

Book of Abstracts

7th International Symposium on Bioorganometallic Chemistry

ISBOMC 2014, July 22nd – 25th 2014



University of Vienna

Institute of Inorganic Chemistry

Waehringer Str. 42, 1090-Vienna, Austria

Dear ISBOMC participants, dear fellow bioorganometallic chemists,

It is a great honor and pleasure to welcome all of you at the ISBOMC14, the 7th International Symposium on Bioorganometallic Chemistry in Vienna. We have nearly 120 participants from 21 countries attending the symposium which will cover all aspects of bioorganometallic chemistry, such as metalloenzymes and organometallic drugs, and in addition coordination compounds with a close relationship to this research area.

This will be a special occasion as it is the first time since its inception that this scientific event will take place in Austria. We have scheduled sessions featuring excellent, internationally renowned plenary and award lecturers, keynote and oral speakers. The exciting lectures will be complemented by 50 poster presentations.

The financial support of many organizations and companies is gratefully acknowledged. We would like to specifically thank Elsevier for sponsoring again the Bioorganometallics Award and we invite you to submit an article to the ISBOMC14 special issue in Journal of Organometallic Chemistry.

As the chairmen to this conference, we wish you a scientifically exciting and stimulating meeting and a pleasant stay in Vienna!

Sincerely,



Univ.-Prof. Bernhard Keppler



Prof. Christian Hartinger



Dr. Wolfgang Kandioller

Sponsors



universität
wien



ELSEVIER



ORGANOMETALLICS

Scientific & Local Organizing committees

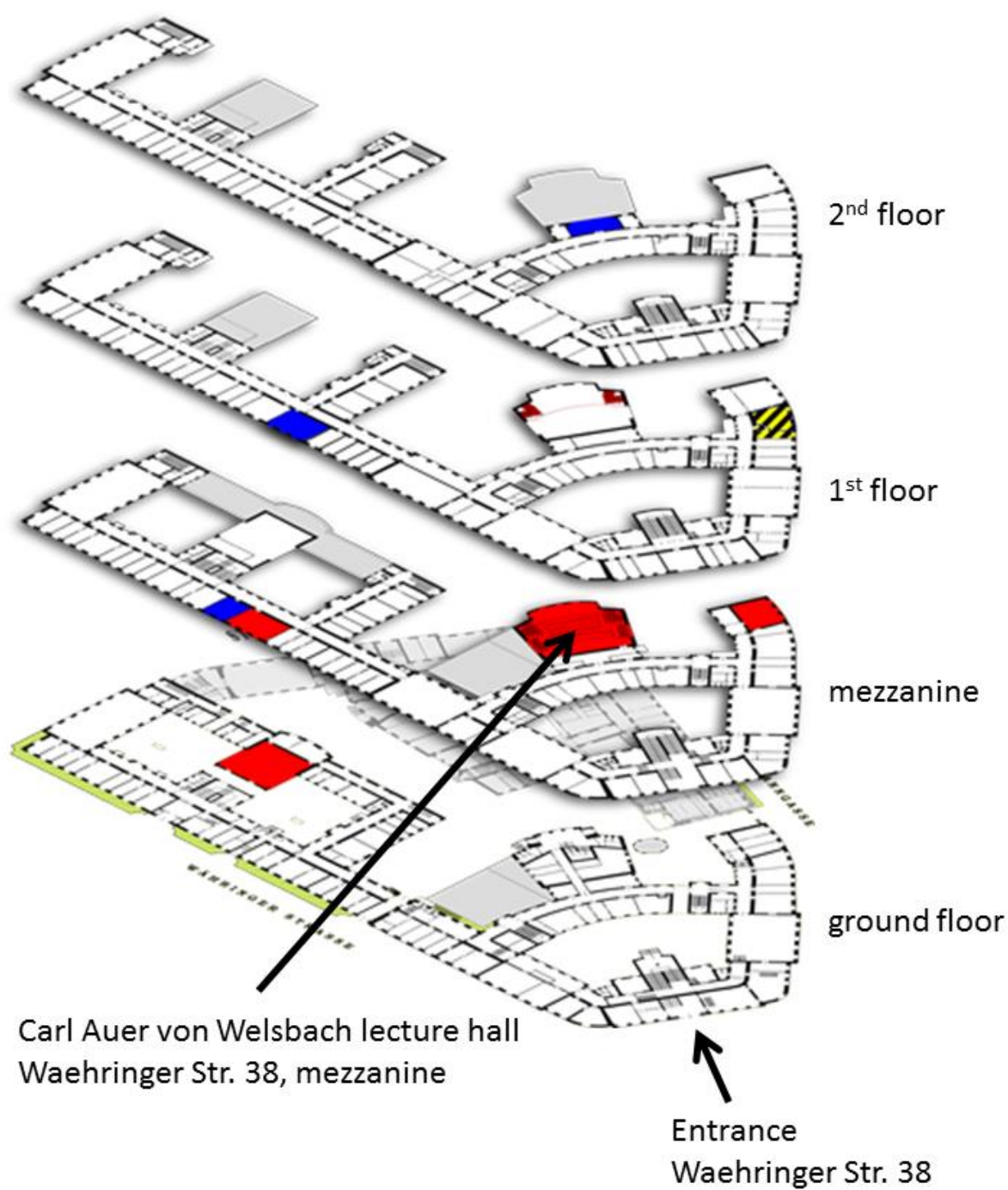
Bernhard K. Keppler (chair, Vienna, AT)
Christian G. Hartinger (co-chair, Auckland, NZ)
Wolfgang Kandioller (co-chair, Vienna, AT)
Walter Berger (Vienna, AT)
Alexey A. Nazarov (Moscow, RU)
Matthias Tacke (Dublin, IE)
Karl A. Kirchner (Vienna, AT)
Christian Kowol (Vienna, AT)
Elfriede Limberger (Vienna, AT)
Edith Engelberger (Vienna, AT)

ISBOMC Advisory Board

Roger Alberto (Zürich, CH)
Paul Dyson (Lausanne, CH)
Richard H. Fish (Berkeley, US)
Roberto Gobetto (Turin, IT)
Toshikazu Hirao (Osaka, JP)
Gerard Jaouen (Paris, FR)
Bernhard K. Keppler (Vienna, AT)
Heinz-Bernhard Kraatz (Toronto, CA)
Nils Metzler-Nolte (Bochum, DE)
Edward Rosenberg (Missoula, US)

Venue and Program

The conference venue is the Institute of Inorganic Chemistry, and the lectures will be held in the Carl Auer von Welsbach lecture hall (Währinger Str. 38, 1090 Vienna, Austria).



