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[Tris(pyrazolyl)methane]ruthenium Complexes Capable of Inhibiting Cancer Cell Growth

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The [tris(pyrazolyl)methane]ruthenium complexes [(κ^3-tpm)RuCl(solv)$_2$]PF_6 [tpm = tris(pyrazolyl)methane; solv = MeCN, dmso] and [(κ^3-tpm)RuCl(LL)]PF_6 [LL = κ^2-dppe, κ^2-dppp, κ^2-dppb, $(PMePh_2)_2$] have been prepared, characterized and screened in vitro for their antiproliferative properties against the MCF-7 (breast) and HeLa (cervical) cancer cell lines by using the MTT assay. Although the MeCN and dmso complexes showed no activity under the conditions used, the phosphane complexes exhibited remarkable cytotoxic behaviour.

Introduction

Platinum metal drugs continue to occupy a prominent position in the arsenal of anticancer agents used in the treatment of various malignancies. Following the approval of the first-generation drug *cisplatin* in 1978, a number of variants have emerged, with several receiving worldwide (e.g., *carboplatin* and *oxaliplatin*) or at least limited (e.g., *nedaplatin*, *lobaplatin* and *heptaplatin*) approval as chemotherapeutic agents for clinical use.[1] Although there have been some improvements in reducing the undesirable toxicities often associated with these clinical drugs,[1b] it remains unclear whether or not they are effective beyond the narrow range of tumours against which *cisplatin* is already active.[2] Furthermore, comparatively poor aqueous solubilities and the development of tumour resistance towards these drugs remain as current challenges in their clinical applications.[3]

The issues surrounding the platinum-based drugs continue to drive the intense search for new metal-based anticancer compounds,[4] and ruthenium has played a prominent role in this capacity.[5] Ruthenium complexes bearing nitrogen-containing heterocyclic ligands have received considerable attention. For example, (arylazopyridine)-,[6] (aryliminopyridine)-[7] and (polypyridyl)ruthenium[8] complexes have shown promise as anticancer agents. The ruthenium drug candidates NAMI-A[9] (an antimetastatic agent) and KP1019[10] are presently undergoing clinical evaluation. A large number of other preclinical candidates have also displayed encouraging potential, in particular the piano-stool ruthenium complexes independently studied by Dyson[11] and Sadler[12] which contain, as a common group, a coordinated face-capping arene ligand. We contemplated employing a ligand with similar facially coordinating properties, but that could also be easily modified, and thus allow access to a wide range of candidates for screening. Indeed, research emerging from the Alessio group has revealed that the arene ligand is not a necessary feature for activity, and that substituting the arene ligand for other face-capping ligands (e.g., 1,4,7-trithiacyclononane) might yield new classes of piano-stool-type anticancer complexes.[13] The tris(pyrazolyl)methane (tpm) ligand[14] is a flexible polydentate ligand that, in its κ^3 form, is isoelectronic with the η^6-arene ligand. What is especially encouraging is that a number of (tpm)metal complexes have already proven to function as potent cytotoxic agents in vitro.[15] One particular advantage of the tpm ligand is that the basic scaffold is readily modified, both on the pyrazole rings[14,16] and at the bridgehead carbon atom,[17] so that the electronic, steric and coordination properties can be tailored as desired. In addition, simple modifications to the tpm ligand can impart aqueous solubility on its complexes.[18] Included along with the basic (tpm)ruthenium scaffold, we also chose to focus initially on phosphanes as supporting ligands, since there are extensive reports of (phosphane)metal complexes displaying antitumour activities, particularly for the coinage metals.[19]

