, ^3J = 8.6 Hz, H-3), 7.87 (s, 1H, H-6), 7.79 (dd, 1H, ^3J = 8.7, ^3J = 5.0 Hz, H-2), 4.39 (s, 6H, H-21), 4.06–3.86 (m, 6H, H-20), 1.76–1.75 (m, 15H, H-11) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 165.2 (C-8), 152.9 (C-1), 141.8 (C-9), 137.2 (C-3), 136.5 (C-6), 127.9 (C-4), 124.7 (C-2), 114.4 (C-5), 100.1 (C-10), 82.1 (C-7), 72.8 (C-21), 49.2 (C-20), 9.3 (C-11) ppm. $^{31}P\{^1H\}$ NMR (161.87 MHz, $CDCl_3$): δ −40.2 (d, ^1J = 147 Hz) ppm.

*3.11. [(1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane)(8-quinolinolato-κ^2N,O)(η^5-pentamethylcyclopentadienyl)iridium(III)]triflate **4a***

The synthesis was performed according to the general procedure using **G** (0.50 g, 0.99 mmol), silver triflate (0.27 g, 1.04 mmol) and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (0.16 g, 1.04 mmol) to afford **4a** as a yellow powder (0.71 g, 93%). Single crystals suitable for X-ray diffraction analysis were grown by slow diffusion of diethyl ether into a solution of the complex in dichloromethane. Anal. Calcd. for $(IrC_{25}H_{33}N_4OP)(SO_3CF_3)$: %C, 40.15; %H, 4.28; %N, 7.20. Found %C, 39.88; %H, 4.18; %N, 7.07. MS (ESI^+): *m/z* 629.2040 $[M - CF_3SO_3]^+$ (m_{calc} = 629.2017). MS

(ESI^-): *m/z* 148.0531 $[CF_3SO_3]^-$ (m_{calc} = 148.9526). ^1H NMR (399.89 MHz, $CDCl_3$): δ 9.03 (d, 1H, ^3J = 5.0 Hz, H-1), 8.18 (d, 1H, ^3J = 8.4 Hz, H-3), 7.66 (dd, 1H, ^3J = 8.4, ^3J = 5.0 Hz, H-2), 7.41 (t, 1H, ^3J = 8.0 Hz, H-6), 6.96 (d, 1H, ^3J = 7.4 Hz, H-7), 6.89 (d, 1H, ^3J = 7.9 Hz, H-5), 4.43–4.32 (m, 6H, H-21), 3.97–3.84 (m, 6H, H-20), 1.79–1.78 (m, 15H, H-11) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 168.7 (C-8), 152.0 (C-1), 145.3 (C-9), 139.2 (C-3), 130.7 (C-4), 130.6 (C-6), 124.0 (C-2), 115.7 (C-7), 113.3 (C-5), 93.5 (C-10), 72.8 (C-21), 48.1 (C-20), 9.1 (C-11) ppm. $^{31}P\{^1H\}$ NMR (161.87 MHz, $CDCl_3$): δ −64.9 (s) ppm.

*3.12. [(1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane)(5-chloro-7-iodo-8-quinolinolato-κ^2N,O)(η^5-pentamethylcyclopentadienyl)iridium(III)] triflate **4b***

The synthesis was performed according to the general procedure using **H** (0.40 g, 0.60 mmol), silver triflate (0.16 g, 0.63 mmol) and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (0.10 g, 0.63 mmol) to afford **4b** as a yellow powder (0.46 g, 86%). Anal. Calcd. for $(IrC_{25}H_{31}N_4OPICl)(SO_3CF_3)$: %C, 33.29; %H, 3.33; %N, 5.97. Found %C, 32.99; %H, 3.59; %N, 6.32. MS (ESI^+): *m/z* 789.0610 $[M - CF_3SO_3]^+$ (m_{calc} = 789.0585). MS (ESI^-): *m/z* 148.9528 $[CF_3SO_3]^-$ (m_{calc} = 148.9526). ^1H NMR (399.89 MHz, $CDCl_3$): δ 9.14 (d, 1H, ^3J = 5.0 Hz, H-1), 8.48 (d, 1H, ^3J = 8.6 Hz, H-3), 7.90 (s, 1H, H-6), 7.78 (dd, 1H, ^3J = 8.7, ^3J = 5.1 Hz, H-2), 4.47–4.35 (m, 6H, H-21), 4.02–3.82 (m, 6H, H-20), 1.79–1.78 (m, 15H, H-11) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 167.2 (C-8), 153.5 (C-1), 142.5 (C-9), 137.0 (C-6), 136.8 (C-3), 127.9 (C-4), 124.8 (C-2), 115.9 (C-5), 93.7 (C-10), 81.9 (C-7), 72.8 (C-21), 48.0 (C-20), 9.1 (C-11) ppm. $^{31}P\{^1H\}$ NMR (161.87 MHz, $CDCl_3$): δ −64.9 (s) ppm.