	Tuesday 22.7.	Wednesday 23.7.	Thursday 24.7.	Friday 25.7.
9:00	Registration		PL2 Metzler-Nolte	
		KL1 Alberto		
10:00		Coffee/Poster	Coffee/Poster	
		O09 Buglyó O10 Giannini O11 Vock O12 Paul O13 Top O14 Salmain	KL3 Rosenberg	KL4 Hirao
11:00			O15 Legin O16 McGowan O17 Süß-Fink O18 Sonnay	O28 Curran O29 Hess O30 Tucker O31 Tacke
12:00				
13:00	Opening Ceremony	Lunch	Lunch	Lunch
	PL1 Dyson	Award Ceremony	O19 Nazarov O20 Kubanik O21 Milaeva O22 Montagner O23 Vellas	PL3 Kraatz
		Bioorganometallic Award Lecture		
14:00	O01 Gasser O02 Samuelson O03 Soldevila- Barreda	KL2 Jaouen		Closing Ceremony
15:00	Coffee			
		Coffee/Poster	Coffee/Poster	
	O04 Kaiser O05 Perekalin O06 Matczuk O07 Shimakoshi O08 Schatzschneider	Poster	O24 Nardon O25 Oehninger O26 Cisnetti O27 Kaim	
16:00				
17:00				
18:00	Welcome Reception		Conference Dinner	

PL 45+15 min, KL 30 +10 min, O 15 + 5 min

Tuesday, July 22, 2014

13.00–13.15 Welcome and opening ceremony
Bernhard Keppler

Session 1

Session chair. Bernhard Keppler

13.15–14.15 Paul J. Dyson PL1

14.15–14.35 Gilles Gasser O01

14.35–14.55 Ashoka Samuelson O02

14.55–15.15 Joan Soldevila-Barreda O03

Coffee break

Session 2

Session chair. Christian Hartinger

15.45–16.05 Manuel Kaiser O04

16.05–16.25 Dmitry S. Perekalin O05

16.25–16.45 Magdalena Matczuk O06

16.45–17.05 Hisashi Shimakoshi O07

17.05–17.25 Ulrich Schatzschneider O08

Welcome Reception

Arkadenhof

University of Vienna, main building

Wednesday, July 23, 2014

Session 3

Session chair. Ingo Ott

9.20–10.00	Roger Alberto	KL1
------------	---------------	-----

Coffee break

10.30–10.50	Péter Buglyó	O09
10.50–11.10	Federico Giannini	O10
11.10–11.30	Carsten A. Vock	O11
11.30–11.50	Lydia Paul	O12
11.50–12.10	Siden Top	O13
12.10–12.30	Michèle Salmain	O14

Lunch

Session 4

Session chair. Bernhard Keppler

13.30–13.45	Award Ceremony	
13.45–14.45	Bioorganometallics Award Lecture	
14.45–15.25	Gérard Jaouen	KL2

Coffee break

Poster Session

Thursday, July 24, 2014

Session 5

Session chair. Hans-Günter Schmalz

9.00–10.00	Nils Metzler-Nolte	PL2
------------	--------------------	-----

Coffee break

10.30–11.10	Edward Rosenberg	KL3
-------------	------------------	-----

11.10–11.30	Anton Legin	O15
-------------	-------------	-----

11.30–11.50	Patrick C. McGowan	O16
-------------	--------------------	-----

11.50–12.10	Georg Süss-Fink	O17
-------------	-----------------	-----

12.10–12.30	Marjorie Sonnay	O18
-------------	-----------------	-----

Lunch

Session 6

Session chair. Damian Plazuk

13.30–13.50	Alexey A. Nazarov	O19
-------------	-------------------	-----

13.50–14.10	Mario Kubanik	O20
-------------	---------------	-----

14.10–14.30	Elena Milaeva	O21
-------------	---------------	-----

14.30–14.50	Diego Montagner	O22
-------------	-----------------	-----

14.50–15.10	Sreedhar K. Vellas	O23
-------------	--------------------	-----

Coffee break

Session 7

Session chair. Renzo Cini

16.00–16.20	Chiara Nardon	O24
16.20–16.40	Luciano Oehninger	O25
16.40–17.00	Federico Cisnetti	O26
17.00–17.20	Wolfgang Kaim	O27

Conference Dinner at the “Heuriger Ing. Werner Welser”, Probusgasse 12, 1190 Vienna

Friday, July 25, 2014

Session 8

Session chair. Anne Vessières

9.40–10.30	Toshikazu Hirao	KL4
11.10–11.30	Timothy P. Curran	O28
11.30–11.50	Jeannine Hess	O29
11.50–12.10	James H. R. Tucker	O30
12.10–12.30	Matthias Tacke	O31

Lunch

Session 9

Session chair. Bernhard Keppler

13.30–14.30	Heinz-Bernhard Kraatz	PL3
-------------	-----------------------	-----

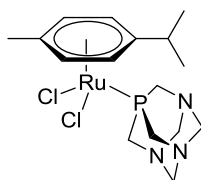
14.30 Closing Ceremony
 Bernhard Keppler

RAPTA-C - from molecule mechanism to macroscopic properties

Paul J. DYSON

Institute of Chemical Sciences and Engineering, Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland; paul.dyson@epfl.ch

The lecture will focus on the pre-clinical development of the organometallic ruthenium(II)-arene complex, RAPTA-C. Two main themes will be explored. The first is concerned with the molecular mechanism of action of RAPTA-C. The second is focused on pre-clinical studies of RAPTA-C as a monotherapy and in combination.



RAPTA-C

While the full mechanism of action of RAPTA-C remains to be elucidated a number of key findings, demonstrated at various levels, help to provide an understanding on the biological properties of the compound [1]. In this respect, RAPTA-C displays strong antiangiogenic effects in vivo that results in an inhibition of the growth of primary tumors and solid metastatic tumors [2]. Based on extensive in vivo data and applying both rational and screening approaches several relevant combinations have been found and demonstrated in pre-clinical models to reduce the growth of primary tumors. These studies, the underlying mechanisms, and their clinical relevance will be explored during the lecture.

References:

- [1] Adhireksan, Z.; Davey, G. E.; Campomanes, P. R.; Groessl, M.; Clavel, C.; Yu, H.; Nazarov, A. A.; Yeo, C. H. F.; Ang, W. H.; Dröge, P.; Roethlisberger, U.; Dyson, P. J.; Davey, C. A., Ligand substitutions between two ruthenium-cymene compounds can control protein versus DNA targeting and anticancer activity. *Nature Commun.*, 2014, 5, 3462.
- [2] Weiss, A.; Berndsen, R. H.; Dubois, M.; Müller, C.; Schibli, R.; Griffioen, A. W.; Dyson, P. J.; Nowak-Sliwinska, P., In vivo anti-tumor activity of the organometallic ruthenium(II)-arene complex [Ru(η^6 -p-cymene)Cl₂(pta)] (RAPTA-C) in human ovarian and colorectal carcinomas, submitted for publication.

Organometallic Peptide Conjugates

Nils METZLER-NOLTE

*Ruhr-Universität Bochum, Universitätsstraße 150, 44801 Bochum, Germany;
nils.metzler-nolte@rub.de*

We are using the unique spectroscopic and chemical properties of organometallic complexes for the detection and modification of bioactive peptides. The peptides are prepared by solid phase peptide synthesis (SPPS) techniques either manually or on an automated peptide synthesizer. Over the years, we have gained significant experience in devising mild, biocompatible synthesis protocols for covalently binding metal complexes to these peptides. This contribution will provide an overview of the synthetic toolbox that is available along with selected applications for the resulting metal-peptide bioconjugates.

