A Trojan Horse For Cancer Cells

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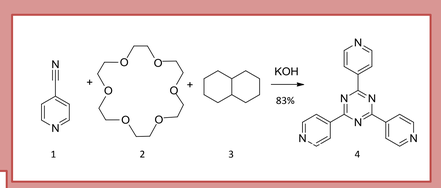
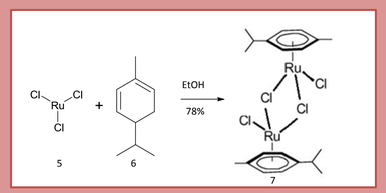
Introduction: For many years, platinum based drugs, such as cis-platin, have been used to treat cancer. These drugs, however, can cause some severe side effects such as nephrotoxicity, neurotoxicity, and vomiting.[1] Ruthenium based cancer drugs have now been studied in place of platinum for various reasons.[1] The most important reason for this is because ruthenium is less toxic than platinum. Furthermore, ruthenium has many oxidation states with a low energy barrier to transition between these states which allows for the complex to interconvert easily. Ruthenium also possesses many of the same characteristics as iron since they belong in the same group. Thus, ruthenium can mimic iron by bonding with nitrogen and sulfur donor molecules found in proteins and be delivered to the tumor by the body's natural uptake and transport of iron to blood cells.[1] Since cancer cells need a lot of iron to sustain their rapid growth, most of the cancer drug will be delivered to the tumor.[1] Finally, ruthenium has a slower ligand exchange rate which makes it more kinetically stable and inert where the complex can remain intact until it reaches its target.

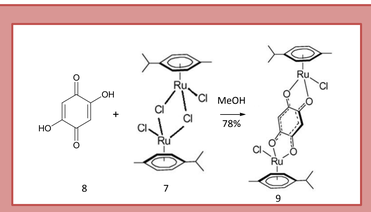
Discussion: The metalla-complex created was produced in order to increase the selectivity of the cancer drug being delivered to the tumor and decrease the selectivity of it being delivered to healthy tissues. This macromolecule can do this by targeting the enhanced permeability and retention (EPR) effect in tumors.[1] The EPR effect arises in tumors from an increase in angiogenesis by neovascularization. Here, the tumor becomes abnormal in form and starts to lack lymphatic drainage where it becomes much larger than healthy plasma. Therefore, the macromolecule will only be able to penetrate through the enlarged tumor cells but not through the small blood vessels. Once inside the tumor, the cancer drug is leached from the metalla-complex that acts as a carceplex.

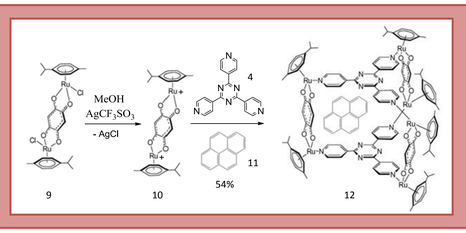
Conclusion: By combining the positive medicinal properties of ruthenium based drugs with the EPR effect of the tumor, a ruthenium based metalla-complex was created. This compound was produced through a four step processes where all of the compounds were confirmed using ^{1}H NMR and IR spectroscopy.

Reactions:









Experimental:

Step 1: 4-cyanopyridine (1), 18-crown-6 (2), and decalin (3) were stirred under reflux at 200°C in KOH before being washed in hexanes. A sublimation under reduced pressure then produced 2,4,6-tris(4-pyridyl)-1,3,5-triazine (4) as a yellow solid (0.981 g, 83%): mp >300°C (lit[2] >300°C); ν_{max} (neat) 3037.54, 1317.42 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 8.15 (d, 6 H), 8.26 (d, 6H).

Step 2: Ruthenium trichloride (5) and α-phellandrene (6) were stirred under reflux in ethanol for 4 hours before being gravity filtered to produce ruthenium complex **7** as a maroon solid (1.801 g, 78%): ν_{max} (neat) 2959.96, 1388.59 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.255 (d, 12H), 2.23 (s, 6H), 2.29 (sep, 2H), 5.4 (d, 4H), 5.5 (d, 4H).

Step 3: 2,5-dihydroxy-1,4-benzoquinone (8) and ruthenium complex **7** were stirred in methanol for 2 hours before being vacuum filtered to produce ruthenium complex **9** as a dark brown solid (0.158 g, 78%): ν_{max} (neat) 1509.05, 1373.73, 1254.78 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 1.255 (d, 12 H), 2.23 (s, 6H), 2.29 (sep, 2H), 5.4 (d, 4H), 5.65 (d, 4H), 5.8 (s, 2H).

