

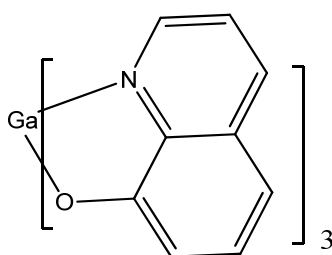
**Update, September 2009**  
**John Spencer, University of Greenwich**

### **Current Metallodrugs in Cancer**

Metals occupy an important role in oncology, exemplified by platinum complexes, outlined in Chapters 9.3.4 and 21.2.3.2 of *An Introduction to Medicinal Chemistry, 4<sup>th</sup> Edition*. The low spectrum of cancers that can be treated, the side effects e.g. nephrotoxicity (kidney toxicity) and tumour resistance to these drugs have necessitated the search for newer, more effective drugs. Many platinum agents have been assessed with a relatively small degree of success and a number of alternative metal prototype drugs have been investigated with the goal of circumventing many of the shortcomings of *cis*-platin and its congeners. A small selection of investigational “metallodrugs” is presented below and subdivided according to the metal.

#### **Gallium**

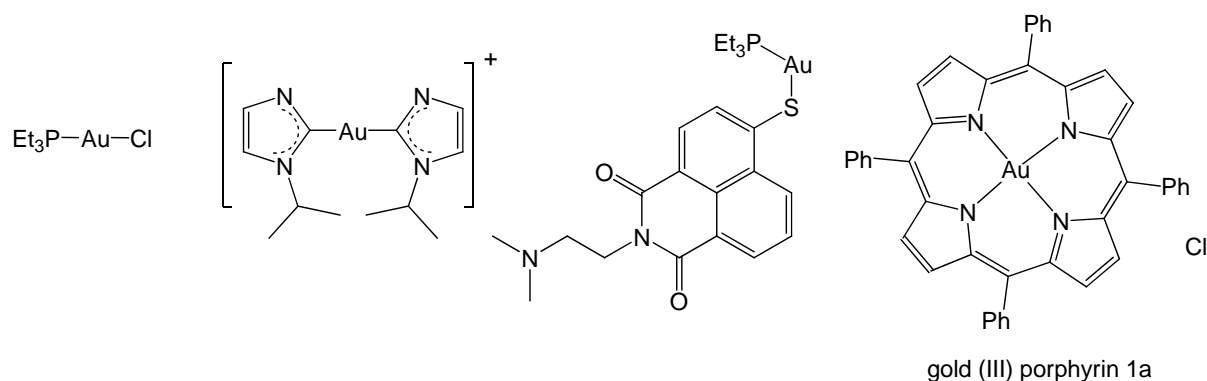
Gallium (III) compounds, such as gallium nitrate, are being evaluated for the treatment of cancer, including hypercalcaemia (large levels of serum calcium associated with several late stage cancers). Many gallium compounds are thought to interfere with iron metabolism since Ga(III) and Fe(III) are chemically very similar. A current compound KP46 is illustrated, whereby an organic ligand, in this case, quinolin-8-ol, has been used to lower the toxicity and improve the bioavailability characteristics of Ga(III) (Fig. 1).



**Figure 1. KP46, an anticancer drug.**

#### **Gold**

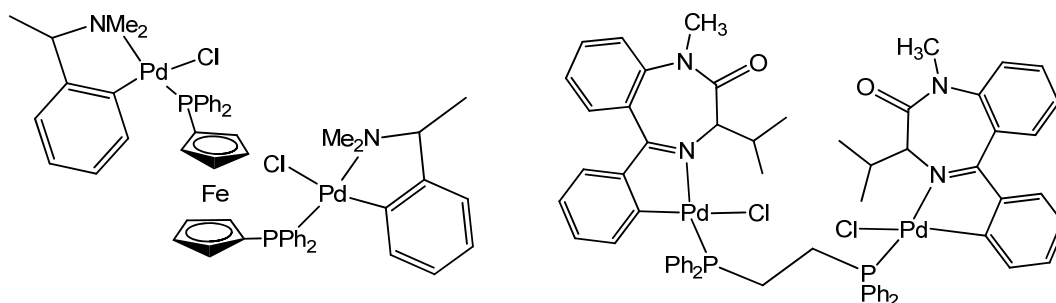
Traditionally, gold complexes have found uses in the treatment of rheumatoid arthritis. Recently, gold complexes have been investigated as anticancer agents, some due to their inhibition of the enzyme thioredoxin reductase (TrxR), which is involved in tumour growth. Recent Au complexes are illustrated in Figure 2.