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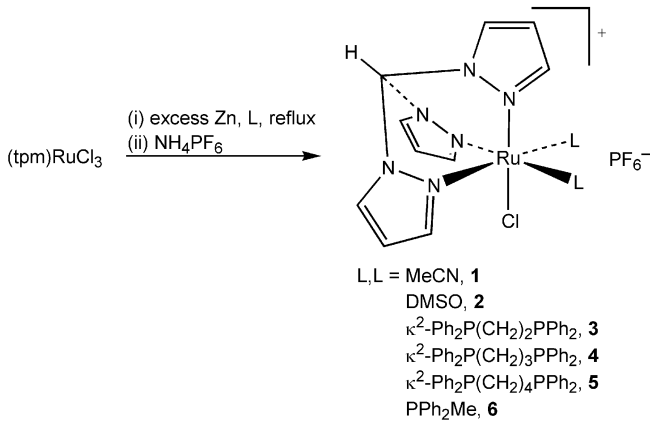
Results and Discussion

Our initial efforts were directed towards establishing a practical synthetic strategy which would allow access to our target (tpm)ruthenium complexes, and also allow the auxiliary ligand environment to be varied easily. We reasoned that this would eventually enable us to synthesize and screen a wide variety of candidates for their antiproliferative properties. A zinc reduction method[20] employing (tpm)-$RuCl_3$ as a precursor[21] has been reported; however, no experimental details were provided. We chose to experiment with this approach, and eventually found it to be a relatively simple and versatile method of preparing our target complexes in reasonable yields. For example, reductions of methanol suspensions of (tpm)$RuCl_3$ with a slight excess of zinc dust in the presence of excess MeCN or dmso, followed by salt metathesis with $(NH_4)PF_6$, yielded the solvent complexes [(κ^3-tpm)RuCl(solv)$_2$]PF_6 [solv = MeCN (**1**), dmso (**2**)] in good yields (Scheme 1). Structurally similar solvent complexes {e.g., [(κ^3-tpm)$RuCl_2$(dmso)]} have been reported previously, but were isolated from ethanol mixtures of *cis*-[$RuCl_2$(dmso)$_4$] and tpm.[22] Originally we had hoped the solvent ligands of **1** and **2** would be readily substituted for our intended ligands. Indeed, the previously reported synthesis of [(κ^3-tpm)RuCl(κ^2-dppe)]PF_6 (**3**) {which can be prepared through a lengthy, multi-step process beginning with [$RuCl_2$(COD)]$_n$},[23] suggested our proposed target complexes were accessible. Unfortunately, complex **1** proved to be poorly labile, although the dmso ligands of **2** could be replaced by phosphanes under forcing conditions (e.g., in refluxing 1,2-dichlorobenzene over 24 h). Alternatively, and more conveniently, when the same zinc reduction procedure is applied, but instead in the presence of a phosphane, our target complexes [(κ^3-tpm)RuCl(LL)]PF_6 [LL = κ^2-dppe (**3**), κ^2-dppp (**4**), κ^2-dppb (**5**), ($PMePh_2$)$_2$ (**6**)] could be isolated by using conventional workup procedures. The phosphane complexes **3**–**6** are analogous to the complexes [(κ^3-tpm)RuCl(PPh_3)$_2$]X (X = Cl or BF_4),[24] which are prepared from $RuCl_2(PPh_3)_3$ and tpm. In separate experiments, we explored replacing the triphenylphosphane ligands of these complexes as a possible alternate pathway to **3**–**6**. Unfortunately, the triphenylphosphane ligands were observed to be poorly labile, despite investigating a variety of experimental conditions. Complexes **1**–**6** were only slightly soluble in water, but dissolved more readily in organic solvents such as chloroform, dichloromethane, acetone and dmso at the concentrations examined (up to ca. 50 mM).

