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Ruthenium(II)–arene and triruthenium-carbonyl cluster complexes with new water-soluble phopsphites based on glucose: Synthesis, characterization and antiproliferative activity

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ABSTRACT

New water-soluble 3,5,6-bicyclophosphite ligands based on glucose modified with uracil, 5-fluorouracil or thymine are reported. The phosphite ligands were subsequently reacted with bis[dichlorido(η^6-*p*-cymene)ruthenium(II)] and tririutheniumdodecacarbonyl to afford monoruthenium analogues of RAPTA-C and triruthenium clusters with 1–3 phosphite ligands, respectively. The influence of ligands on the stability of the compounds and the antiproliferative activity of the compounds was investigated.

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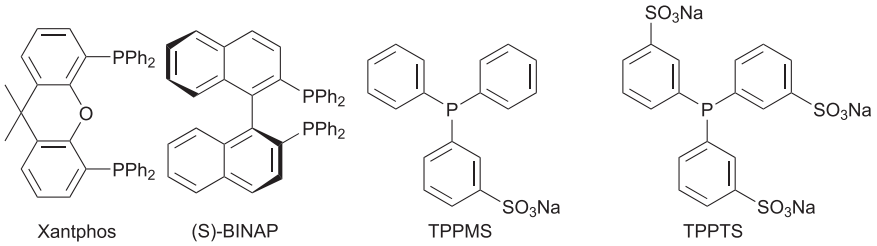
1. Introduction

Phosphorus-based ligands (e.g. Xantphos, (S)-BINAP) are an important class compounds with widespread uses in catalysis and medicinal chemistry [1–7]. While many phosphorus-based ligands are hydrophobic, their increasing use in aqueous environments, e.g. in aqueous-organic biphasic catalysis and therapeutic applications, has led to the development of amphiphilic and hydrophilic analogues, such as the classic sulfonated phosphines TPPMS (sodium 3-(diphenylphosphino) benzenesulfonate) and TPPTS (triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt) [8–11].



Xantphos (S)-BINAP TPPMS TPPTS

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The chemistry of Ru compounds with phosphorus ligands is well developed and has found many applications in catalysis. As examples, water-soluble ruthenium complexes containing TPPTS catalyzes the selective reduction of the carbonyl group in α,β-unsaturated aldehydes [12,13], $RuCl_2(TPPTS)_3$ has been used as a catalyst for the hydrogenation of unsaturated hydrocarbons [14] and in formic acid dehydrogenation [15–17]. The cage phosphine, 1,3,5-triaza-7-phosphaadamantane (PTA), first reported in 1974 by Daigle is amphiphilic in character and has been extensively used in the catalysis [18–20]. The complex $[RuCl_2(PTA)_4]$ catalyzes the selective reduction of carbonyl groups [21] and acts as a catalyst precursor for hydrogenation of CO_2 and bicarbonate in aqueous solution [22]. The Ru-cyclopentadienyl complex $CpRuCl(PTA)_2$ demonstrates regioselective catalytic activity for the hydrogenation of unsaturated ketones under aqueous biphasic conditions [23], and a related complex catalyzes nitrile hydration [24].

The Ru(η^6-*p*-cymene)Cl_2PTA, termed RAPTA-C, is a pre-catalyst for hydrogenation reactions [25], but is better known for its anticancer properties [26–28], primarily when used in combination with other drugs [29–33]. In addition to RAPTA-C, an extensive range of RAPTA-type complexes has been studied encompassing Ru with an arene ligand, PTA or modified PTA ligand and additional co-ligands [34]. An alternative series of compounds are known in which the PTA ligand is replaced by other phosphorus donor ligands. Examples include RAPTA analogues with phosphite-carbohydrate ligands [35–38], which potentially target cancer cells via the Warburg effect [39].

Interestingly, Ru-carbonyl clusters with the same ligand show anticancer and anti-angiogenic activity [40]. However, the limited solubility of the complexes and clusters in aqueous media represents a significant limitation of the compounds for pharmacological applications. Consequently, we decided to prepare a new class of water-soluble bicyclophosphites bearing uracil, 5-fluorouracil or thymine moieties. Glucose modified compounds bearing natural or artificial nucleobases can be seen as antimetabolites, known class of active chemotherapeutic agents such as folic acid, pyrimidine or purine analogues. Antimetabolites have similar structures as naturally occurring molecules used in nucleic acid synthesis but differ enough that they interfere with normal cell functions. These agents are used for a variety of cancer therapies, including leukaemia, breast, ovarian and gastrointestinal cancers [41,42].

5-Fluorouracil (5-FU) is a pyrimidine base containing a fluorine atom at the 5-carbon position on the ring and inhibits DNA synthesis due to mimicking the natural base. 5-FU is used for the treatment of many malignancies, including in co-administration with oxaliplatin [43,44]. Recently several reports were published in which the activity of Ru complexes with 5-fluorouracil [45–47] against several cancer cell lines, including HCT116 [48] was reported.

In this report, RAPTA-type complexes and Ru-carbonyl clusters were prepared based on the new phosphite ligands and their antiproliferative activity against several cancer cell lines was evaluated.