4. Stability studies

For solution stability studies, a small amount (*ca.* 2 mg) of the compound was dissolved in D_2O or DMSO-d_6 (500 μL). ^1H NMR spectra were recorded at t = 0, 12, 24, 48, 72 h, 1 week and 1 month to determine the stability.

5. Solubility studies in water

The aqueous solubility was determined by adding a weighed sample of each complex, dissolved in a minimum amount of DMSO, to α-MEM spiked with 5% FCS and the solution was visually inspected for any undissolved complex after vortexing the mixture.

6. Cell cytotoxicity

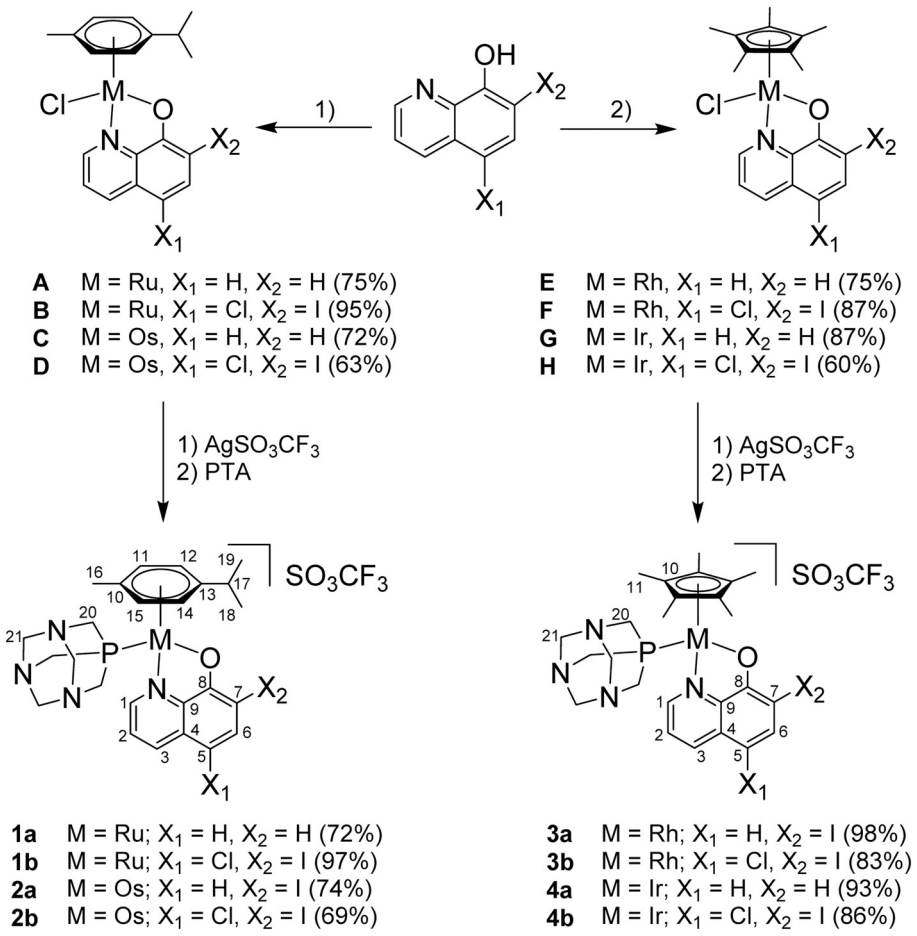
HCT116, SW480 and NCI-H460 cells were supplied by ATCC, while SiHa cells were supplied from Dr. David Cowan, Ontario Cancer Institute, Canada. The cells were grown in α-MEM (Life Technologies) supplemented with 5% fetal calf serum (Moregate Biotech) at 37 °C in a humidified incubator with 5% CO_2. The cytotoxicity was determined by the sulforhodamine B assay as described previously [50].