Conceptually, there are four positions where a single metal complex may be placed within a given peptide: *N*- or *C*-terminally, as part of the peptide side chain, or as part of the peptide backbone itself. Our group has provided examples for all four possibilities. While backbone substitution and conjugation to the *N*-terminus may be regarded as part of the regular SPPS process, the *C*-terminus is much less accessible since this is usually the place of attachment to the resin during SPPS. To make the *C*-terminus amendable to bioconjugation with metals, my group has recently invented a new silyl-based alkyne linker (so-called SAM linker) that allows selective, quantitative *C*-terminal modification in a one-step "cleavage-conjugation" procedure.[1] Side-chain derivatization should also use a bioorthogonal strategy, and we have employed metal-catalyzed coupling reactions for this purpose, such as the Sonogashira reaction or the Cu-catalyzed azide-alkyne coupling ("click" chemistry). In a few exquisite examples the special reactivity of the metal complex itself leads to selective derivatization of particular peptide side chains.[2, 3] Selected applications from our recent work will highlight the use of such metal-peptide conjugates.

References:

- [1] M. Strack, S. Langklotz, J. E. Bandow, N. Metzler-Nolte, H. B. Albada, Silyl-Based Alkyne-Modifying Linker for the Preparation of *C*-Terminal Acetylene-Derivatized Protected Peptides. *J. Org. Chem.* (2012) 77, 9954 – 9958
- [2] H. B. Albada, F. Wieberneit, I. Dijkgraaf, J. H. Harvey, J. L. Whistler, R. Stoll, N. Metzler-Nolte, R. H. Fish, The Chemoselective Reactions of Tyrosine-Containing G-Protein-Coupled Receptor Peptides with [Cp*Rh(H₂O)₃](OTf)₂, *J. Am. Chem. Soc.* (2012) 134, 10321 - 10324
- [3] S. D. Köster, H. Alborzinia, S. Can, I. Kitanovic, S. Wölfl, R. Rubbiani, I. Ott, P. Riesterer, A. Prokop, K. Merz, N. Metzler-Nolte, A Spontaneous Gold(I)-Azide Alkyne Cycloaddition Reaction Yields Gold-Peptide Bioconjugates which Overcome Cisplatin Resistance in a p53-Mutant Cancer Cell Line. *Chem. Sci.* (2012) 3, 2062 – 2072.

Teaching an Old Dog New Tricks: Towards Ferrocene-Peptide Materials. Structure, Self-Assembly, and Gelator Properties

Heinz-Bernhard KRAATZ

*Department of Physical and Environmental Sciences, University of Toronto
Scarborough, Toronto, Ontario, Canada and Department of Chemistry, University of
Toronto, Toronto, Ontario, Canada; bernie.kraatz@utoronto.ca*

The design of structurally well-defined peptide motifs has been an active area of research aimed at generating models of biological systems, or to develop novel biomaterials. Peptide structural motifs such as α -helices and β -sheets have been designed *de novo* using non-proteinogenic amino acids. In this context, disubstituted ferrocenes are becoming popular scaffolds, which are known to induce turn-like structures that enable efficient hydrogen bonding interactions between peptide chains.

Work in the Kraatz group focuses on the design of ferrocene-peptide derivatives for the structural mimicry of β -sheets and helices and on molecules that can recognize ions, small molecules, or even proteins. Here, a summary is presented of the synthesis and use of some ferrocene-peptide conjugates. Examples are discussed of their properties as gelators forming organogels that are responsive to external stimuli [1]. For example, ferrocenoyl-Val-Phe-Phe-OMe undergoes a redox and ultrasound directed self-assembly and displays a redox-controlled reorganization between gel nanofibers and spherical micelles [2].

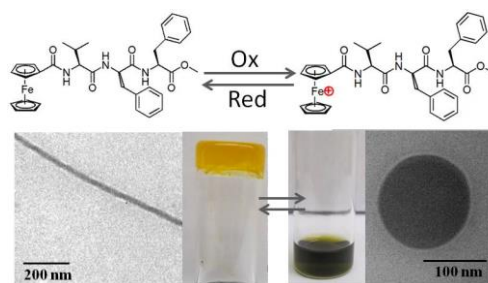


Fig1. Schematic representation of redox induced morphological transformations of FcCO-Val-Phe-Phe-OMe.

References

1. B. Adhikari, R. Afrasiabi, and H.-B. Kraatz, *Organometallics* **2014**, 32, 5899.
2. B. Adhikari and H.-B. Kraatz, *Chem. Commun.* **2014**, 50, 5551.

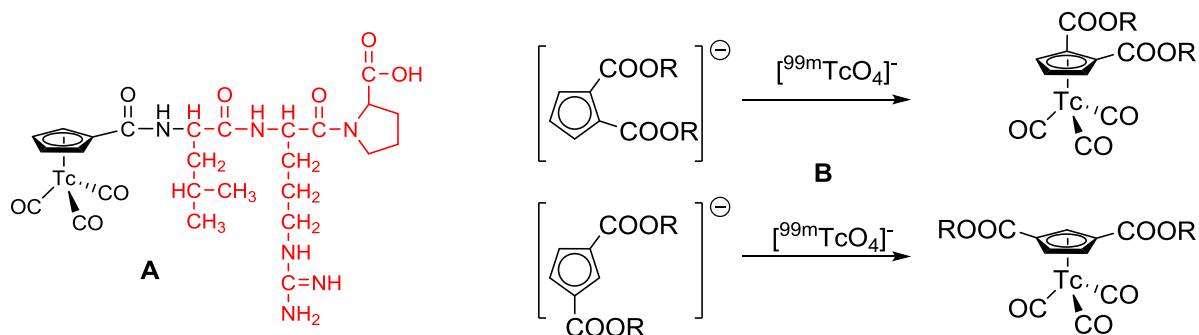
Technetium and Rhenium in the Theranostic Concept

Roger ALBERTO, Michael FELBER, Sebastian IMSTEPF, Samer URSILLO, Henrik BRABAND, Michael BENZ

Department of Chemistry, University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland; ariel@chem.uzh.ch

Bioorganometallic complexes of technetium are used for (radio)imaging purposes in Single Photon Emission Computed Tomography (SPECT). Conjugated to a targeting biomolecule, the ^{99m}Tc tag should be innocent, e.g. not interact with the target or influence pharmacology. In extension to this approach, the Technetium complex can act as a structural moiety in pharmaceutically active lead structures. The accessibility of complexes of the type $[(\text{Cp-R})^{99m}\text{Tc}(\text{CO})_3]$ opened a pathway to the so-called phenyl-Cp analogy.¹ The Cp complex can be a tag, as will be shown with peptides (A),² but it can also be an integral part of an overall structure in which it plays an essential role for receptor recognition. Examples with CA and HDAC inhibitors will be presented.³ Replacing Technetium by Rhenium will yield a homologue with almost identical, pharmacological properties but with therapeutic potential. Thus, the ^{99m}Tc compound is for imaging while the "cold" Rhenium homologue is therapeutically active; a new strategy in a theranostic concept.