2. Results and discussion

The 3,5,6-bicyclophosphites with uracil **8**, 5-fluorouracil **9** or thymine **10** moieties were prepared according to the route shown in Scheme 1. In the first step **1** was treated with O,O′-bis(-trimethylsilyl)-uracil (prepared *in situ*), O,O′-bis(trimethylsilyl)-5-fluorouracil (commercially available) or O,O′-bis(trimethylsilyl)-thymine (prepared *in situ*) in the presence of trimethylsilyltrifluoromethane sulfonate. The trimethylsilyl protecting groups were removed by treatment with $NaHCO_3$ and the pure compounds **2**–**4** obtained by column chromatography. This procedure leads to the exclusive formation of the β-isomer, which affords one set of signals in the ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectra of **2**–**4** signals from the uracil (in **2**), 5-fluro-uracyl (in **3**) or thymine (in **4**) moieties were observed. The propanoyl protecting groups were removed by treatment of **2**–**4** with ammonia in methanol [49] to afford the modified sugars **5**–**7**. The ^{1}H and ^{13}C NMR spectra of **5**–**7** confirm the disappearance of signals attributable to the protecting groups.

Phosphorylation of **5**–**7** with hexaethylphosphoroustriamide leads to the formation of the 3,5,6-bicyclophosphite ligands **8**–**10** [50]. ^{31}P NMR spectroscopy was used to monitor the progress of the reaction and, with time, a signal at ca. 119 ppm increases in intensity which confirms the formation of the bicyclophosphite unit. The ^{13}C NMR spectra of **8**–**10** show the expected $J_{C\text{-}P}$ (C4–P~2 Hz, C5–P~4 Hz, C6–P~5.6 Hz, C3–P<1 Hz) coupling constants confirming the formation of the product.

The 3,5,6-bicylophosphite ligands based on a sugar moiety reported in the literature [51] are insoluble or only sparingly soluble in water. Still, they are reasonably stable towards oxidation and

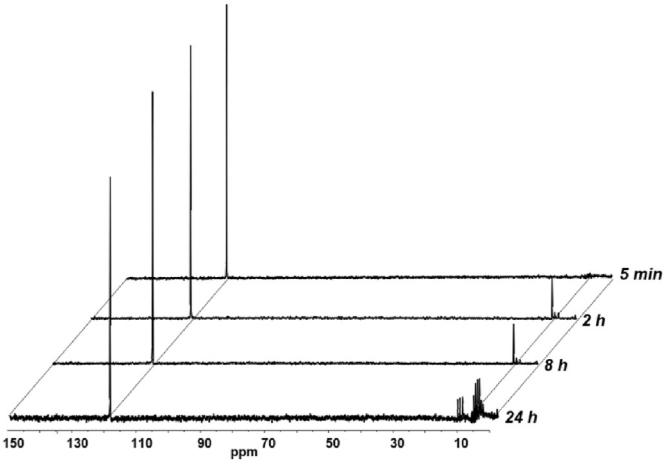
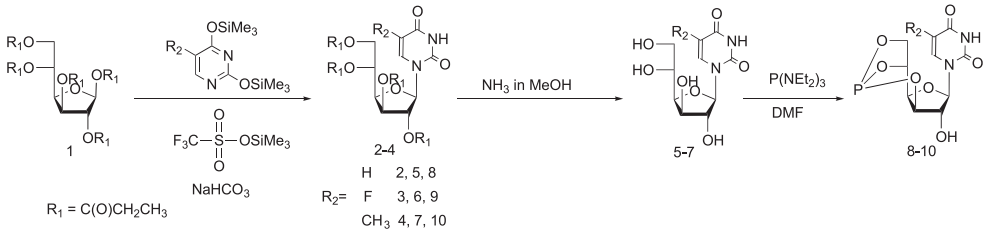
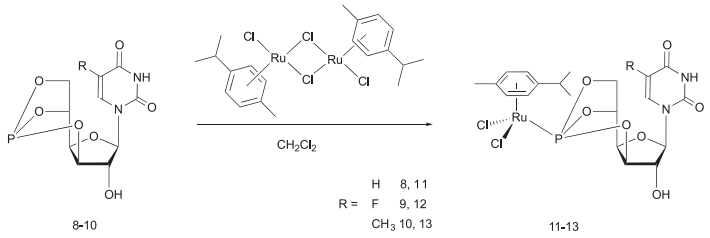


Fig. 1. ^{31}P NMR spectra **8** in water over 24 h.



Scheme 1. Synthesis of 3,5,6-bicylophosphite ligands **8**–**10**.



Scheme 2. Synthesis of Ru(II)-arene complexes **11**–**13**.

moisture in comparison to noncyclic phosphites. In contrast, **8**–**10** have a much higher solubility in the polar solvents such as acetone or water. The stability of **8**–**10** in water was studied by ^{31}P NMR spectroscopy (see Fig. 1 for the spectra of **8**), with hydrolytic decomposition taking place and ca. 30% decomposition observed after 24 h.

The reaction of **8**–**10** with bis[dichlorido(η^6-*p*-cymene)ruthenium(II)] in CH_2Cl_2 at room temperature afforded the Ru(II)-arene complexes **11**–**13** in high yield (Scheme 2).

The characteristic change in the resonance in the ^{31}P NMR spectra were observed upon coordination of the phosphite ligands, with the singlet shifting from ca. 119 ppm to ca. 135 ppm. Complexes **11**–**13** are soluble in methanol, acetone, and water, with their water solubility being at least five times higher than their dichlorido(η^6-*p*-cymene)(3,5,6-bicyclophosphite-1,2-O-isopropylidene-α-D-glucofuranoside)ruthenium(II) analogues. Nevertheless, in aqueous solution **11**–**13** slowly hydrolyze, as observed for related compounds [35], but at a much slower rate. After 8 h in the water, about 50% of original complex remains present (determined by ^{31}P NMR spectroscopy), whereas only 10% remains for the previously reported compounds.