7. Results and discussion

In order to improve the aqueous solubility of anticancer active organometallic compounds of hydroxyquinoline derivatives, PTA, a water-soluble and air-stable ligand, was coordinated to the metal center by replacing the labile chlorido ligand through a two-step reaction procedure [26]. As PTA contains multiple nitrogen atoms to act as H acceptors, they can be readily protonated and have been shown to increase the aqueous solubility of metal complexes [51,52].

The preparation of the $[M^{II/III}(cym/Cp^*)(L)Cl]$ complexes as precursors for the complexation of PTA was conducted following literature procedures [26,49,53]. All complexes were produced in one-pot reactions with L = 8-HQ or clioquinol, their respective dimeric metal precursors $[M^{II/III}(cym/Cp^*)Cl_2]_2$ (cym: M = Ru, Os; Cp*: M = Rh, Ir) and either sodium methoxide (Ru and Os) or triethylamine (Ir and Rh), as illustrated in Scheme 1. The compounds were characterized with standard methods and the ^1H and $^{13}C\{^1H\}$ NMR spectra featured the expected peaks. In case of the new clioquinol complexes **D**, **F** and **H**, the general low solubility did not allow for the collection of $^{13}C\{^1H\}$ NMR spectra.

The complexation of PTA onto the metal centers is a facile process which was performed *via* an adapted procedure outlined by Pettinari et al. [54]. This route was instigated by stirring a suspension of $[M^{II/III}(cym/Cp^*)(L)Cl]$ precursors (**A–H**) with silver triflate to form the $[(triflate)M^{II/III}(cym/Cp^*)(L)]$ intermediates and silver chloride, which was subsequently removed by filtration through celite. The filtrate and PTA were then stirred to afford the $[(PTA)M^{II/III}(cym/Cp^*)(L)]^+$ complexes, generating sizeable yields in the range of 69–98% (Scheme 1).



Scheme 1. Preparation of the $[M^{II/III}(cym/Cp^*)(L)Cl]$ precursor complexes and their complexation to PTA, as well as the used NMR numbering scheme. Conditions: 1) $AgSO_3CF_3$, MeCN, 1 h, r.t.; 2) PTA, MeCN, 24 h, r.t. Conditions: 1) $[M(cym)Cl_2]_2$, NaOMe, MeOH, 4–5 h, reflux; 2) $[M(Cp^*)Cl_2]_2$, Et_3N, DCM, 1 h, r.t. The syntheses of compounds **A**, **B**, **C**, **E** and **G** have been reported earlier but are included here for comparison purposes [26,49,53].

All new complexes were characterized by ^1H, $^{31}P\{^1H\}$ and $^{13}C\{^1H\}$ NMR spectroscopy (Figs. S1–S29). The ^1H NMR spectra featured the usual peaks originating from cym/Cp*, hydroxyquinoline-derived and PTA ligands. The most deshielded proton was H-1 next to endocyclic nitrogen of hydroxyquinoline and it appeared at about 9 ppm in all compounds. For the Cp* complexes, the Cp* methyl groups gave more than one signal, presumably due to H/D exchange in the NMR sample [55]. For some of the PTA complexes, such as **2b**, it proved difficult to record $^{13}C\{^1H\}$ NMR spectra and gave low quality spectra. The $^{31}P\{^1H\}$ NMR spectra showed distinctive peaks dependent on the metal center at about −34 for Ru (**1a**, **1b**), −72 for Os (**2a**, **2b**), −39 for Rh (**3a**, **3b**) and −65 ppm for Ir (**4a**, **4b**) complexes. In **3a** and **3b**, coupling between P and Rh was observed with ^1J values of about 147 Hz. ESI-mass spectra recorded in positive ion mode yielded base peaks corresponding to $[M - CF_3SO_3]^+$ cations.