Previously, we used mono-carboxylated Cp derivatives, now, we have extended the approach to cyclopentadienyl derivatives with two carboxylato groups (B). This will allow the coupling of two identical or different, bioactive functionalities to one ^{99m}Tc or Re complex, thereby allowing either higher selectivity or affinity for one target. The corresponding chemistry with $[\text{C}_5\text{H}_4(\text{COOR})_2]^-$ will be presented. Finally, for replacing a phenyl ring in a pharmaceutical by a "true" phenyl ring, first insights in arene chemistry will be given.



References:

- [1] Liu, Y.; Spingler, B.; Alberto, R. et al., J. Am. Chem. Soc., 2008, 130, 1554-1556.
- [2] Nadeem, Q.; Can, D.; Alberto, R. et al., Org. & Biomol. Chem., 2014, 12, 1966-1974
- [3] Can, D.; Spingler, B.; Alberto, R.; et al., Angew. Chem. Int. Edit., 2012, 51, 3354-3357.

Ferrocifen constructs against cancers resistant to apoptotic stimuli. Novel strategies, new active metabolites and latest nanoengineering data.

G rard JAOUEN

*Chimie ParisTech, 11 rue P. et M. Curie, 75231 Paris Cedex 05, France;
gerard.jaouen@chimie-paristech.fr*

The social challenge represented by those cancers that still have alarmingly poor outcomes- melanomas, triple-negative breast cancers and malignant gliomas, for example- can only be met by a capacity for medical innovation, drawing from a judicious alliance of groundbreaking chemistry, novel biology and the latest tools of medical intervention. These difficult to cure peculiar cancers share the characteristic of intrinsic resistance to pro-apoptotic stimuli, which limits the effectiveness of the available chemotherapies; hence the need to discover new therapeutic approaches able to induce cell death by other means. In this endeavor, a new medicinal chemistry based on the unique behavior of organometallic complexes of transition metals may provide a turning point.

The mechanisms of action of three different types of ferrocifen constructs against cancer resistant to standard treatments will be discussed and biological data provided. Due to their hydrophobic nature, preclinical evaluation of these organometallic compounds requires the use of a specialized drug delivery system. A nanocarrier with an oily core, termed lipid nanocapsules (LNC), using a solvent-free process of phase inversion that is easily scalable for commercial purposes, could answer this need.

Considering the gulf that currently exists in oncology between available therapies and the needs of patients, the discovery of a non-apoptotic mechanism of action such as senescence, based on novel species, and enhanced by a proven method of delivery using innovative bioengineering could represent for these molecules a decisive turning point towards the clinical development of a new therapeutic tool.

[1] G. Jaouen, S. Top, in *Advances in Organometallic Chemistry and Catalysis: The Silver/Gold Jubilee International Conference on Organometallic Chemistry Celebratory Book* (Ed.: A. J. L. Pombeiro), Wiley, 2014, chapt.42 , pp. 563-580.

Photophysical Properties of Ru Complexes in Membrane Model Systems

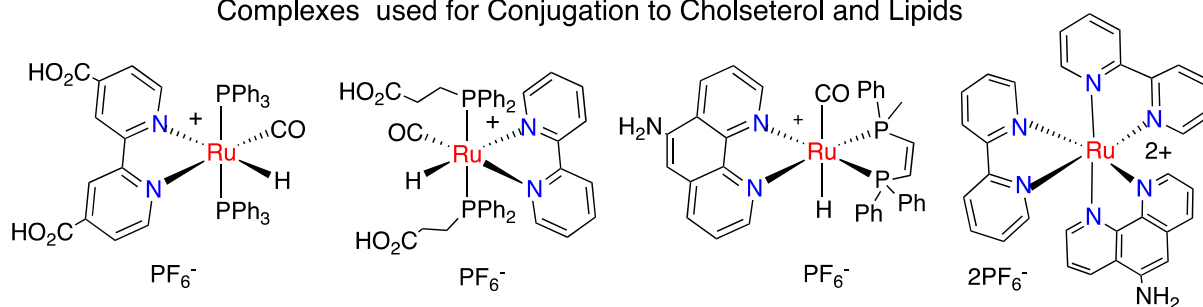
Edward ROSENBERG, Ayesha SHARMIN, J. B. Alexander ROSS, Geoffrey ABBOTT, Michelle TERWILLIGER

*Department of Chemistry and Biochemistry, University of Montana
32 Campus D, Missoula, MT 59812; edward.rosenberg@mso.umt.edu*

We have been studying the polarized emission of low-symmetry Ru complexes with the goal of understanding the dynamics of protein binding to membrane models and the formation of lipid rafts. Starting with the complexes $[\text{Ru}(\text{H})(\text{trans-PPh}_3)_2(\text{dcbpy})\text{CO}][\text{PF}_6]$ (**1**) and $[\text{Ru}(\text{dppene})(5\text{-amino-phen})\text{CO}(\text{H})][\text{PF}_6]$ (**2**) and $[\text{Ru}(\text{bpy})(\text{bis-dppa})(\text{CO})\text{H}][\text{PF}_6]$ (**3**) (dcbpy = 4,4'-dicarboxy bipyridine, dppene = 1,2-diphenylphosphino ethene, dppa = diphenylphosphino propionic acid 5-amino phen = 5-amino phenanthroline) we have used standard techniques to covalently conjugate these molecules to two and one phosphatidyl ethanolamine molecules, respectively via the diimine ring and the phosphine ligands.^{1,2} For comparison we also examined the previously reported lipid conjugate of $[\text{Ru}(\text{bpy})_2(5\text{-amino phen})][\text{PF}_6]$ (**4**), a tris-diimine complex.³ Complexes **2** and **4** have also been conjugated to cholesterol via reaction with cholesterol chloroformate. The cholesterol conjugates both exhibit typical red-shifted emissions and relatively long life times in lipid vesicles. However, the less symmetrical complex **2** shows longer temperature dependent lifetimes and higher anisotropy in both liposomes and in protein belted nano-discs. Complex **2** incorporated in the lipids of the nano-discs shows a longer lifetime than in the liposomes and the lifetime does not change when the probe is diluted with unlabeled cholesterol. This suggests that there are essentially no probe-probe interactions and that the probe will only respond to protein-probe interactions. Studies directed towards labeling the belt protein of the nano-discs will also be discussed.

The lipid conjugates, with the exception of **4**, exhibit unusual photophysical properties both in solution and in the membrane models. Complexes **1** and **2** show no emissions in solution while complex **3** shows a weak blue-shifted emission with a very short, ns lifetime in the same solvents. In the liposomes complexes **1** and **2** show intense blue shifted emissions with very short lifetimes and very high anisotropies. Complex **4**, on the other hand exhibits the same emission and excited state lifetime in liposomes as in solution. Analysis of the anisotropy decay as a function of temperature from the conjugated probes in vesicles reveals interesting differences in the probe motion and location within the vesicle.