Previously, triruthenium-carbonyl clusters derivatized with the 3,5,6-bicyclophosphite-1,2-*O*-isopropylidene-α-D-glucofuranoside ligand were shown to exhibit anticancer and antiangiogenic properties depending on the number of phosphorus ligands coordinated to the cluster core [40]. However, their low water solubility complicated studies and limit applications. Triruthenium dodecacarbonyl, $Ru_3(CO)_{12}$, was reacted with varying stoichiometries of **8** to afford **14**–**16** (Scheme 3). Changing the stoichiometry of the reactants (ruthenium carbonyl cluster:trimethylamine-N-oxide:bicyclophosphite ligand) allows one to three carbonyl ligands to be substituted by the phosphite ligand. The reactions were monitored by ^{31}P NMR spectroscopy with the singlet corresponding to the free ligand at 119 ppm shifting to 150–152 ppm following coordination to the ruthenium-carbonyl cluster. Clusters **14**–**16** (Table 1.) are approximately twice as water-soluble than those

Table 1
Lipophilicity and solubility of cluster compounds **14**–**16.**

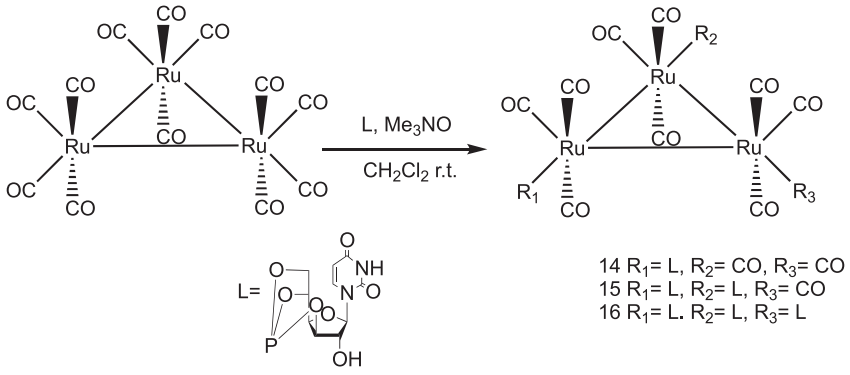
Compound	LogP o/w	Solubility, μM		
		0.1% DMSO	0.3% DMSO	0.5% DMSO
14	5.25	297	910	1177
15	4.17	70	85	177
16	3.89	115	128	202

Table 2
Antiproliferative activity against human ovarian cancer cells.

Compounds	IC_{50} (μM)	
	A2780	A2780R
6	>5000	>5000
9	>5000	>5000
11	477 ± 23	659 ± 117
12	1227 ± 119	579 ± 67
13	537 ± 118	1249 ± 264
14	0.87 ± 0.03	0.50 ± 0.09
15	45 ± 14	41 ± 15
16	81 ± 3	>100

derivatized with the 3,5,6-bicyclophosphite-1,2-O-isopropylidene-α-D-glucofuranoside ligand and this can be attributed to use of new water soluble ligand **8** [40].

The antiproliferative activity of compounds **6**, **9** and **11**–**16** was studied against human ovarian cancer (A2780) cells and the cisplatin-resistant variant (A2780R), see Table 2. The glucose and phosphorylated derivatives of 5-fluorouracil, i.e. **6** and **9** respectively, are inactive. The Ru(II)-arene complexes **11**–**13** are active only at a high micromolar range and may be considered as essentially non-toxic. The most cytotoxic was found to be triruthenium cluster with one phosphorus ligand coordinated to the cluster core followed by compounds with two and tree phosphite ligands. A similar dependence of cytotoxicity on the number of coordinated



Scheme 3. Synthesis of triruthenium-carbonyl clusters **14**–**16**.

phosphorus ligands was observed for previously reported ruthenium-carbonyl clusters [40,52].

3. Experimental

All solvents were purified and degassed prior to use. ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Bruker Avance II 400 spectrometer at room temperature. Spectra were referenced to the ^{1}H signal of the NMR solvent or by the inclusion of an external reference: H_3PO_4 for $^{31}P\{^{1}H\}$ NMR. ESI-mass spectra of the compounds were obtained in MeOH on a ThermoFinnigan LCQ Deca XP Plus quadrupole ion-trap instrument operated in positive ion mode over a mass range of *m*/*z* 150−1000. The ionization energy was set at 5.0 V and the capillary temperature at 150 °C. Melting points were determined with a Stuart Scientific SMP3 apparatus and are uncorrected. Flash chromatography system Varian 971-FP and prepacked Silica Gel columns (Luknova, US) were used for purification. Elemental analyses were carried out at the microanalytical laboratory EPFL. The bis[dichlorido(η^6-*p*-cymene)ruthenium(II)] [53], 1,2,3,5,6-Penta-*O*-propanoyl-β-d-glucofuranose **1** [54], 1-β-d-glucofuranosyluracil **5** [49] were synthesized according to literature procedures and all analytical data was similar to the reported in the literature.

3.1. Log P values measured by reversed-phase HPLC

The log P values were measured by reversed-phase HPLC on a 150 mm C-18 column following the method already described in the literature [40,55−57]. The correlation between log K_w and log P was established based on the compounds with known logP (4-methoxyanilin: 0.95, 4-bromanilin: 2.26, naphthalene: 3.30, tert-butylbenzene: 4.11, pyrene: 4.50). For solubility measurements compounds were solubilized in DMSO and diluted with water to achieve a final concentration of 300 μM. In all cases the precipitation of compounds was observed, sample shacked for 30 min, filtered and concentration of complexes in the aqeous phase was estimated by HPLC. The calibration curve was plotted.