The X-ray crystal structure of the dppp complex **4** (Figure 1) confirmed the general structure proposed for complexes **1**–**6**.[25] The ruthenium centre of **4** adopts an approximately octahedral geometry, with the tpm ligand occupying a face of the octahedron, and the chelate phosphane and chlorido ligands occupying the remaining positions. The distances between the ruthenium atom and the metal-bound pyrazolyl nitrogen atoms compare well with those observed in the structure of [(κ^3-tpm)RuCl(κ^2-dppe)]PF_6.[23] These same distances are also asymmetric, with longer distances observed for the pyrazolyl rings *trans* to the dppp



Scheme 1. General synthetic strategy for preparing complexes **1**–**6**.

phosphorus atoms [2.124(3) Å and 2.197(3) Å] compared to the pyrazolyl ring *trans* to the chlorido ligand [2.095(3) Å], thus illustrating the greater *trans* influence of the dppp ligand (vs. the chlorido ligand). The somewhat constrained "bite" of the tpm ligand in **4** is exemplified by the N–Ru–N bond angles [82.22(10), 82.67(10), 87.44(10)°], which are smaller than the 90° expected for perfect octahedral geometry. The three methylene spacers allow the dppp ligand in **4** to adopt a P–Ru–P bond angle [93.58(3)°] close to the ideal angle of 90°. Not surprisingly, by removing one of the methylene links, as in [(κ^3-tpm)RuCl(κ^2-dppe)]PF_6, leads to a smaller bite angle;[23] the corresponding bis(triphenylphosphane) complex [(κ^3-tpm)RuCl(PPh_3)$_2$]Cl has a larger P–Ru–P bond angle [103.9(1)°] than **4** as a consequence of the steric bulk of the PPh_3 ligands.[24]

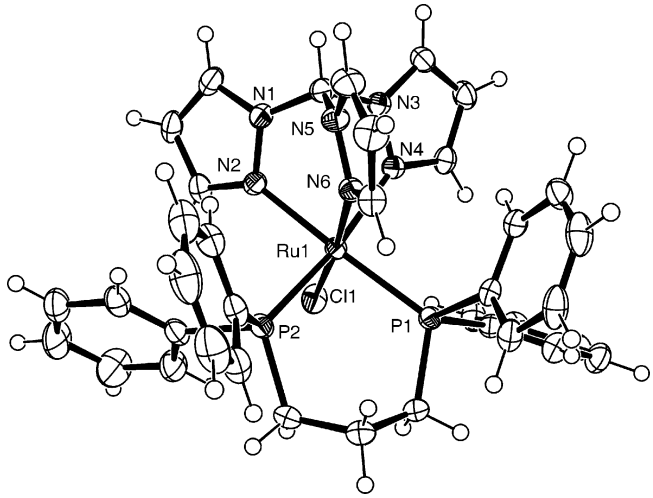


Figure 1. ORTEP representation of the cation of complex **4**. Selected bond lengths [Å] and angles [°]: Ru(1)–N(6) 2.095(3), Ru(1)–N(2) 2.124(3), Ru(1)–N(4) 2.197(3), Ru(1)–P(2) 2.3035(9), Ru(1)–P(1) 2.3235(9), Ru(1)–Cl(1) 2.4056(8); N(2)–Ru(1)–N(4) 82.22(10), N(6)–Ru(1)–N(4) 82.67(10), N(6)–Ru(1)–N(2) 87.44(10), N(2)–Ru(1)–P(1) 174.43(8), N(4)–Ru(1)–P(2) 172.12(8), N(6)–Ru(1)–Cl(1) 173.59(8), P(2)–Ru(1)–P(1) 93.58(3).

The complexes **1**–**6** were readily characterized by NMR spectroscopy. Perhaps the most revealing of their structures, the ^{1}H NMR spectra show (along with the signal attributed

to the unique bridgehead hydrogen atom) two sets of three tpm resonances with intensities in the ratio of 2:1 corresponding to the three pyrazolyl ring hydrogen atoms in the 3-, 4-, and 5-positions.[24] Thus, the C_s symmetry of these complexes requires the two pyrazolyl rings *trans* to the solvent ligands in **1** and **2**, and *trans* to the phosphorus atoms in **3**–**6**, to be equivalent, with the pyrazolyl ring *trans* to the chlorido ligand being unique. Each of the phosphane complexes shows a singlet in its respective $^{31}P\{^1H\}$ NMR spectrum at room temperature, also consistent with overall C_s symmetry. We note that, given the ability of the dppb ligand to bridge metal centres,[26] complex **5** could also adopt the alternative structure $\{[(\kappa^3\text{-tpm})RuCl(\mu\text{-dppb})]PF_6\}_2$, yet still give NMR and microanalytical data consistent with a monomeric structure. Unfortunately, X-ray quality crystals were not obtained.

