Organoruthenium Anticancer Agents: Scope and Reactivity

Mark Ringenberg Literature Seminar November 6, 2007

Organometallic compounds have emerged as attractive scaffolds for drug development due to the reactivity that is intrinsic to metal centers and ligand variability leads to several geometries.[1,2] Cisplatin, $PtCl_2(NH_3)_2$, and related platinum based drugs have been extensively used as anti-cancer treatments and are highly effective, but suffer from several problems: some cancer lines are resistant to Cisplatin, and these drugs cause severe side effects. Tremendous effort is being expended to develop better platinum drug therapies, but this talk will focus on recent advances in the use of alternative metal centers for organometallic based drugs, primarily those based on ruthenium.

Interest in ruthenium based complexes arose from Clarke *et al*. discovery that the ruthenium(III) ammine $RuCl_3(NH_3)_3$ showed anticancer activity but was insufficiently soluble to be a competitive anti-cancer agent.[3] Two ruthenium compounds, NAMI-A[4] and KP1019[5] (**Figure 1**), were developed from Clarke's work that have favorable solubility and have displayed anticancer and antitumor activity in clinical trials.[6]

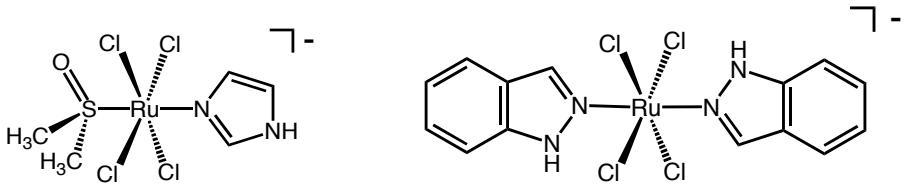


Figure 1: NAMI-A and KP1019 anticancer ruthenium drugs

Ruthenium complexes tend to adopt octahedral coordination geometries versus the square planar geometries exhibited by platinum(II). Organoruthenium complexes are appealing in drug design because, like platinum complexes, they exhibit slow rates of ligand dissociation in biological systems, allowing for a more controlled release of active drug.[7] In drug design, ligand stability is important; fast ligand dissociation causes deactivation of the drug before it reaches target cells, resulting in a decrease in drug activity and an increase in the potential for side effects.

Ruthenium-arene complexes are substitutionally inert under biological systems,[8] and serve as an excellent platform for drug development in cancer therapies.[9-12] Ancillary ligands, such as maltolato, modify the target of drug binding to different DNA nucleobases such as adenine;[11] in comparison Cisplatin preferably binds guanine due to presence of the H-bonding amine ligand (**Figure 2**).[13] For the ruthenium complexes, chloride aides transport of the drug into the cell due to the concentration gradient between inter- and extra- cellular chloride concentrations. The activated drug is formed when dissociation of the chloride occurs; opening a coordination site on ruthenium that can bind DNA.

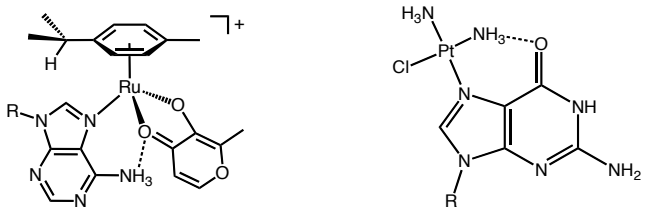
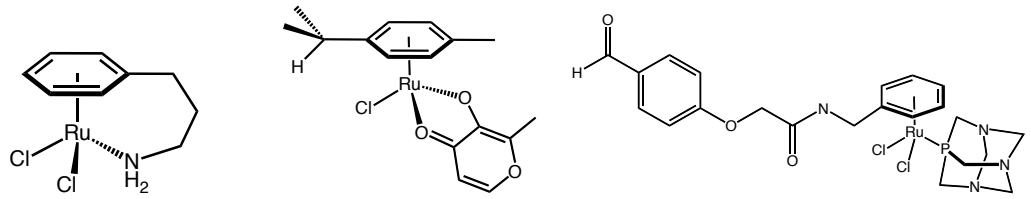


Figure 2. Comparisons of ruthenium-maltalato biding to adenine (Left) vs platinum binding to guanine (Right)

Organoruthenium systems developed by Sadler *et al*. (**Figure 3**) have not been shown to be cytotoxic but they do transport into cells intact better than Cisplatin due to the presence of the lipophilic arene.[10, 14] Sadler's group has also revealed that chloride dissociation is the limiting factor to the effectiveness of organoruthenium compounds in causing cell death. Dyson *et al*. have demonstrated that ruthenium arene complexes containing a 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]-decane (RAPTA) ligand exhibit favorable pharmacological anti-tumor activity (**Figure 3**).[15] To increase the effectiveness of this system Dyson *et al*. proposed to link the arene group to a biocompatible macromolecule, in this case a modified recombinant human serum albumin (rHSA). Although ruthenium RAPTA has limited anti-cancer activity, the effective activity was found to be much higher when the organometallic drug was tethered to rHSA, which causes better delivery of the ruthenium complex into the target cell.



1 **2** **3**

Figure 3. Two ruthenium arene systems developed by Sadler **(1,2)** and RAPTA with protein rHSA linker **(3)**

Meggers *et al*. recently developed a ruthenium anti-cancer drugs that has a different mechanism than cancer chelation therapy. The system was designed to act as an analog of staurosporine, an effective organic drug protein kinase inhibitor (**Figure 4**).[16] The organometallic analog of staurosporine worked better than staurosporine in inhibiting growth of cancer cells.

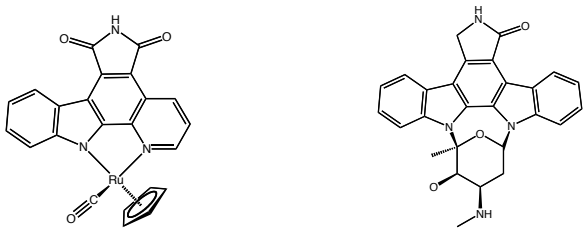


Figure 4 ruthenium analog of staurosporine (Left) and comparison to staurosporine (Right)

The octahedral coordination geometry favored by ruthenium(II) complexes makes them attractive because they are more tunable anticancer agents than platinum(II) compounds. The recent discoveries of organoruthenium anticancer drugs suggest that other organometallic compounds may also be useful as therapeutic agents.

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