**Figure 2. Anticancer gold complexes.**

### Palladium

Palladium, being above platinum in the Periodic Table, has also been evaluated for anticancer activity although the *cis*-platin like complex  $cis\text{-}[\text{Pd}(\text{NH}_3)_2\text{Cl}_2]$  is known to isomerise and rapidly hydrolyse, rendering it unsuitable for anticancer evaluation, since it is unstable *in vivo* and is consumed (creating toxicity and side effects) before reaching the target. A few recent palladium complexes with anticancer activity are known to inhibit cathepsin B (catB), an intracellular cysteine protease involved in tumour growth. The compounds in question are known as palladacycles.

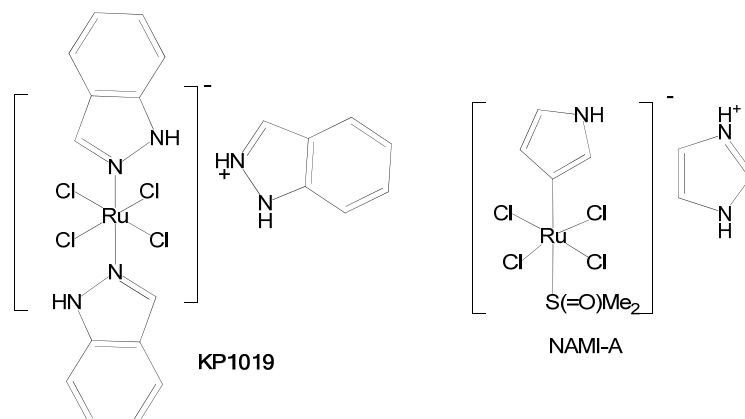


**Figure 3. Palladacycle catB inhibitors.**

### Ruthenium

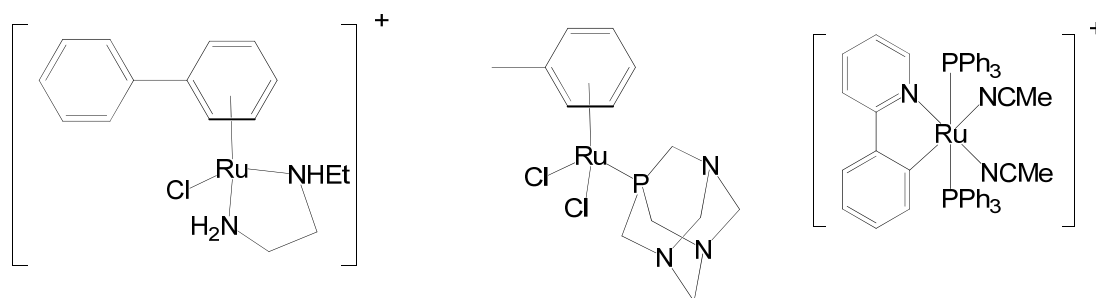
The cisplatin-like  $[\text{RuCl}_3(\text{NH}_3)_3]$  was an early ruthenium complex evaluated for anticancer activity although its poor solubility led to the search for more suitable candidates. Indeed, a number of ruthenium *prodrugs* are now showing promising activity in clinical trials. They are able to enter cancer cells via a transferrin receptor (usually used for iron transport and upregulated in “iron” hungry cancer cells) due to the similarity of Ru to Fe. Once inside the cell, the hypoxic conditions (low oxygen levels) lead to reduction of Ru(III) to Ru(II).