Complexes used for Conjugation to Cholesterol and Lipids



1. Ayesha Sharmin, Reuben C. Darlington, Kenneth I. Hardcastle, Mauro Ravera, Edward Rosenberg, J. B. Alexander Ross *J. Organometal. Chem.* (2009) **694**, 988-1000.
2. E. Rosenberg, G. Abbott, J. B. A. Ross, R. Brooks, M. Terwilliger, L. Salassa *Inorg Chem* **2013** 52 10835
3. Lakowicz, J. R. et al *Anal. Biochem.* 1997, 254, 179

Chirality-Organized Bioorganometallic Compounds

Toshikazu HIRAO^{a,b)}

a) Department of Applied Chemistry, Graduate School of Engineering, Osaka University,
Yamada-oka, Suita, Osaka 565-0871, Japan
b) JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan
e-mail: hirao@chem.eng.osaka-u.ac.jp

The field of bioorganometallic chemistry has drawn great attention and undergone rapid development. Considerable efforts have focused on designing secondary structure mimics composed of short peptides to gain fundamental insight into the factors affecting the protein structures and stability, and to facilitate the rational design of pharmacologically useful compounds. Chirality organization of ferrocene-dipeptide bioconjugates to obtain a peptidomimetic basis for protein folding and to construct highly-ordered molecular assemblies will be described [1].

The double helical DNA is created by A-T and G-C base pairs, which are controlled mainly by hydrogen bonds, π - π interactions, and hydrophobic effects. Utilization of self-assembling properties of nucleobases in bio-inspired systems offers the flexibility of exploiting four different binding motifs. On the other hand, square-planar d^8 or d^{10} transition metal complexes possess the intriguing photophysical, photochemical, and catalytic properties. In particular, luminescent platinum(II) and gold(I) compounds have been studied because of their interesting luminescence properties based on metallophilic interactions. Herein, tuning of the emission properties of the bioorganometallic platinum(II) and gold(I) compounds composed of nucleobases will be also described [2].

References:

- [1] Moriuchi, T.; Hirao, T. *Acc. Chem. Res.* **2010**, 43, 1040.
- [2] (a) Meng, X.; Moriuchi, T.; Kawahata, M.; Yamaguchi, K.; Hirao, T. *Chem. Commun.* **2011**, 47, 4682. (b) Meng, X.; Moriuchi, T.; Tohnai, N.; Miyata, M.; Kawahata, M.; Yamaguchi, K.; Hirao, T. *Org. Biomol. Chem.* **2011**, 9, 5633. (c) Meng, X.; Moriuchi, T.; Sakamoto, Y.; Kawahata, M.; Yamaguchi, K.; Hirao, T. *RSC Advances* **2012**, 2, 4359.

Organometallic Compounds to fight Schistosomiasis

Malay PATRA,^{a)} Katrin INGRAM,^{b)} Jennifer KEISER,^{b)} Gilles GASSER^{a)}

a) Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland; gilles.gasser@chem.uzh.ch

b) Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, University of Basel, Basel, Switzerland

Despite its importance in tropical regions, where 280,000 deaths are reported annually, schistosomiasis is still a relatively unknown parasitic disease in the western world. A racemic mixture of Praziquantel (PZQ, Fig. 1) is currently the frontline chemotherapeutic drug to fight schistosomiasis. However, despite its success, PZQ presents several important drawbacks, which include a low metabolic stability and inactivity against juvenile schistosomes. This inactivity makes it necessary to retreat patients after a few weeks to remove parasites that have since matured. Potentially more worrying, as millions of people are regularly treated with this drug, it is likely that PZQ resistant parasites will emerge in the near future. In fact, reduced susceptibility against *S. mansoni* to PZQ was recently observed. In order to tackle this problem, we have embarked upon a program to assess the use of organometallic compounds as novel antischistosomal drug candidates (Fig. 1). During this talk, our latest in vitro and in vivo results will be presented.[1-3]

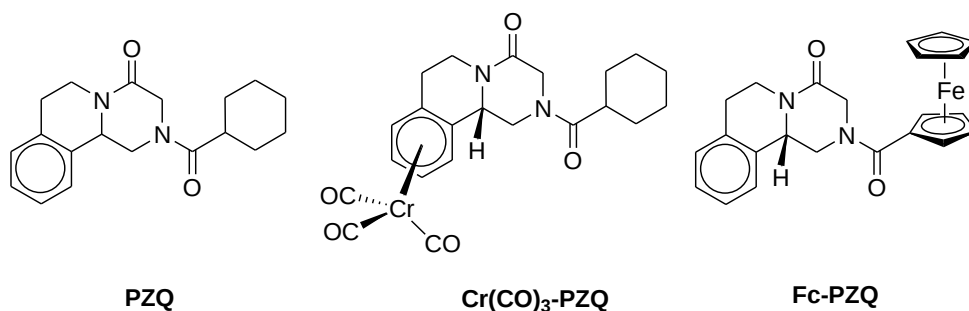


Fig. 1. Structures of PZQ and of organometallic compounds studied as antischistosomal drug candidates.

References:

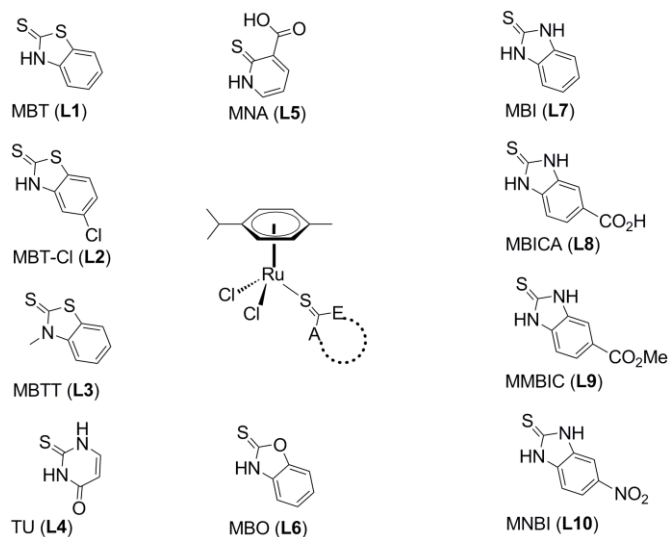
- [1] Patra, M.; Ingram, K.; Pierroz, V.; Ferrari, S.; Spingler, B.; Keiser, J.; Gasser, G., *J. Med. Chem.* 2012, 55, 8790-8798.
- [2] Patra, M.; Ingram, K.; Pierroz, V.; Ferrari, S.; Spingler, B.; Gasser, R.B.; Keiser, J.; Gasser, G. *Chem. Eur. J.* 2013, 19, 2232-2235.
- [3] Patra, M.; Ingram, K.; Leonidova, A.; Pierroz, V.; Ferrari, S.; Robertson, M.; Todd, M.H.; Keiser, J.; Gasser, G., *J. Med. Chem.* 2013, 56, 9192-9298.