Single crystals for X-ray diffraction of the 8-HQ complexes were grown *via* the slow diffusion of diethyl ether into a saturated solution of the compound in dichloromethane. The key bond lengths and angles are given in Table 1 along with those for the ruthenium precursor **A** for comparison. Full X-ray crystallographic data for all 8-HQ complexes are given in Table S1. Complexes **1a** and **2a** crystallized in the monoclinic $P2_1/n$ space group, whereas both **3a** and **4a** complexes crystallized in the triclinic *P*-1 space group. As the metals are stereogenic centers, all complexes crystallized as mixtures of enantiomers with triflate as the counterion (Fig. 1). The 8-HQ ligand forms a five-membered ring as it binds to the metal center through the nitrogen and oxygen atoms. However, no hydrogen bonding or π stacking was observed. All complexes display the characteristic pseudo octahedral piano-stool configuration with 8-HQ and PTA ligands forming the legs of the stool and the π-bound cym or Cp* rings acting as the seat *via* a η^6- or η^5-coordination,

Table 1
Key bond lengths (Å) and angles (°) in the molecular structures of **1a–4a** and, for comparison, of precursor **A**.

Bond/angle	1a	2a	3a	4a	A[a]
M–N1	2.0996(13)	2.1076(19)	2.092(2)	2.090(3)	2.094(2)
M–O1	2.0820(11)	2.0921(15)	2.1031(19)	2.115(2)	2.073(2)
M–P1/Cl	2.2965(4)	2.3076(6)	2.2859(7)	2.2766(8)	2.4219(7)
O1–C8	1.323(2)	1.324(3)	1.317(3)	1.324(4)	1.311(3)
O1–M–N1	78.84(5)	78.00(7)	79.23(8)	78.51(10)	78.80(6)
O1–M–P1/Cl	86.67(3)	87.01(5)	85.73(6)	85.62(6)	86.48(5)
N1–M–P1/Cl	87.15(4)	86.87(5)	89.09(6)	88.71(7)	84.25(5)

[a] Taken from ref. [33].

respectively. Complexes **1a** and **2a** are arranged such that the methyl and isopropyl groups on the *p*-cymene ligand are positioned between the 8-HQ and PTA ligands, reducing the steric constraints about the metal center.

As expected, the structures do not differ significantly by changing the metal center with differences in metal–ligand bond lengths no greater than 0.0176, 0.033 and 0.031 Å for the M–N1, M–O1 and M–P1 bonds, respectively. The complex with the longest bond between the metal and PTA ligand is **2a** (2.3076(6) Å), which also has the longest M–N1 bond (2.1076(19) Å). The longest M–O bond was found for **4a** (2.115 (2) Å). There is minimal difference within the O1–C8 bonds between the four complexes, although in all cases, this bond is longer than observed for precursor **A** (1.311(3) Å). The addition of the PTA ligand results in O1–M–P1 angles close to 90° with the largest found in the structure of **2a** (87.01(5)°) followed by **1a** (86.67(3)°). In both Cp* complexes this angle was smaller than for the *p*-cymene complexes, presumably due to steric constraint imposed by the position of the