3.2. Cell culture experiments and conditions

Human A2780 and A2780cisR ovarian carcinoma cell lines were obtained from the European Centre of Cell Cultures (ECACC, Porton Down, Salisbury, UK). Human MCF-7 breast carcinoma was obtained from the American Type Culture Collection (ATCC). These cells are routinely grown in Dulbecco's Modified Eagle Medium containing 4.5 g/L glucose and glutamax and were supplemented with 10% heat-inactivated fetal bovine serum and antibiotics. Cultures were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. All cell culture reagents were purchased from Gibco-BRL, Basel Switzerland. For cell viability experiments tests, cells were grown in 96-well plates (Costar, Integra Biosciences, Cambridge, MA, USA) as monolayers for 24 h in complete medium with 10% FCS to reach sub-confluence. Then fresh complete medium with 5% FCS was added together with the drugs, and the culture was continued for another 72 h. The compounds were predissolved at 20 mM in DMSO and then added to the cell culture medium at the required concentration with a maximum DMSO content of 0.5 v/v% to be incubated for 72 h. At these concentrations, DMSO does not affect cell viability. Cell viability was determined using the MTT assay, which quantifies the mitochondrial activity in metabolically active cells, essentially as reported previously [58]. Briefly, following drug exposure, MTT (Sigma, final concentration 0.2 mg/mL) was added to the cell culture medium for the final 2 h, then the culture medium was aspirated and the violet formazan precipitate dissolved in 0.1 M HCl in 2-propanol. The optical density, which is directly proportional to the number of surviving cells, was quantified at 540 nm using a multiwell plate reader (iEMS Reader MF, Labsystems, USA) and the percentage of surviving cells was calculated from the absorbance of untreated cells.

3.3. 1-(5-Fluorouracil)-2,3,5,6-tetra-O-propanoyl-β-D-glucofuranosyl **3**

Trimethylsilyltrifluoromethanesulfonate (2.24 g, 10.07 mmol) was added dropwise to a solution of 1,2,3,5,6-penta-*O*-propanoyl-β-D-glucofuranose (2.25 g, 4.89 mmol) and *O,O′*-bis(trimethylsilyl)-5-fluorouracil (2.0 mL, 7.65 mmol) in acetonitrile (50 mL) at 0 °C under N_2 atmosphere. The reaction mixture was refluxed for 5 h, cooled down to 0 °C and saturated solution of $NaHCO_3$ (50 mL) was added. The product was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organic fractions were washed with brine and dried over $MgSO_4$. The pure product was isolated by flash chromatography ($CHCl_3$:MeOH 99:1). Yield: 1.83 g (72.6%), mp: 49−50 °C, elem. anal. calcd (%) for $C_{22}H_{29}N_2O_{11}F$: C 51.16, H 5.66, N 5.42; found: C 51.07, H 5.77, N 5.27.^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 9.14 (d, *J* = 4.4 Hz, 1H, NH), 7.56 (d, *J* = 5.9 Hz, 1H; CH═CF), 6.07 (tr, *J* = 1.7 Hz, 1H; H-1), 5.48 (d, *J* = 2.9 Hz, 1H; H-3), 5.38 (m, 1H; H-5), 5.06 (d, *J* = 2.0 Hz, 1H; H-2), 4.61 (dd, *J* = 12.2; 2.4 Hz, 1H; H-6), 4.38 (dd, *J* = 9.3; 2.9 Hz 1H; H-4), 4.13(dd, *J* = 12.3; 4.9 Hz, 1H, H-6′), 2.58−2.28 (m, 8H, CH_2), 1.21−1.10 (m, 12H, CH_3) ppm.$^{13}C\{^{1}H\}$ NMR (100.63 MHz, $CDCl_3$): δ = 173.9 (CO), 173.0 (CO), 172.5 (CO), 171.9 (CO), 156.7 (*J* = 26.7 Hz, *C*(O)CF), 148.8 (CO), 140.8 (*J* = 238.5 Hz, CF), 123.5 (*J* = 34.7 Hz, *C*H═CF), 89.3 (C-1), 80.0 (C-2), 78.8 (C-4), 72.9 (C-3), 66.7 (C-5), 62.7 (C-6), 27.3 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 8.9 (CH_3), 8.7 (CH_3), 8.6 (CH_3), 8.5 (CH_3) ppm. MS (ESI^+): *m*/*z*: 517 $[M+H]^+$.