A search for structure-activity relationships in anti-cancer active half-sandwich complexes of ruthenium(II)

Raja MITRA, Ashoka SAMUELSON, Sangeetha DAS

*Department of Inorganic and Physical Chemistry. Indian Institute of Science,
Bangalore 560 012 India
ashoka@ipc.iisc.ernet.in*

Neutral half sandwich organometallic ruthenium(II) complexes of the type $[(\eta^6\text{-cymene})\text{RuCl}_2(\text{L})]$, where L represents a heterocyclic ligand (mercaptobenzothiazole, mercaptobenzoxazole and mercaptobenzimidazole), have been synthesized and characterized spectroscopically. Structure-activity relationships were sought by varying the hetero atom of the heterocycle and the substituents on the aromatic ring juxtaposed to the heterocycle. In vitro studies show that inhibition of cancer cell growth involves primarily G1 arrest as well as generation of ROS. Surprisingly, biophysical studies show that cytotoxic complexes differ in their interaction with DNA, either causing biphasic melting of DNA. Substitution of the aromatic ring of the heterocycle with a carboxylic acid or ester or changing the O or S to NH on the heterocycle reduces the cytotoxicity. However, addition of halogens, especially a fluorine, enhances the activity of the complex in a remarkable fashion. Interestingly, inhibition of thioredoxin reductase activity by these complexes gives a clue to the fact that there are multiple pathways by which these complexes trigger anticancer activity



References:

- [1] Mitra, R.; Das, S.; Shinde S.V. ; Sinha S.; Somasundaram, K., Anticancer Activity of Hydrogen-Bond-Stabilized Half-Sandwich RuII Complexes with Heterocycles. *Chem. Eur. J.*, 2012, 18 (39), 12278-12291.

Transfer hydrogenation catalysis in cancer cells

Joan SOLDEVILA-BARREDA, Isolda ROMERO-CANEÓN, Abraha HABTEMARIAM, Peter J. SADLER

*Chemistry Department, Warwick University. Gibbet hill Road CV4 7AL, UK
J.J.Soldevilla@warwick.ac.uk*

The coenzyme 1,4-NADH participates in many metabolic reactions, including regulation of energy metabolism, regulation redox state, DNA repair and transcription, immunological functions and cell death.¹ Disruption of NAD⁺ and NADH levels is a potential new mechanism for the treatment of e.g. Alzheimer's and Parkinson's diseases, and cancer.

We have synthesized a series of Ru(II) and Ir(III) compounds capable of performing transfer hydrogenation reactions under physiologically relevant conditions, using NADH as a hydride donor. In particular, [(Cp^xPhPh)Ir(PhPy)py]⁺ can decrease the level of NADH in cells.^{2,3}

Reduction of NAD⁺ to NADH via transfer hydrogenation can be achieved by Ru(II) arene complexes of the type [(η⁶-arene)Ru(L)Cl]PF₆ (arene = hexamethylbenzene, p-cymene, indane; L is ethylenediamine) which catalyze the reduction of NAD⁺ under physiological conditions, and using formate as the hydride source.⁴

Here, we present a new series of Ruthenium(II) complexes, containing Noyori-type ligands, which catalyze the reduction of NAD⁺ to NADH via transfer hydrogenation with formate.⁵ We have investigated the antiproliferative activity of six complexes in A2780 ovarian cancer cells in co-administration with non-toxic doses of sodium formate as a hydride source. We have also studied the dependence of activity and NAD⁺/NADH ratio on the formate concentrations. Our results suggest that it is possible to design catalytic antioxidant organometallic anticancer drugs.

Acknowledgements. We thank IAS (Warwick), ERC and EPSRC for support, and COST Action CM1105 for stimulating discussions.

References:

- [1] Ying W., NAD⁺/NADH and NADP⁺/NADPH in cellular functions and cell death: regulation and biological consequences. *Antioxid. Redox Signal.*, **2008**, 10, 179-206.
- [2] Betanzos-Lara S., Liu Z., Habtemariam A., Pizarro A.M., Qamar B., Sadler P.J., Organometallic Ruthenium and Iridium Transfer-Hydrogenation Catalysts Using Coenzyme NADH as a Cofactor. *Angew. Chem. Int Ed*, **2012**, 51, 3897–3900.
- [3] Liu Z., Romero-Canelón I., Qamar B., Hearn J. M., Habtemariam A., Barry N. P. E., Pizarro A. M., Clarkson, G. J., Sadler, P. J., The Potent Oxidant Anticancer Activity of Organoiridium Catalysts. *Angew. Chem. Int. Ed*. **2014**, 53, 3941-3946.
- [4] Yan Y.K., Melchart M., Habtemariam A., Peacock A.F., Sadler P.J., Catalysis of regioselective reduction of NAD⁺ by ruthenium(II) arene complexes under biologically relevant conditions. *Biol. Inorg. Chem.*, **2006**, 11, 483-488.

Synthesis and Characterization of Bidentate Sulfur-Ligands for the Development of Novel [FeFe]-Hydrogenase Model-Compounds

Manuel KAISER, Günther KNÖR

*Institute of Inorganic Chemistry, Johannes Kepler University (JKU),
Altenberger Straße 69, 4040 Linz, Austria; manuel.kaiser@jku.at*

Platinum-group metals still play a dominant role as catalyst materials for technical hydrogen production. In natural systems, uptake and release of H₂ is catalyzed by a highly efficient class of metalloenzymes (hydrogenases) carrying organometallic reaction centers with low-valent iron sites as their common functional subunits [1]. Biomimetic hydrogenase models based on Fe-complexes therefore represent an interesting alternative to replace the role of precious metals for electro- and photocatalytic H₂-production [2,3]. Following the structural key-features of natural hydrogenases (Fig. 1a), frequently polynuclear iron carbonyl clusters with bridging thiolate ligands are investigated in this context.

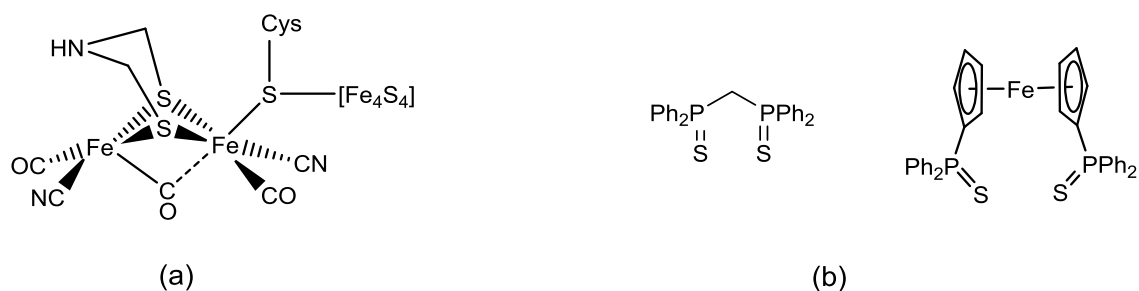


Figure 1: (a) Active site of the reduced form of [FeFe]H₂ase [1] (b) Examples of ligands used for the synthesis of novel bio-inspired transition metal carbonyl catalysts.

The aim of our current project is to extend this important class of compounds by applying a series of modified phosphane- and phosphane-sulfide ligands (Fig. 1b). Synthesis, characterization and reactivity of new polynuclear iron carbonyl complexes are presented. A special focus is given on the application of functionalized sulfur ligands carrying redox-active and chromophoric moieties, which could possibly contribute to the development of novel photocatalytic hydrogenase models.