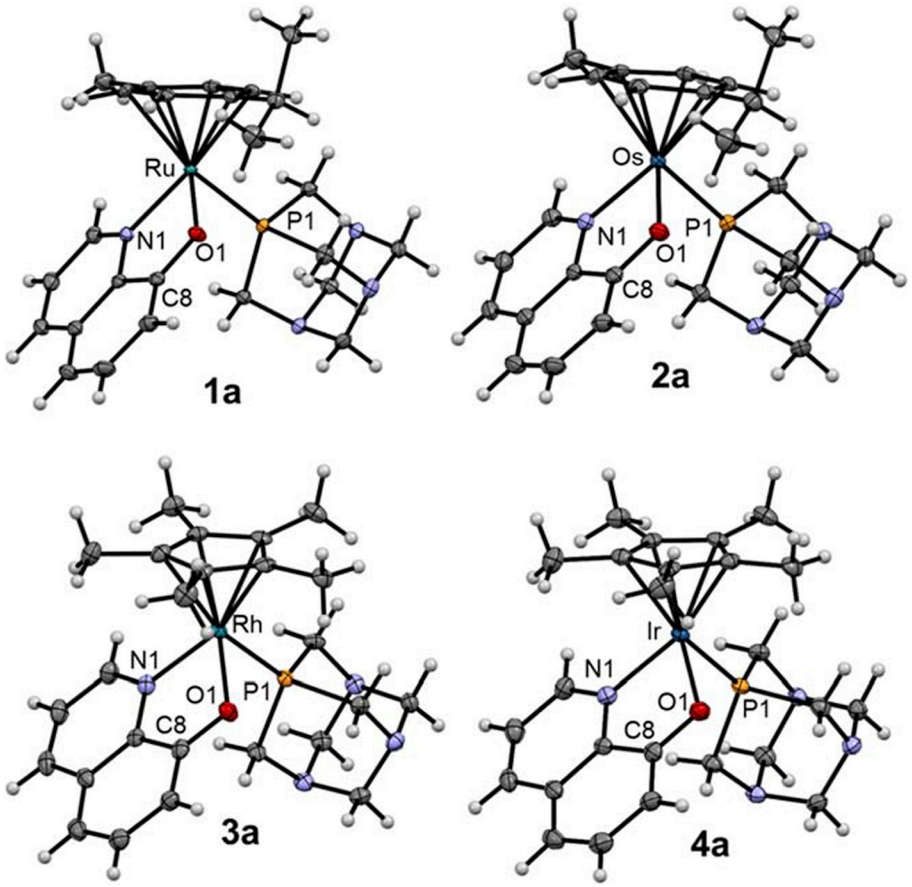


Fig. 1. Molecular structures of complexes **1a**, **2a**, **3a** and **4a** drawn at 50% probability level. The triflate counter anions have been removed for clarity.

isopropyl group between O1 on the 8-HQ ligand and PTA. The precursor **A** has a similar O1–M–Cl angle as **1a** at 86.48(5)°. In contrast, the N1–M–P1 angle is larger for the Cp* complexes than for the cym derivatives, and for all complexes this angle is significantly larger than the analogous N1–M–Cl angle of **A** (84.25(5)°).

We used ^{1}H and ^{31}P{^{1}H} NMR spectroscopy to evaluate the stability of the complexes in D_2O and in DMSO-d_6. The complexes were shown to be highly stable in aqueous solution and the spectra hardly changed over the course of up to a month. However, only the Os, Rh and Ir complexes were stable in DMSO-d_6 solution. Both Ru complexes fully degraded over the course of 1 month, while they were stable for at least 3 d. The stability studies conducted for **1a** are illustrated in Figs. S30–S33.

Aqueous solubility is an important factor for the administration of drugs and can be the limiting factor once a drug is translated to clinical trials. However, if a drug is too hydrophilic, it may not be able to effectively cross cell membranes and accumulate in tumor cells. By substituting the halido ligands in the precursors **A** and **B** with amphiphilic PTA, we aimed to increase the aqueous solubility of the complex type. The aqueous solubility was determined by adding a weighed sample of each complex, dissolved in minimum amount of DMSO, to α-MEM spiked with 5% fetal calf serum (FCS). All of the compounds displayed very high aqueous solubility. The concentrations reached for each complex exceeded 3 mM and the solubility maximum was not reached by the method used. When comparing the solubilities of precursors **A** and **B** to **1a** and **1b**, they increased considerably, demonstrating the effect that the PTA ligand has on the aqueous solubility of these complexes. This is also reflected in studies reported earlier on the *n*-octanol/water partition coefficients (log *P*) as a measure of the lipophilicity of **A** and **B** compared to **1a** and **1b** [26,56]. The log *P* value is an important factor for estimation of the oral bioavailability and cellular uptake of drugs.

