"Medicinal Organometallic Chemistry"

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Introduction

The Topics in Organometallic Chemistry series from Springer presents critical overviews of research results in organometallic chemistry, covering a broad range of topics in pure and applied organometallic chemistry. The theme of Volume 32 in this series, "Medicinal Organometallic Chemistry", is the potential medical applications of organometallic compounds. Edited by Gérard Jaouen and Nils Metzler-Nolte, this book describes recent advances in the design, synthesis, mechanistic understanding and medical application of organometallic compounds.

Medicinal Organometallic Chemistry

This volume encompasses the medicinal organometallic complexes of iron, titanium, technetium and gold among other metals; however this review will focus on those chapters featuring the platinum group metals (pgms). The discovery of the anticancer properties of cisplatin was arguably one of the major discoveries for anticancer chemotherapy in the twentieth century and now platinum anticancer drugs feature in multiple chemotherapy regimens (1). Though cisplatin is a simple inorganic complex (*cis*-$PtCl_2(NH_3)_2$), it has had a major impact on all aspects of inorganic medicinal chemistry including organometallic medicinal chemistry. The mechanism of action of cisplatin is believed to be the formation of DNA intrastrand crosslinks. Much of the early work on metal-based compounds focused on their interaction with DNA. However, it is now increasingly apparent that many metal complexes with potential antitumour activity do not behave like cisplatin, and it has been proposed that we should move away from the 'platinum paradigm' by developing drugs based on other metals such as ruthenium which have a different mechanism of action (2, 3) (**Figure 1**). Another apparent misconception is that organometallic compounds are too unstable to be useful as drugs, but

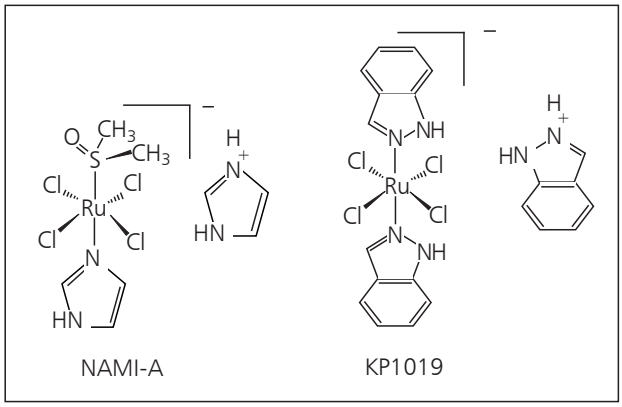


Fig. 1. Moving away from the 'platinum paradigm'. Structures of NAMI-A and KP1019, ruthenium compounds with mechanisms of action different to that of cisplatin

many organometallic compounds are now being developed that are stable under physiological conditions. These concepts are exemplified by many of the contributions in this book.

Ana Pizarro *et al.* (University of Warwick, UK) take up these themes in the second chapter by reviewing the activation mechanisms of organometallic complexes with potential anticancer activity. The hypothesis is that their cytotoxic activity towards cancer cells is based upon the substitution of one or more of the metal ligands by the biological target molecule. The first step in this substitution reaction is hydrolysis to form an aqua complex, followed by a second substitution with the target biomolecule. However, it is essential to control the aqueous reactivity to prevent potential complex hydrolysis reactions. A series of ruthenium- and osmium-arene complexes have been designed to interact differently to the platinum drugs with DNA. These compounds consist of an arene ligand, a neutral chelating ligand and a monoanionic ligand, forming a 'piano-stool' structure (**Figure 2**). The arene ligand and the chelate ligand provide stability to the structure, while the monoanionic ligand provides potential for substitution reactions with biomolecules. The choice of suitable ligands can control the thermodynamic and kinetic stability of the molecules, and hence their biological activity. These compounds are designed to interact with DNA in a bifunctional manner by both intercalation and direct metallation.

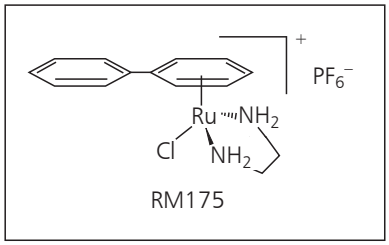


Fig. 2. RM175, a Ru-arene with the 'piano stool' structure

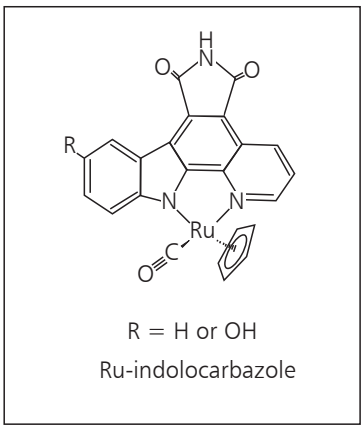
Various ruthenium complexes have demonstrated antitumour activity in preclinical studies and it is apparent that for many of these the primary biological target is not DNA. Angela Casini *et al.* (École Polytechnique Fédérale de Lausanne, Switzerland) describe in the third chapter the biological target of Ru-arene compounds with the formula $[Ru(\eta^6\text{-arene})Cl_2(pta)]$ (pta = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane), named RAPTA compounds. Interestingly, in mouse cancer models these compounds are able to inhibit tumour metastasis without affecting the growth of the primary tumour. This has led to a search for alternative biological targets, with a focus on two enzymes: thioredoxin reductase and cathepsin B, both of which contain cysteine in their active site. Though in general RAPTA compounds were found to be weak inhibitors of thioredoxin reductase, they were able to inhibit cathepsin B by coordination of the Ru(II) to the cysteine in the active site.