3.4. 1-(2,3,5,6-Tetra-O-propanoyl-β-D-glucofuranosyl) thymine **4**

1,1,1,3,3,3-Hexamethyldisilazane (15.4 mL, 73.5 mmol) was added to a suspension of thymine (630 mg, 5 mmol) and $(NH_4)_2SO_4$ (60 mg, 0.45 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was refluxed for 2 h and the resulting clear solution was concentrated in vacuo to yield the *O,O′*-bis(trimethylsilyl)-thymine as a colourless oil, which was redissolved in dry acetonitrile (25 mL) and 1,2,3,5,6-penta-*O*-propanoyl-β-D-glucofuranose (1.3 g, 2.83 mmol) was added. The reaction mixture was cooled down to 0 °C and trimethylsilyltrifluoromethane sulfonate (1.12 g, 5.03 mmol) was added dropwise. After 5 h of refluxing the mixture was cooled to 0 °C with an ice bath and a saturated solution of $NaHCO_3$ (20 mL) was added to quench the reaction. The product was isolated by extraction with CH_2Cl_2 (4 × 20 mL) and purified by column chromatography ($CHCl_3$:MeOH 99:1). Yield: 1.0 g (69.0%), mp: 53−54 °C, elem. anal. calcd (%) for $C_{23}H_{32}N_2O_{11}$: C 53.90, H 6.29, N 5.47; found: C 53.85, H 6.63, N 5.13.^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 9.33 (s, 1H, NH), 7.56 (d, *J* = 1.5 Hz, 1H; CH═CCH_3), 6.11 (tr, *J* = 2.3 Hz, 1H; H-1), 5.46 (d, *J* = 3.5 Hz, 1H; H-3), 5.38 (m, 1H; H-5), 5.05 (d, *J* = 2.3 Hz, 1H; H-2), 4.62 (dd, *J* = 12.3; 2.3 Hz, 1H; H-6), 4.35 (dd, *J* = 9.6; 3.2 Hz 1H; H-4), 4.09(dd, *J* = 12.3; 5.3 Hz, 1H, H-6′), 2.49−2.25 (m, 8H, CH_2), 1.97 (d, *J* = 1.2 Hz, 3H, CH_3), 1.23−1.06 (m, 12H, CH_3) ppm.$^{13}C\{^{1}H\}$ NMR (100.63 MHz, $CDCl_3$): δ = 174.0 (CO), 173.1 (CO), 172.6 (CO), 171.8 (CO), 163.5 (*C*(O)CCH_3), 150.1 (CO), 134.9 (*C*CH_3), 111.9 (*C*H═C(CH_3)), 88.9 (C-1), 80.4 (C-2), 78.4 (C-4), 73.3 (C-3), 66.8 (C-5), 62.9 (C-6), 27.4 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 12.7 (C(*C*H_3)), 9.0 (CH_3), 8.8 (CH_3), 8.7 (CH_3), 8.6 (CH_3) ppm. MS (ESI^+): *m*/*z*: 535 $[M+Na]^+$.

3.5. 1-(5-Fluorouracil)- β-D-glucofuranosyl **6**

1-(5-Fluorouracil)-2,3,5,6-tetra-O-propanoyl-β-D-glucofuranosyl (5.0 g, 9.68 mmol) was dissolved in saturated ammonia in MeOH (100 mL) and left at room temperature for 24 h. The solvent was removed at reduced pressure and the pure product was isolated by flash column chromatography on silica gel ($CHCl_3$:CH_3OH:NH_3aq 84:15:1). Yield: 2.12 g (75.0%), mp: 186–187 °C decomp., elem. anal. calcd (%) for $C_{10}H_{13}N_2O_7F$: C 41.10, H 4.48, N 9.59; found: C 41.19, H 4.54, N 9.47.^{1}H NMR (400.13 MHz, MeOH): δ = 8.10 (d, *J* = 7.0 Hz, 1H; CH═CF), 5.79 (t, *J* = 1.4 Hz, 1H; H-1), 4.18–4.15 (m, 2H; H-3, H-4), 4.14–4.10 (m, 2H; H-5, H-2), 3.84 (dd, *J* = 11.7; 3.2 Hz, 1H; H-6), 3.69 (dd, *J* = 11.7; 5.6 Hz, 1H, H-6′) ppm.^{13}C{^{1}H} NMR (100.63 MHz, MeOH): δ = 158.1 (*J* = 26.8 Hz, *C*(O)CF), 149.4 (CO), 139.8 (*J* = 231.0 Hz, CF), 125.8 (*J* = 35.3 Hz, *C*H═CF), 92.2 (C-1), 82.9 (C-4), 81.0 (C-2), 74.8 (C-3), 69.3 (C-5), 63.8 (C-6) ppm. MS (ESI$^+$): *m*/*z*: 315 [M+Na]$^+$.

3.6. 1-β-D-Glucofuranosylthimine **7**

Similar to compound **6** starting from 1-(2,3,5,6-tetra-O-propanoyl-β-D-glucofuranosyl)thymine (2.0 g, 4.00 mmol) compound **7** was obtained. Yield: 0.89 g (77.4%), mp: 210–213 °C decomp., elem. anal. calcd (%) for $C_{11}H_{16}N_2O_7$: C 45.83, H 5.59, N 9.72; found: C 45.77, H 5.75, N 9.49.^{1}H NMR (400.13 MHz, MeOH): δ = 7.80 (d, *J* = 1.1 Hz, 1H; CH═CCH_3), 5.80 (d, *J* = 0.9 Hz, 1H; H-1), 4.20–4.10 (m, 4H; H-3, H-4, H-5, H-2), 3.83 (dd, *J* = 11.7; 2.9 Hz, 1H; H-6), 3.68 (dd, *J* = 11.7; 5.3 Hz, 1H, H-6′) ppm. ^{13}C{^{1}H} NMR (100.63 MHz, MeOH): δ = 165.1 (*J* = 26.8 Hz, *C*O), 151.0 (CO), 137.8 (*J* = 231.0 Hz, CCH_3)), 109.0 (*C*H), 92.0 (C-1), 82.4 (C-4), 81.2 (C-2), 75.1 (C-3), 69.3 (C-5), 63.8 (C-6), 11.1 (CH_3) ppm. MS (ESI$^+$): *m*/*z*: 311 [M+Na]$^+$.