8. Cytotoxicity studies

All complexes were tested against HCT116 (human colon cancer), NCI-H460 (human breast cancer), SiHa (human cervical cancer) and SW480 (human colon cancer) cell lines by the sulforhodamine B cytotoxicity assay (Table 2). While the Ru, Os and Ir derivatives showed very low cytotoxic activity, the Rh compounds were surprisingly active with IC_{50} values close to, or lower than, their corresponding quinoline ligand 8-HQ and clioquinol, as well as cisplatin. When comparing the Ru complexes **1a** and **1b** to their corresponding precursors (**A** and **B**), there is a significant decrease in antiproliferative activity, very likely due to reduced cellular uptake of the more hydrophilic PTA complexes. However, as seen in biological studies with RAPTA-C, such organometallic PTA complexes may be active *in vivo* which does not translate to *in vitro* studies [16]. This is particularly interesting as several PTA derivatives reported here were more potent than RAPTA-C in the cell lines used.

9. Conclusions

A series of $M^{II/III}$(cym/Cp*) (cym: M = Ru, Os; Cp*: M = Rh, Ir) complexes, bearing either 8-hydroxyquinoline or clioquinol bioactive ligands, has been synthesized and modified to incorporate the PTA ligand to increase the poor water solubility of the parent halido complexes. The syntheses proved to be facile, generating products in good to very good yields. The complexes were characterized using a combination of 1D and 2D NMR spectroscopy, ESI-MS, elemental analysis and X-ray crystallography. Solubility studies demonstrated that the introduction of the PTA ligand indeed increased the aqueous solubility considerably, which was also reflected in the log *P* values of **1a** and **1b**

Table 2
IC_{50} values (μM) of **1a–4b** and, for comparison, of the ancillary ligands 8-HQ and clioquinol, the precursors **A** and **B**, as well as RAPTA-C and cisplatin against human colorectal (HCT116), non-small cell lung (NCI-H460), colon (SW480) and cervical (SiHa) carcinoma cell lines (exposure time 72 h) expressed as mean ± standard error (n = 3). A value of > 200 μM indicates that the IC_{50} was not reached at the highest concentration used.

	HCT116	NCI-H460	SiHa	SW480
1a	79 ± 12	127 ± 11	161 ± 7	204 ± 15
1b	299 ± 114	151 ± 52	248 ± 119	333 ± 145
2a	1033 ± 180	566 ± 41	768 ± 33	840 ± 106
2b	196 ± 18	129 ± 23	132 ± 16	329 ± 232
3a	0.94 ± 0.23	2.0 ± 0.4	8.2 ± 2.0	2.5 ± 0.1
3b	6.4 ± 0.7	3.1 ± 0.2	11 ± 0.2	8.0 ± 0.5
4a	293 ± 40	239 ± 25	337 ± 14	560 ± 105
4b	122 ± 8	69 ± 2	87 ± 6	313 ± 42
8-HQ	2.0 ± 0.8	2.4 ± 0.4	6.0 ± 0.7	–
Clioquinol	6.3 ± 1.8	3.3 ± 0.4	6.8 ± 0.3	–
A	12 ± 1	11 ± 2	19 ± 2	–
B	7.7 ± 0.6	5.6 ± 0.3	8.5 ± 0.4	–
RAPTA-C	> 200	> 200	> 200	> 200
Cisplatin	2.5 ± 0.3	0.8 ± 0.03	3.0 ± 0.6	8.1 ± 2.9

in comparison to their precursors **A** and **B**. Both aqueous solubility and lipophilicity studies demonstrated the effect of incorporating PTA into these complexes by significantly increasing solubility and converting distinct hydrophobic precursors into effectual hydrophilic complexes. Stability experiments in aqueous solution indicated appreciable stability of these complexes. Cytotoxicity studies *in vitro* in cancer cells revealed that the introduction of the PTA ligand significantly decreased the cytotoxic activity of the compounds compared to their precursors, as would be expected for such a modification. While an improvement in solubility is favorable for the administration and transport of drugs within the body, this can be detrimental for cell entry as the compound may be too hydrophilic to cross cell membranes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jinorgbio.2019.110768.

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