Protein phosphorylation by kinase enzymes is a major regulatory mechanism for protein activity and transmission of intracellular signals. There is a growing trend towards targeted therapy in which cancer drugs are aimed at specific molecular targets such as kinases. An excellent example is the drug imatinib which is targeted at the gene fusion protein breakpoint cluster region-Abelson (bcr-abl) tyrosine kinase and has changed the landscape for chronic myeloid leukemia therapy. Seann Mulcahy and Eric Meggers (Philipps-Universität Marburg, Germany) describe in the sixth chapter the ability of metal-containing compounds to form rigid 3D structures which can then be used as structurally diverse, unique scaffolds for the

design of specific enzyme inhibitors. Staurosporine, an indolocarbazole alkaloid, is a relatively non-selective protein kinase inhibitor. By using cyclopentadienyl half-sandwich Ru complexes as a structural scaffold for staurosporine mimetics, and combining features of the indolocarbazole within the half-sandwich complex, highly potent and specific protein kinase inhibitors have been identified for the protein kinases Pim1, MSK1 and glycogen synthase kinase (GSK3α). These kinases are all potential targets for anticancer drugs (**Figure 3**).

Biopolymers such as DNA and proteins are seen as the conventional biomolecular targets. However, O_2^-, NO and CO are alternative biomolecular targets amenable to interaction with metal complexes. The essential physiological roles of both O_2^- and NO are well understood, whereas the role of CO is an emerging field of study. Like NO, CO may be an important signaling molecule. Brian Mann (University of Sheffield, UK) in the tenth chapter describes the development of Ru carbonyl CO-releasing molecules (CO-RMs) as potential drugs. Much of the work on the biological activity of CO-RMs has focused on two molecules: $[Ru(CO)_3Cl_2]_2$ (CORM-2) and $[Ru(CO)_3Cl(glycinate)]$ (CORM-3). Both of these molecules have shown activity in a variety of biological and disease models. It is unclear what the clinical development path is for these molecules.

The pgms get a brief mention in other chapters. Elizabeth Hillard *et al.* (École Nationale Supérieur de Chimie de Paris, France) in the fourth chapter discuss development of the ferrocene functionalised modulators known as hydroxyferrocifens as anticancer agents. The hydroxyferrocifens consist of ferrocene linked to the active metabolite of tamoxifen,



R = H or OH

Ru-indolocarbazole

Fig. 3. A Ru-indolocarbazole kinase inhibitor

a breast cancer drug which targets the oestrogen receptor ('ER'), the aim being to combine the anti-oestrogen effect of tamoxifen with the cytotoxic properties of metal complexes. Ruthenium analogues termed hydroxyruthenocifens were prepared but only showed activity against an ER^+ cell line, suggesting that the organometallic moiety gave no additional advantage over tamoxifen itself. Lastly for the pgms, Christophe Biot (Université de Lille 1, France) and Daniel Dive (Université Lille Nord de France) in the seventh chapter describe the antimalarial properties of ferrocene complexes and briefly mention studies on the coordination of chloroquine (CQ) to Rh(COD)Cl.

Conclusions

Overall this is an informative book and will be welcomed by those working in the field of inorganic medicinal chemistry. The main areas of interest from a pgm perspective are the two chapters describing work on the Ru-arene complexes and their potential antitumour activity, and the chapter on metal complexes as scaffolds for novel kinase inhibitors. The chapter on CO-RMs is of interest but is disappointing with a writing style consisting of multiple bullet points with brief supporting text.

One of the appealing aspects of this book is its historical perspective. The introduction by the book's two editors, Gérard Jaouen and Stéphane Gibaud, traces the history of bioorganometallic chemistry from the elucidation of the crystal structure of cyanocobalamin to the discovery of the arsenical drug salvarsan by Erlich, to the antitumour activity of the titanocene complexes and the more recent Ru-arene complexes, set within the context of the discovery of cisplatin. This historical perspective is encapsulated in the chapter on arsenic drugs which have progressed from Fowler's solution for malaria (first proposed for use in 1786) to arsenic trioxide which is currently being evaluated as a drug for acute promyelocytic leukemia. The main disappointment in this book is the lack of translation of the chemistry to a clinical perspective. Ultimately it will be the clinical translation of medicinal organometallic chemistry which will be the true measure of its success.

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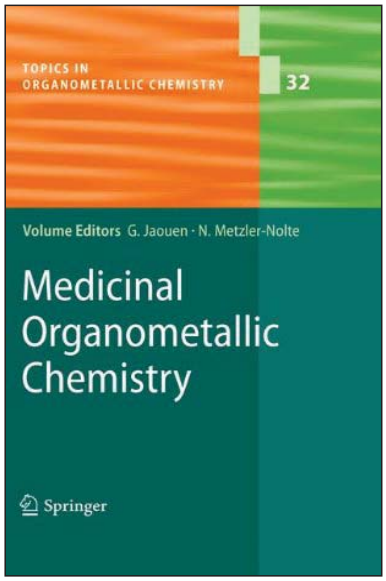

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