

# MEDICINAL PROPERTIES OF TRANSITION METAL COMPLEXES

Reported by Yen-Jun Ho

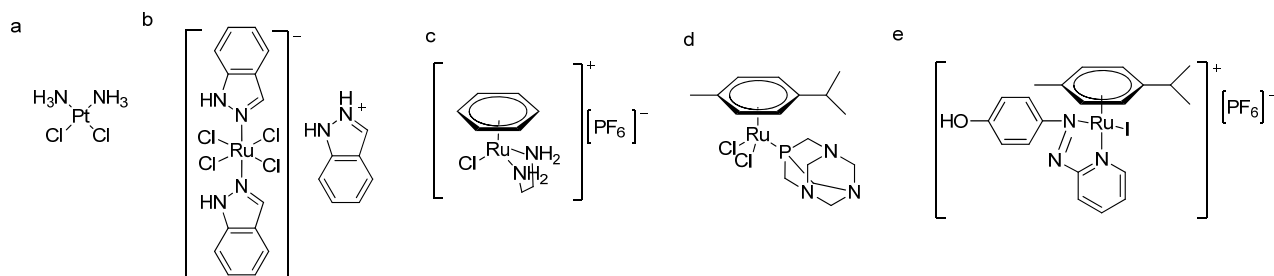
Oct. 4 2010

## INTRODUCTION

Transition metals and medicinal applications were once thought to be mutually exclusive. The metals were expected to be highly toxic and unstable in aqueous media. However, with the serendipitous discovery of the antiproliferative effects of *cis*-diamine-dichloro-platinum(II) (cisplatin) in 1965 by Rosenberg and coworkers, a new field of research emerged.<sup>1,2</sup> Since then, transition metal complexes have been used as radiation therapeutic, diagnostic and imaging agent, and as small molecule drugs. This seminar will focus on the application of transition metals as small molecule drugs describing the benefits and limitations of their use.

## INTERACTIONS WITH DNA

Platinum-based and ruthenium-based metal complexes bind DNA and allow the design of cancer therapeutics. Cisplatin (Figure 1a) forms intra-strand crosslinks with DNA, which leads to cell death and is used as an anticancer compound.<sup>3</sup> Although it is being used by 50-70% of all cancer patients, cisplatin and its derivatives do have drawbacks, such as toxicity, rapid development of drug resistance, and ineffectiveness against breast, prostate and colorectal cancer.<sup>4</sup> Developments to improve upon the drawbacks of cisplatin led to the discovery of several ruthenium complexes, such as KP1019 (Figure 1b) and variations of ruthenium(II) arene complexes (Figure 1c-e).<sup>5</sup> These compounds retain cisplatin's antiproliferative effects while reducing general toxicity as a result of preferential delivery to cancer cells.<sup>6,7</sup> Using the ability of the metal center to coordinate with DNA, cisplatin and the ruthenium complexes are designed to be effective anticancer compounds.



**Figure 1** Structure of transition metal complex (a) cisplatin (b) KP1019 (c)  $[(\eta^6\text{-C}_6\text{H}_5)\text{Ru}(\text{N},\text{N}\text{-en})\text{Cl}]^+ [\text{PF}_6]^-$  by Sadler (d)  $(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr})\text{Ru}(\text{P}\text{-pta})\text{Cl}_2$  by Dyson (e)  $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(\text{hydroxyphenyl}\text{-azopyridine})\text{I}]^+ [\text{PF}_6]^-$  by Sadler

## GENERATION OF REACTIVE OXYGEN SPECIES

Besides binding to DNA, transition metal complexes can alter cellular equilibrium involving reactive oxygen species (ROS). Jaouen and coworkers broadened the therapeutic scope of tamoxifen through synthesis of a tamoxifen-ferrocene conjugate (ferrocifen). It is hypothesized that the generation of ROS through one electron oxidation of iron allows ferrocifen to be effective for both hormone-independent (ER-) and hormone-dependent (ER+) breast cancer as compared to tamoxifen which is only effective for ER+ breast cancer.<sup>8</sup> Another example involves Sadler and coworkers who discovered a ruthenium complex (Fig. 1e) that catalyzes the oxidation of glutathione (GSH) to glutathione dimers (GSSG), sensitizing cancer cells to ROS leading to an inhibition of growth.<sup>9</sup> In both cases alteration of ROS concentration in the cell leads to an observed therapeutic effect.

## INHIBITION OF PROTEIN FUNCTION

Coordination around a metal center can lead to a more selective and potent protein kinase inhibitor. Meggers and coworkers designed a metal scaffold to replace a portion of the organic framework in staurosporine, a known protein kinase inhibitor. The metal complex allowed for rapid optimization due to the ease of screening coordinating ligands. The resulting metal complex demonstrated increased and selective inhibition of GSK-3, which is involved in the insulin signaling pathway.<sup>10</sup> The coordination of ligands around the metal center allowed for efficient optimization of a protein kinase inhibitor.

## CONCLUSION AND OUTLOOK

Metal complexes can interact in the body by (1) binding to DNA (2) affecting cellular equilibrium and (3) inhibit protein function. However, their use is still limited by observed toxicities related to off-target effects and indiscriminate activity with biological nucleophiles. Thus, more work must be done to discover compounds which can be more selective in interacting with therapeutic targets.

## REFERENCES

- (1) Chavain, N.; Biot, C. *Curr. Med. Chem.* **2010**, *17*, 2729–2745.
- (2) Krigas, T.; Camp, L. V.; Rosenberg, B. *Nature* **1965**, *205*, 698–699.
- (3) Fricker, S. P. *Dalton Trans.* **2007**, *43*, 4903–4917.
- (4) Hannon, M. J. *Pure Appl. Chem.* **2007**, *79*, 2243–2261.
- (5) Suss-Fink, G. *Dalton Trans.* **2009**, *39*, 1673–1688.
- (6) Keppler, B.; Hartinger, C. *et al. J. Inorg. Biochem.* **2006**, *100*, 891–904.
- (7) Sadler, P. J. *et al. Inorg. Biochem.* **2010**, *104*, 79–86.
- (8) Jaouen, G. *et al. Dalton Trans.* **2005**, *4*, 529–541.
- (9) Sadler, P. J. *et al. Proc. Nat. Acad. Sci. U.S.A.* **2008**, *105*, 11628–11633.
- (10) Meggers, E. *et al. ChemBioChem* **2006**, *7*, 1443–1450.