We next turned our attention towards screening complexes **1**–**6** for their antiproliferative properties (Table 1). For comparison, we also included in these studies an arene analogue of complex **4**, specifically $[(\eta^6\text{-}p\text{-cymene})RuCl(\kappa^2\text{-dppp})]Cl$,[27] as well as *cisplatin*.

Table 1. Growth inhibition of MCF-7 (breast) and HeLa (cervical) cancer cells after 72 h of exposure to complexes **1**–**6**, $[(\eta^6\text{-}p\text{-cymene})RuCl(\kappa^2\text{-dppp})]Cl$ and *cisplatin*.

Complex	IC_{50} [μM]	
	MCF-7	HeLa
1	>50	>50
2	>50	>50
3	8.1 ± 4.6	4 ± 0.00
4	2.9 ± 0.07	6.9 ± 1.31
5	2.9 ± 0.07	5.8 ± 0.35
6	4.7 ± 0.07	7.4 ± 0.21
$[(\eta^6\text{-}p\text{-cymene})RuCl(\kappa^2\text{-dppp})]Cl$	0.8 ± 0.00	1.4 ± 0.07
Cisplatin[a]	>18	12.4 ± 0.85

[a] Supplied as a saline solution (see the Supporting Information).

MTT assays[28] were performed in vitro for each complex by using the MCF-7 (breast) and HeLa (cervical) cancer cell lines. The effects of **1**–**6**, $[(\eta^6\text{-}p\text{-cymene})RuCl(\kappa^2\text{-dppp})]Cl$ and *cisplatin* on the growth of these cell lines were evaluated after 72 h. The solvent complexes **1** and **2** showed no significant cytotoxicity under the conditions employed. However, substituting the solvent ligands with phosphane ligands impacts their activity dramatically, as complexes **3**–**6** displayed exceptional cytotoxic behaviour, and were more active than *cisplatin*, even on the MCF-7 breast cancer cells which showed greater resistance towards *cisplatin* than the cervical cancer HeLa cell line. The arene complex $[(\eta^6\text{-}p\text{-cymene})RuCl(\kappa^2\text{-dppp})]Cl$ also displayed remarkable activity. Perhaps these results are not unexpected since there are other reports of (phosphane)ruthenium complexes exhibiting marked cytotoxicity.[29] For example, the complexes [CpRu(PP)L]OTf [PP = dppe, $(PPh_3)_2$; L = pyridazine, 1,3,5-triazine][29b] yielded IC_{50} values in the submicromolar range against the LoVo human colon adenocarcinoma and MiaPaCa pancreatic cancer cell lines. The differences in activity between the complex with monophosphanes (**6**) and those with chelate phosphanes (**3**, **4**, and **5**) were only marginal, suggesting the linkage between donor atoms is not crucial here. Likewise, chelate ring size does not appear to influence activity dramatically.