Step 4: Ruthenium complex **9** and $AgCF_3SO_3$ were stirred in methanol for 2 hours to make a reaction intermediate **10**. Tpt **4** and pyrene (11) where then added and allowed to stir for 2 days before removing the methanol *in vacuo* to produce a red solid. This solid was re-dissolved in DCM and precipitated out with ether to produce the cage complex **12** as a black solid (0.048g, 54%): ν_{max} (neat) 1512.61, 1372.60, 1253.00, 1222.54, 1150.84, 1027.13, 808.27 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.40 (d, 36H), 2.24 (s, 18 H), 2.98 (sep, 6H), 6.00 (d, 12 H), 6.18 (s, 6H), 6.22 (d, 12H), 8.07 (d, 12H), 8.58 (d, 12 H).

Results:

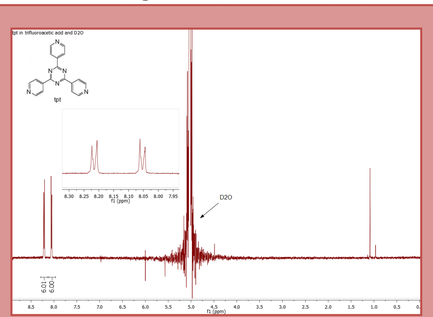


Figure 1: ^{1}H NMR for tpt complex **4** in $C_2HF_3O_2$ and D_2O

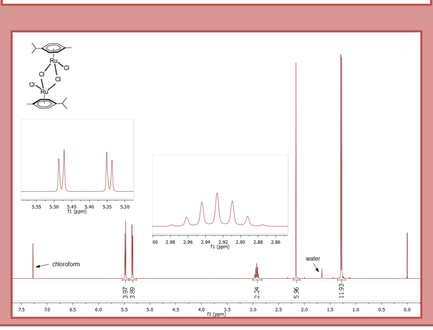


Figure 2:^{1}H NMR for [Ru2(*p*-Pr^{i}C6H4Me)2(μ-Cl)Cl]$_2$(7) in $CDCl_3$

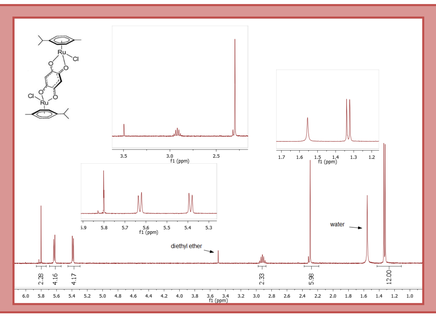


Figure 3:^{1}H NMR for [Ru_2(p-Pr^i(C_6H_4Me)$_2$($C_6H_2O_4$)Cl_2] (9) in $CDCl_3$

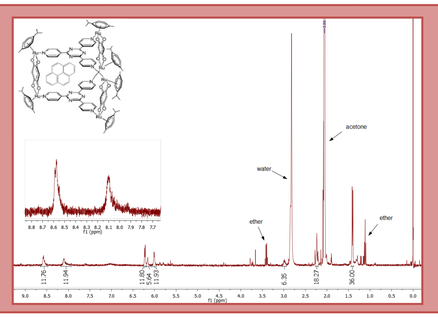


Figure 4: ^{1}H NMR for [$C_{16}H_{10}$⊂Ru_6(pPr^i(C_6H_4Me)$_2$($C_6H_2O_4$)Cl_2]][CF_3SO_3] (12) in acetone-d_6

References:

1) Mattsson, J.; Zava, O.; Renfrew, A. K.; Sei, Y.; Yamaguchi, K.; Dyson, P. J.;Therrien, B. *Dalton Trans.* **2010**, *39, 8254.*
2) Anderson, H. L.; Anderson, S.; J. Sanders, K. M. *J. Chem. Soc., Perkin Trans.,* **1995**, *2231-2245.*
3) Bennett, M. A.; Huang, T.-N.; Matheson, T. W.; Smith, A. K. *Inorganic Synthesis,* 21st ed.; John Wiley: New York, 1982, 74-76.
4) Therrien, B.; Suss-Fink, G.; Govindaswamy, P.; Renfrew, A. K.; Dyson, P. J.*Angew. Chem., Int. Ed.*, **2008**, *47, 3773*.

Future work: Pyrene was chosen for the encapsulation process since it possesses fluorescence capabilities. So for future work, the metalla-complex obtained will be injected into tumor cells where the uptake and release of the pyrene can be monitored by fluorescence spectroscopy.

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