3.7. 3,5,6-Bicyclophosphite-1-β-D-glucofuranosyluracil **8**

Hexaethylphosphoroustriamide (0.9 g, 3.6 mmol) was added to a solution of 1-β-D-glucofuranosyluracil **5** (1.0 g, 3.6 mmol) in DMF (50 mL) and the reaction mixture was stirred at 95–99 °C for 5 h. The solvent was removed at reduced pressure and the pure compound was isolated by column chromatography with the ethyl acetate as eluent. Yield: 0.7 g (64.0%), mp: 177–179 °C decomp., elem. anal. calcd (%) for $C_{10}H_{11}N_2O_7P$: C 39.75, H 3.67, N 9.27; found: C 40.06, H 4.00, N 9.25.^{1}H NMR (400.13 MHz, d_6-acetone): δ = 10.10 (brs, 1H, NH), 8.17 (d, *J* = 7.8 Hz, 1H; CH═CH), 5.84 (s, 1H; H-1), 5.72 (d, *J* = 8.3 Hz, 1H; CH═CH), 5.28 (brs, 1H, OH), 5.11 (m, 1H; H-5), 4.62 (dd, *J* = 9.3; 4.4 Hz, 1H; H-6), 4.42–4.39 (m, 2H; H-3, H-4), 4.26 (s, 1H; H-2), 4.01 (dd, *J* = 9.3; 6.4 Hz, 1H, H-6′) ppm.^{13}C{^{1}H} NMR (100.63 MHz, d_6-acetone): δ = 162.7 (CO), 150.8 (CO), 140.0 (CH), 100.8 (CH), 93.3 (C-1), 79.9 (C-2, C-3), 74.6 (*J* = 2.1 Hz, C-4), 71.6 (*J* = 4.4 Hz, C-5), 67.1 (*J* = 5.9 Hz, C-6) ppm. ^{31}P{^{1}H}NMR (161.98 MHz, d_6-acetone): δ = 120.2 ppm. MS (ESI$^+$): *m*/*z*: 325 [M+Na]$^+$.

3.8. 3,5,6-Bicyclophosphite-1-(5-fluorouracil)-β-D-glucofuranosyl **9**

Similar to compound **8** starting from 1-(5-fluorouracil)-β-D-glucofuranosyl **3** (0.9 g, 3.08 mmol) and hexaethylphosphoroustriamide (0.76 g, 3.08 mmol) compound **9** was synthesized. Yield: 0.62 g (62.8%), mp: 242–243 °C decomp., elem. anal. calcd (%) for $C_{10}H_{10}N_2O_7FP$: C 37.51, H 3.15, N 8.75; found: C 37.62, H 3.27, N 8.73.^{1}H NMR (400.13 MHz, d_6-acetone): δ = 8.37 (d, *J* = 7.3 Hz, 1H; CH═CF), 5.80 (s, 1H; H-1), 5.17 (m, 1H; H-5), 4.64 (ddd, *J* = 9.3; 4.7, 0.6 Hz, 1H; H-6), 4.46 (m, 1H; H-3), 4.43 (m, 1H; H-4), 4.31 (s, 1H; H-2), 4.03 (ddd, *J* = 9.3; 5.3, 1.5 Hz, 1H, H-6′) ppm.^{13}C{^{1}H} NMR (100.63 MHz, d_6-acetone): δ = 156.7 (*J* = 26.8 Hz, *C*(O)CF), 148.9 (CO), 140.1 (*J* = 230.8 Hz, CF), 124.3 (*J* = 36.0 Hz, *C*H═CF), 93.4 (C-1), 80.3 (*J* = 3.5 Hz, C-3), 79.7 (C-2), 74.3 (*J* = 2.1 Hz, C-4), 71.7 (*J* = 3.5 Hz, C-5), 67.1 (*J* = 5.6 Hz, C-6) ppm.^{31}P{^{1}H}NMR (161.98 MHz, d_6-acetone): δ = 120.2 ppm. MS (ESI$^-$): *m*/*z*: 319 [M − H]$^-$.

3.9. 3,5,6-Bicyclophosphite-1-β-D-glucofuranosylthimine **10**

Similar to compound **8** starting from 1-β-D-thimineglucofuranosyl **4** (1.0 g, 3.47 mmol) and hexaethylphosphoroustriamide (0.86 g, 3.47 mmol) compound **10** was synthesized. Yield: 0.76 g (69.5%), mp: 241–242 °C decomp., elem. anal. calcd (%) for $C_{11}H_{13}N_2O_7P$: C 41.78, H 4.14, N 8.86; found: C 42.19, H 4.21, N 8.53.^{1}H NMR (400.13 MHz, d_6-acetone): δ = 10.04 (s. 1H, NH), 8.03 (d, *J* = 1.2 Hz, 1H; CH═C(CH_3)), 5.86 (d, *J* = 0.9 Hz, 1H; H-1),5.24 (d, *J* = 4.1 Hz, 1H; HO), 5.12 (m, 1H; H-5), 4.62 (dd, *J* = 9.4; 4.7 Hz, 1H; H-6), 4.41 (m, 2H; H-3, H-4), 4.24 (brs, 1H; H-2), 4.02 (m, 1H, H-6′), 1.88 (d, *J* = 1.2 Hz, 3H; CH_3) ppm.^{13}C{^{1}H} NMR (100.63 MHz, d_6-acetone): δ = 163.4 (C(O)), 150.4 (CO), 135.9 (*C*H═C(CH_3)), 108.8 (CH═*C*(CH_3)), 93.0 (C-1), 80.0 (C-2), 79.7 (*J* = 3.5 Hz, C-3), 74.7 (C-4), 71.7 (C-5), 67.1 (*J* = 5.6 Hz, C-6), 11.8 (CH_3) ppm.^{31}P{^{1}H}NMR (161.98 MHz, d_6-acetone): δ = 120.0 ppm. MS (ESI$^-$): *m*/*z*: 315 [M − H]$^-$.