NAMI-A and KP1019 have excellent antimetastatic action and the former exhibits relatively low cytotoxicity. Both are in clinical trials, showing promising results.



**Figure 4. Ruthenium anticancer agents in clinical trials.**

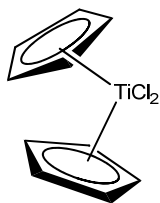
Given the likelihood of the lower oxidation state being the bioactive form of such complexes against cancer cells, a number of groups have directly synthesised Ru(II) analogues, which show good anticancer activity.



**Figure 5. Ru(II) anticancer agents.**

## Titanium

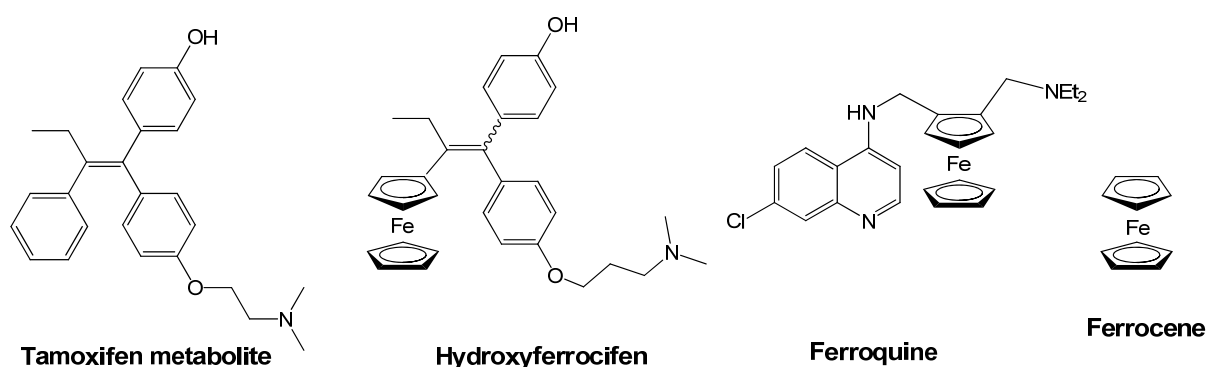
Titanocene dichloride was evaluated for anticancer activity due to its similarity to *cis*-platin but it was found to only weakly interact with DNA and was not successful due to its water instability. Its interactions with DNA were not as anticipated since it binds mainly to the phosphate backbone.