It is not obvious at this stage why the phosphane complexes display such promising cytotoxic behaviour. The enhanced cytotoxicities we observed might possibly be related to an increase in lipophilic character (vs. **1** and **2**), which could facilitate cellular uptake. Organophosphanes can be cytotoxic, and some (phosphane)gold complexes are thought simply to function as a vehicle and transport the phosphane ligand to the cancer cells.[30] Although we have not yet unequivocally ruled out this scenario, we see no evidence of phosphane dissociation occurring in solution (^{31}P NMR, $[D_6]$dmso) even over several days. Metal chloride complexes in some cases can undergo chlorido ligand substitution with a polar, coordinating solvent.[31] Again, the NMR spectra of complexes **3**–**6** in $[D_6]$dmso (the protio solvent was used in the growth inhibition assays; see the Supporting Information) remain unchanged at room temperature up to 72 h, suggesting complexes **3**–**6** resist solvolysis and remain intact in this coordinating solvent. Finally, there is, as yet, no clear indication of the role of the tpm ligand in the active complexes, especially since the phosphane variants show activities comparable to the arene complex also examined as part of this investigation. We note that the identity of the arene ligand in $[(\eta^6\text{-arene})RuCl(LL)]^+$ (LL = chelate ligand) does influence the cytotoxicity of the complex.[32] This will also be the focus of future studies.

Conclusions

The (phosphane)(tpm)ruthenium complexes examined as part of this preliminary study have displayed very promising cytotoxic activity against the MCF-7 and HeLa cell lines. At this point, the roles of the phosphane and tpm ligands are unclear; however, we hope that our continued investigation of these and related complexes will provide more insight into their function and activity.

Experimental Section

General: A sample synthetic procedure for one of the active complexes (**4**) is provided here. All of the remaining experimental details are provided in the Supporting Information.

$[(\kappa^3\text{-tpm})RuCl(\kappa^2\text{-dppp})][PF_6]$ (4): A flask was charged with (tpm)$RuCl_3{\cdot}1.5H_2O$ (0.243 g, 0.541 mmol), dppp (0.224 g, 0.543 mmol) and Zn dust (0.055 g, 0.841 mmol). Next, MeOH (30 mL) was added, and the solution was stirred at reflux for 25 h. After this time, a dark green solid had deposited from a clear orange supernatant. The mixture was allowed to cool to room temperature before filtering through Celite into a flask containing NH_4PF_6 (0.088 g, 0.540 mmol). The mixture was stirred at reflux for 1 h before the volatiles were removed under reduced pressure. The green-yellow residue was redissolved in CH_2Cl_2 (20 mL) and filtered through Celite. The volatiles were removed from the orange-yellow filtrate under reduced pressure to yield an orange-yellow solid. The solid was washed with H_2O (30 mL) followed by diethyl ether (20 mL).

The solid was dried under reduced pressure. Yield 0.230 g (47%). $C_{37}H_{36}ClF_6N_6P_3Ru{\cdot}H_2O$ (926.07): calcd. C 47.98, H 4.13, N 9.08; found C 48.03, H 3.97, N 8.93. ^{1}H NMR (499.9 MHz, 22°C, $CDCl_3$): δ = 9.11 (s, 1 H, Pz_3CH), 8.30 (br. m, 2 H, H5 of Pz), 8.20 (br. m, 1 H, H5′ of Pz), 7.74 (br. m, 4 H, Ph), 7.43 (m, 2 H, Ph), 7.34 (m, 4 H, Ph), 7.31 (m, 2 H, Ph), 7.10 (m, 4 H, Ph), 6.65 (br. m, 2 H, H3 of Pz), 6.56 (br. m, 4 H, Ph), 6.12 (m, 2 H, H4 of Pz), 5.32 (m, 1 H, H4′ of Pz), 5.08 (m, 1 H, H3′ of Pz), 3.01 (m, 2 H, CH_2 of dppp), 2.93 (m, 1 H, CHH of dppp), 2.88 (m, 2 H, CH_2 of dppp), 2.38 (m, 1 H, CHH of dppp) ppm. $^{31}P\{^1H\}$ NMR (202.3 MHz, $CDCl_3$, 22°C): δ = 32.9 (s, dppp), –142.6 (sept, PF_6^-) ppm.

Supporting Information (see footnote on the first page of this article): Complete details on the synthesis of complexes **1**–**6**, the X-ray crystallographic study of **4**,[33] and the MTT assays.

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[33] CCDC-735039 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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