3.10. Dichlorido(((η^6-p-cymene)(3,5,6-bicyclophosphite-1-β-D-glucofuranosyluracil) ruthenium(II) **11**

A solution of bis[dichlorido(η^6-*p*-cymene)ruthenium(II)] (100 mg, 0.16 mmol) in dry CH_2Cl_2 (5 mL) was added to a suspension of 3,5,6-bicyclophosphite-1-β-D-glucofuranosyluracil (100 mg, 0.33 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 12 h. The solvent was evaporated and the crude product was dissolved in acetone (5 mL) and precipitated by addition of ether, filtered, washed with ether (3 × 5 mL) and dried under vacuum. Yield: 170 mg (85.0%), mp: >220 °C decomp., elem. anal. calcd (%) for $C_{20}H_{25}N_2O_7PRuCl_2$: C 39.48, H 4.14, N 4.60; found: C 39.33, H 4.48, N 4.85.^{1}H NMR (400.13 MHz, *d4-MeOH*): δ = 11.40 (brs, 1H, NH), 7.83 (d, *J* = 8.3 Hz, 1H; CH═CH), 6.23 (d, *J* = 4.4 Hz, 1H; H-1), 5.91 (s, 1H, OH), 5.87 (d, *J* = 5.9 Hz, 1H; H_{Ar}), 5.83 (d, *J* = 5.9 Hz, 1H; H_{Ar}), 5.73 (d, *J* = 4.9 Hz, 1H; H_{Ar}), 5.71 (d, *J* = 4.9 Hz, 1H; H_{Ar}), 5.62 (d, *J* = 8.3 Hz, 1H; CH═CH), 5.21 (m, 1H; H-5), 4.74 (t, *J* = 10.3 Hz, 1H; H-6), 4.65 (s, 1H; H-3), 4.40 (s, 1H; H-4),4.24 (m, 1H, H-6′), 4.14 (d, *J* = 3.9 Hz, 1H; H-2), 2.66 (m, 1H, CH), 2.02 (s, 3H, CH_3), 1.12 (d, *J* = 4.9 Hz, 6H; CH_3) ppm. ^{31}P{^{1}H}NMR (161.98 MHz, *d4-MeOH*): δ = 134.9 ppm. MS (ESI$^+$): *m*/*z*: 573 [M − Cl]$^+$.

3.11. Dichlorido(η^6-p-cymene)(3,5,6-bicyclophosphite-1-(5-flurouracyl)- β-D-glucofuranosyl) ruthenium(II) **12**

Similar to compound **11** starting from bis[dichlorido(η^6-*p*-cymene)ruthenium(II)] (100 mg, 0.16 mmol) and 3,5,6-bicyclophosphite-1-(5-fluorouracil)-β-D-glucofuranosyl (104 mg, 0.33 mmol) compound **12** was obtained with yield: 184 mg (89.0%), mp: >220 °C decomp., elem. anal. calcd (%) for $C_{20}H_{24}N_2O_7PFRuCl_2$: C 38.34, H 3.86, N 4.47; found: C 38.01, H 4.23, N 4.42.^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 10.54 (brs, 1H, NH), 8.10 (d, *J* = 6.4 Hz, 1H; CH═CF), 5.92 (s, 1H; H-1), 5.78 (tr, *J* = 5.9 Hz, 2H; H_{Ar}), 5.66 (d, *J* = 6.4 Hz, 1H; H_{Ar}), 5.62 (d, *J* = 5.9 Hz, 1H; H_{Ar}), 5.30 (m, 1H; H-5), 4.82–4.74 (m, 2H; H-6, H-3), 4.56 (s, 1H; H-4), 4.45 (s, 1H; H-2), 4.35 (m, 1H, H-6′), 2.81 (m, 1H, CH), 2.12 (s, 3H, CH_3), 1.12 (d, *J* = 6.9 Hz, 6H; CH_3) ppm. ^{31}P{^{1}H}NMR (161.98 MHz, DMSO-d_6): δ = 134.5 ppm. MS (ESI$^+$): *m*/*z*: 591 [M − Cl]$^+$.

3.12. Dichlorido((η⁶-p-cymene)(3,5,6-bicyclophosphite-1-β-D-glucofuranosylthimine) ruthenium(II) **13**

Similar to compound **11** starting from bis[dichlorido(η⁶-*p*-cymene)ruthenium(II)] (100 mg, 0.16 mmol) and 3,5,6-bicyclophosphite-1-β-D-glucofuranosylthimine **l** (104 mg, 0.33 mmol) compound **13** was obtained with yield: 180 mg (88.0%), mp: >220 °C decomp., elem. anal. calcd (%) for $C_{21}H_{27}N_2O_7PRuCl_2$: C 40.52, H 4.37, N 4.50; found: C 40.36, H 4.41, N 4.28.^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.59 (d, J = 1. Hz, 1H; CH═CCH$_3$), 6.31 (d, J = 4.7 Hz, 1H; H-1), 6.06 (d, J = 2.6 Hz, 1H; O), 5.92 (m, 2H; H$_{Ar}$), 5.78 (tr, J = 7.0 Hz, 2H; H$_{Ar}$), 5.29 (m, 1H; H-5), 4.88 (tr, J = 9.4 Hz, 1H; H-6), 4.78 (d, J = 2.0 Hz, 1H; H-3), 4.47 (q, J = 2.6 Hz,1H; H-4), 4.43 (m, 1H, H-6′), 4.34 (dd, J = 4.7, 2.6 Hz,1H; H-2), 2.80 (m, 1H, CH), 2.12 (s, 3H, CH$_3$), 1.99 (s, 3H, CH$_3$), 1.22 (d, J = 6.7 Hz, 6H; CH$_3$) ppm. ^{31}P{^{1}H}NMR (161.98 MHz, DMSO-d_6): δ = 134.2 ppm. MS (ESI$^+$): m/z: 587 [M − Cl]$^+$.