**Figure 6. Titanocene dichloride.**

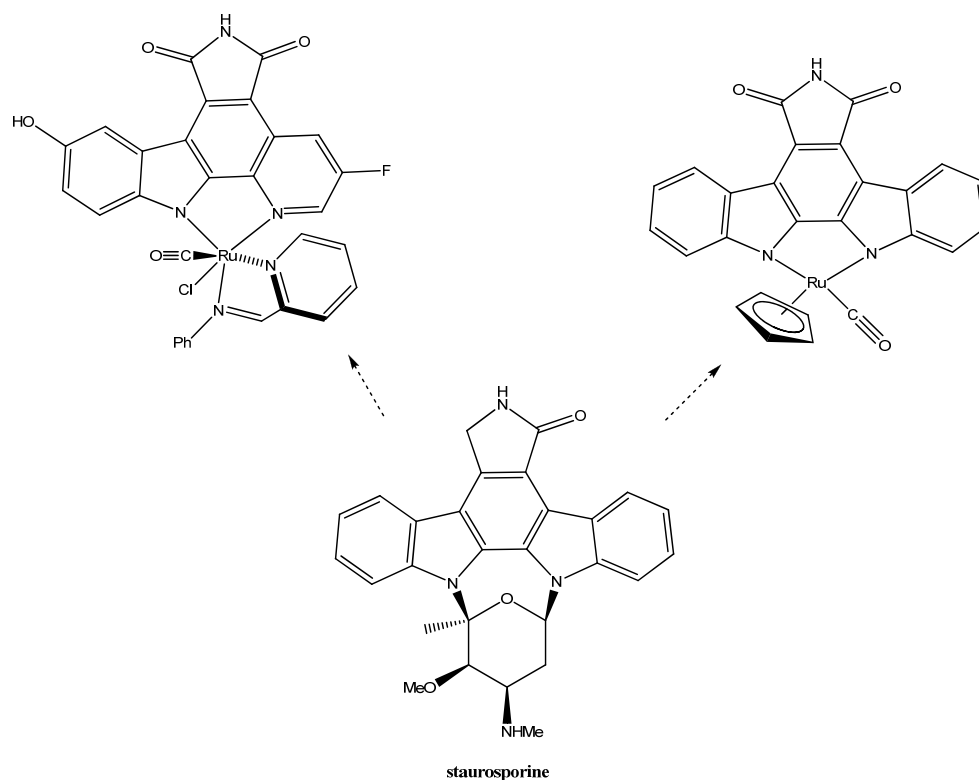
### New generation metal complexes

Recent anticancer agents with biological action have been designed whereby the high coordination number achievable in metal complexes (>4 compared with carbon) and the shape of the metal complexes can be put to use. Ferrocene resembles a three dimensional phenyl group and hydroxyferrocifen (a ferrocene based analogue of a metabolite of tamoxifen) was shown to have excellent anticancer action against breast cancer cell lines. To put these results into perspective, a ferrocene analogue of chloroquine (ferroquine) has progressed through clinical trials for the treatment of malaria, demonstrating that such metallodrugs are not merely academic curiosities.



**Figure 7. Ferrocene metallodrugs**

Meggers has coined the phrase “hypervalent carbon” in the use of metal complexes such as those of ruthenium. Many complexes have a hexacoordinate metal centre and allow the substituents to take up positions, and interact with enzymes or proteins, that are unachievable in traditional four coordinate carbon based organic chemistry (in Fig. 8, the metal scaffold replaces the sugar unit in staurosporine (see Figure 21.56 in book)). Consequently, these complexes are being used as highly selective chemical probes for elucidating the crystal structures of a number of biologically important kinases and proteins in cancer as the presence of a metal, and its high electron density, not only aids the refinement of the crystal structure but aids in stabilising the protein through binding.



**Figure 8. Ruthenium analogues related to staurosporine.**

### Conclusion

The selected examples above highlight some recent developments in bioinorganic chemistry and emphasise the significance of coordination and organometallic chemistry (molecules with a metal carbon bond) in the development of potential new anticancer agents. In many instances, DNA is not the principle target of these new metallodrugs; enzymes such as cathepsin B or reductases expressed in cancer cells and later stage cancers are emerging as important targets. Finally, metal complexes are being used as chemical probes for proteins involved in a range of diseases and may pave the way to the design of new drugs by providing structural information on the binding sites of such proteins to be exploited by molecular modelling.

### Reviews and General Reading

**Transition Metals in Cancer:** Alama, A. *et al. Drug Disc. Today* **2009**, *14*, 500. Page, S.M. *et al. Future Med. Chem.* **2009**, *1*, 541.

**Gallium:** Timerbaev, A.R. *Metallomics* **2009**, *1*, 193.

**Gold:** Wang, Y. *et al. Eur. J. Pharm.* **2007**, *554*, 113. Ott, I. *et al. J. Med. Chem.* **2009**, *52*, 763. Hickey, J.L. *et al. J. Am. Chem. Soc.* **2008**, *130*, 12570.

**New Generation metallodrugs:** Meggers, E. *Chem. Commun.* **2009**, 1001.

**Palladium:** Caires A.C.F. *Anti-Cancer Agents Med. Chem.* **2007**, 7, 484.

**Platinum:** Kelland, L. *Nature Rev. Cancer* **2007**, 7, 573.

**Ruthenium:** Casini, A. *et al. J. Med. Chem.* **2008**, 51, 6773. Yan, Y.K. *et al. Chem. Commun.* **2005**, 4764.