References:

- [1] J. C. Fontecilla-Camps, A. Volbeda, C. Cavazza, Y. Nicolet, *Chem. Rev.* 2007, 107, 4273–4303.
- [2] G. Knör, U. Monkowius, *Adv. Inorg. Chem.* 2011, 63, 235–289.
- [3] C. Topf, U. Monkowius, G. Knör, *Inorg. Chem. Comm.* 2012, 21, 147-150.

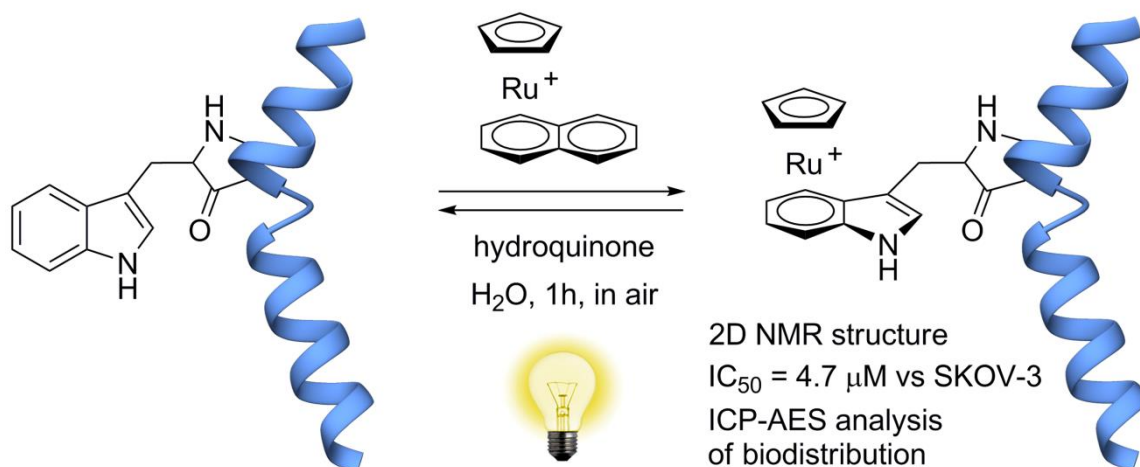
Selective Ruthenium Labeling of the Tryptophan Residue of the Bee Venom Peptide Melittin

Dmitry S. PEREKALIN, Valentin V. NOVIKOV, Alexander R. KUDINOV

*Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences,
28 Vavilova, Moscow, 119991, Russia; dsp@ineos.ac.ru*

We have developed a convenient method for selective labeling of aromatic residues in biomolecules with a $[\text{CpRu}]^+$ cation [1]. The method is based on ligand substitution in the commercially available complex $[\text{CpRu}(\text{C}_{10}\text{H}_8)]^+$ which proceeds in aqueous solution and tolerates the presence of non-aromatic amino acids, sugars, and nucleotides. The $[\text{CpRu}]^+$ label is stable in various biochemical reactions (for example, trypsinolysis); yet it can be selectively removed by irradiation in the presence of hydroquinone.

We have used the developed method to label the tryptophan residue of melittin – the main component of bee venom. It was found that the organometallic moiety does not disturb the secondary structure of melittin, but changes the character of its intermolecular interactions by converting the hydrophobic tryptophan into the hydrophilic cationic complex. Accordingly, ruthenium labeling leads to a 10-fold decrease of the hemolytic activity of melittin without significantly affecting its high anti-cancer activity. ICP-AES detection of ruthenium allowed us to study biodistribution of the labeled melittin in mice.



This work was supported by the Council of the President of the Russian Federation (grant for young scientist # MK-4261.2014.3).

References:

- [1] Perekalin, D. S.; Karslyan, E. E.; Petrovskii, P.V.; Nelyubina, Y.V.; Lyssenko, K.A.; Kononikhin, A. S.; Nikolaev, E.N.; Kudinov, A. R., Simple synthesis of ruthenium pi-complexes of aromatic amino acids and small peptides. *Chem. Eur. J.* 2010, 16, 8466-8470.

Interactions of an anticancer ruthenium(III) drug in human cancer cytosol explored by hyphenated analytical techniques

Magdalena MATCZUK,^{a)} **Monika PRZADKA,**^{a)} **Joanna LEGAT,**^{a)} **Katarzyna PAWLAK,**^{a)} **Andrei TIMERBAEV,**^{b)} **Maciej JAROSZ**^{a)}

a) Chair of Analytical Chemistry, Faculty of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland, mmatczuk@ch.pw.edu.pl

b) Vernadsky Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences, Kosygin 19, 199991 Moscow, Russia

Indazolium trans-[tetrachloridobis(1H-indazole)ruthenate(III)] is one of the most promising non-platinum anticancer drug candidates in current clinical trials. With a rationale that drug's uptake is likely governed by transferrin receptors, the release of low-molecular-mass (and presumably active) forms of ruthenium(II) from the holo-transferrin adduct under simulated intracellular conditions was recently confirmed using tandem ESI-MS [1].

In this contribution, interactions of the released forms with low- and high-molecular-mass components of human cytosol, resulting in pertinent speciation changes, were investigated by separation-based techniques, size-exclusion chromatography and capillary electrophoresis hyphenated with ICP-MS or ESI-MS. With the objective to approach real cancer-cell situation, the cytosolic fraction isolated from colorectal carcinoma cell lines was used in this testing. Cytosolic components that interact with the Ru species were identified by employing capillary HPLC-ESI-MS, aided by constructing a specific ruthenium-bound peptide map as a result of the implementation of enzymatic digestion at the stage of sample preparation.

This work has been supported by the EU in the framework of Regional Development Fund (MPD/2010/4).

References:

[1] Matczuk, M.; Prządka, M.; Aleksenko S.S.; Czarnocki Z.; Pawlak K.; Timerbaev A.R.; Jarosz, M., Metallomics for drug development: a further insight into intracellular activation chemistry of a ruthenium(III)-based anticancer drug gained using a multidimensional analytical approach. *Metallomics* 2014, 6 (1), 147-153.

B₁₂-TiO₂ Hybrid Catalyst for Light-Driven Molecular Transformations

Hisashi SHIMAKOSHI and Yoshio HISAEDA

*Department of Chemistry and Biochemistry, Graduate School of Engineering,
Kyushu University, 744 Motooka Nishi-ku Fukuoka 819-0395 Japan;
shimakoshi@mail.cstm.kyushu-u.ac.jp*

Naturally-occurring B₁₂(cobalamin)-dependent enzymes catalyze various molecular transformations that are of particular interest from the viewpoint of biological chemistry as well as synthetic organic chemistry and catalytic chemistry. For example, the B₁₂-dependent enzyme catalyzes the rearrangement reactions and the methylation reaction as in the synthesis of methionine. All of these reactions are mediated by the cobalt alkylated complex which is generally formed by the reaction of the Co(I) state of the B₁₂ with various electrophiles in vitro. Recently, we have reported the unique catalysis of the B₁₂-titanium oxide (TiO₂) hybrid catalyst in which the B₁₂ complex, cyanoaquacobyrnic acid, is immobilized on the surface of TiO₂ and the B₁₂ complex is reductively activated to form the Co(I) species by electron transfer from TiO₂ under UV-light irradiation. The hybrid catalyst mediated the dehalogenation of various organic halides and was applied to the radical-mediated organic reaction via an alkylated complex as a catalytic intermediate. The great advantage of the catalyst is the facile and efficient formation of Co(I) species by only UV light irradiation. This property prompted us to investigate further applications of the B₁₂-TiO₂ catalyst utilizing the high reactivity of the Co(I) species of the B₁₂ complex. We now report the new catalysis of the B₁₂-TiO₂ for H₂O reduction to form hydrogen. Cobalt complexes have been studied as excellent catalysts for hydrogen production, and the cobalt hydride complex is thought to be an intermediate for the reaction which could be formed by the reaction of Co(I) and a proton. As the metal hydride complexes are widely used for the reduction of unsaturated compounds, such as alkenes, an application of the B₁₂-TiO₂ catalyst for the hydrogenation of C-C multiple bonds was also investigated.