3.13. Ru$_3$(CO)$_{11}$(3,5,6-bicyclophosphite-1-β-D-glucofuranosyluracil) **14**

A solution of 3,5,6-Bicyclophosphite-1-β-D-glucofuranosyluracil **8** (100 mg, 0.33 mmol), in CH_2Cl_2 (5 mL) was added to a solution of $Ru_3(CO)_{12}$ (211 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) under nitrogen at room temperature. The reaction mixture was stirred for 5 min and Me_3NO (24.8 mg, 0.31 mmol) was added. The reaction was stirred for 12 h and the solvent was removed and the compound isolated by flash chromatography (eluent CH_2Cl_2:Et_2O 4:1). Yield 100 mg (33%), m.p. 160–167 °C decomp., elem. anal. calcd.(%) for $C_{21}H_{11}O_{18}PN_2Ru_3$*0.33$Et_2O$: C 28.59, H 1.54, N 2.99; found: C 28.43, H 1.68, N 3.00.^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 10.33 (brs, 1H, NH), 8.37 (d, J = 8.2 Hz, 1H; C*H*═CH), 5.91 (dd, J = 8.3, 1.7 Hz, 1H; H-1), 5.84 (brs, 1H; OH), 5.80 (s, 1H; CH═C*H*), 5.20 (d, J = 15.2 Hz, 1H, H-5), 4.76 (d, J = 1.4 Hz, 1H, H-6), 4.61 (t, 2H; H-3, H-4), 4.55 (d, J = 2.9 Hz; H-2), 4.35–4.31 (m, 1H, H-6′) ppm. ^{31}P{^{1}H}NMR (161.98 MHz, $CDCl_3$): δ = 150.78 ppm. MS (ESI$^+$): m/z: 914 [M − H]$^-$.

3.14. Ru$_3$(CO)$_{10}$(3,5,6-bicyclophosphite-1-β-D-glucofuranosyluracil)$_2$ **15**

Compound **15** was prepared similar to that of **14** starting from 3,5,6-Bicyclophosphite-1-β-D-glucofuranosyluracil **8** (200 mg, 0.66 mmol), $Ru_3(CO)_{12}$ (211 mg, 0.33 mmol) and Me_3NO (74.4 mg, 0.93 mmol). Yield 170 mg (43.3%), m.p. 165–168 °C decomp., elem. anal. calcd.(%) for $C_{30}H_{22}O_{24}P_2N_4Ru_3$: C 30.34, H 1.87, N 4.72; found: C 30.70, H 2.41, N 4.41.^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 10.57 (brs, 2H, NH), 8.87 (d, J = 8.3 Hz, 2H; C*H*═CH), 5.81 (s, 2H; H-1), 5.68 (s, 2H; OH), 5.54 (d, J = 8.0 Hz, 2H; CH═C*H*), 4.98 (d, J = 12.5 Hz, 2H, H-5), 4.37 (d, J = 1.6 Hz, 2H, H-6), 4.29–4.21 (m, 4H; H-3, H-4), 4.12 (brs, 2H; H-2, H-6′) ppm. ^{31}P{^{1}H}NMR (161.98 MHz, $CDCl_3$): δ = 150.12 ppm. MS (ESI$^+$): m/z: 1212 [M+Na]$^+$.

3.15. Ru$_3$(CO)$_9$(3,5,6-bicyclophosphite-1-β-D-glucofuranosyluracil)$_3$ **16**

Compound **16** was prepared similar to that of **14** starting from 3,5,6-Bicyclophosphite-1-β-D-glucofuranosyluracil **8** (300 mg, 0.99 mmol), $Ru_3(CO)_{12}$ (211 mg, 0.33 mmol) and Me_3NO (74.4 mg, 1.24 mmol). Yield 338 mg (70.1%), m.p. >220 °C decomp., elem. anal. calcd.(%) for $C_{39}H_{33}N_6O_{30}P_3Ru_3$*$CH_2Cl_2$: C 31.06, H 2.28, N 5.43; found: C 31.10, H 2.54, N 5.45.^{1}H NMR (400.13 MHz, d_6-acetone): δ = 10.22 (brs, 3H, NH), 8.14 (d, J = 7.5 Hz, 3H; C*H*═CH), 5.88 (s, 3H; H-1), 5.65 (d, J = 8.2 Hz, 3H; CH═C*H*), 5.42 (brs, 3H; OH), 5.20 (d, J = 10.4 Hz, 3H, H-5), 4.78–4.67 (m, 6H; H-3, H-4), 4.59 (brs, 3H, H-6), 4.39–4.33 (m, 6H; H-2, H-6′) ppm. ^{31}P{^{1}H}NMR (161.98 MHz, d_6-acetone): δ = 150.93 ppm. MS (ESI$^+$): m/z: 1486 [M+Na]$^+$.

4. Conclusions

In conclusion, we have prepared and characterized a series of stable and water-soluble phosphites based on the glucose and utilized those new ligands in the synthesis of RAPTA-type Ru(II)-arene compounds and Ruclusters. Ru(II)-arene compounds do not show any significant antiproliferative activity, while for the cluster compounds a change in the number of phosphorus ligands completely switch antiproliferative activity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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