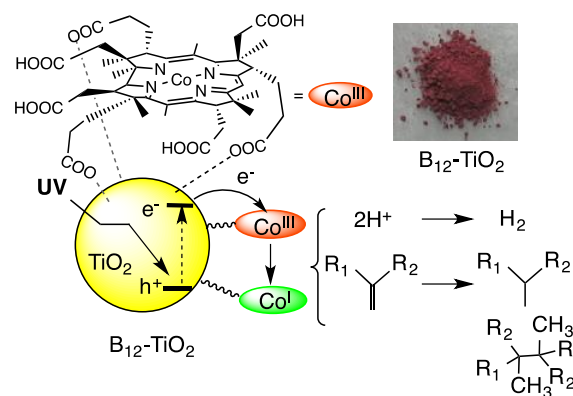


Figure Photo-induced hydrogen evolution and alkene reduction catalyzed by the B₁₂-TiO₂ hybrid.

References:

- [1] Hisaeda, Y.; Shimakoshi, H., in *Handbook of Porphyrin Science*, Kadish, K. M.; Smith, K. M.; Guillard, R., Eds. World Scientific: Singapore, 2010; Vol. 10, pp 313-370.
- [2] H. Shimakoshi *et al*, *Chem. Commun.*, **2011**, 6427-6429; *Dalton Trans*, **2010**, 39, 3302-3307; *Chem. Lett.*, **2009**, 38, 468-469; *Bull. Chem. Soc. Jpn.*, **2010**, 83, 170-172.

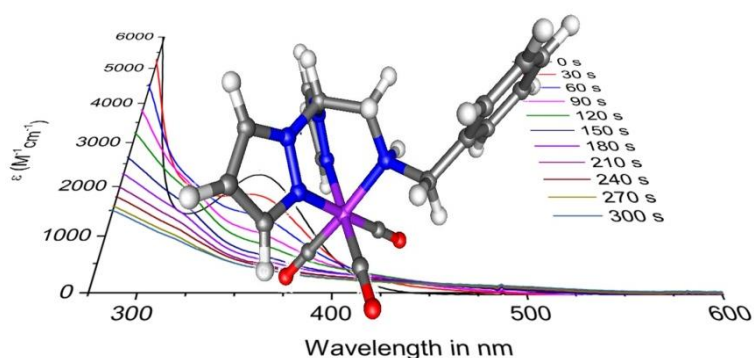
Metal-carbonyl complexes as CO-releasing molecules (CORMs): antibacterial activity and fluorescent detection of carbon monoxide in living cells

Ulrich SCHATZSCHNEIDER^{a)}

*a) Institut für Anorganische Chemie, Julius-Maximilians-Universität Würzburg, Am Hubland,
D-97074 Würzburg, Germany; ulrich.schatzschneider@uni-wuerzburg.de*

In addition to nitric oxide and hydrogen sulfide, carbon monoxide is now also well-established as an endogenously produced small signaling molecule in higher organisms, including humans. Its generation, together with ferrous iron and biliverdin, is due to the enzymatic activity of heme oxygenases (HO) on heme. In addition to its signaling function, CO production also responds to oxidative stress and generally has a tissue-protective function. Increased local concentrations of carbon monoxide are, however, also implicated in anticancer and antimicrobial chemotherapy [1–2].

In order to safely deliver well-defined doses of CO to tissues and cells, transition metal carbonyl complexes are currently explored as CO-releasing molecules (CORMs) and have promise as novel therapeutic agents in a variety of medical indications [3–4].



In this contribution, we will demonstrate the photo-triggered biological activity of new CORMs on bacterial cell cultures, leading to a pronounced growth retardation effect, while the compounds themselves are completely inactive, even at high micromolar concentrations, when kept in the dark, thus establishing them as novel light-activatable prodrugs [5]. In addition, the fluorescent switch-on probe COP-1 was used to demonstrate photoinduced CO release in vitro in human umbilical vein endothelial cells (HUVECs) for the first time [6–7]. This work will thus highlight the most recent developments in the use of bioorganometallic carbonyl compounds in antibacterial chemotherapy.

References:

- [1] R. Motterlini, L.E. Otterbein, *Nature Rev. Drug Discovery* **2010**, 9, 728-743.
- [2] U. Schatzschneider, *Brit. J. Pharmacol.* **2014**, doi: 10.1111/bph.12688.
- [3] J. Niesel, A. Pinto, H.W. Peindy N'Dongo, K. Merz, I. Ott, R. Gust, U. Schatzschneider, *Chem. Commun.* **2008**, 1798-1800.
- [4] H. Pfeiffer, A. Rojas, J. Niesel, U. Schatzschneider, *Dalton Trans.* **2009**, 4292-4298.
- [5] C. Nagel, S. McLean, R. Poole, H. Braunschweig, T. Kramer, U. Schatzschneider, *Dalton Trans.* **2014**, accepted.
- [6] B.W. Michel, A.R. Lippert, C.J. Chang, *J. Am. Chem. Soc.* **2012**, 134, 15668-15671.
- [7] S. Pai, M. Hafftlang, G. Atongo, C. Nagel, J. Niesel, S. Botov, H.-G. Schmalz, B. Yard, U. Schatzschneider, *Dalton Trans.* **2014**, doi:10.1039/c4dt00254g

Interaction between half-sandwich type platinum metal ions and bioligands capable of tridentate coordination

Linda BÍRÓ,^{a)} Dániel HÜSE,^{a)} János PATALENSZKI,^{a)} Zsolt BIHARI,^{a)} Edina BALOGH,^{a)} Attila Cs. BÉNYEI,^{b)} Péter BUGLYÓ^{a)}

a) Department of Inorganic & Analytical Chemistry, Institute of Chemistry, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary; buglyo@science.unideb.hu

b) Laboratory for X-ray diffraction, Institute of Chemistry, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary

When administered, half-sandwich type, organometallic platinum metal complexes with potential antiproliferative activity, may interact with the high and low molecular mass components of the various body fluids. Many, among these small bioligands are capable of tridentate coordination occupying all the available coordination sites of the metal moieties.

Depending upon the size and basicity of the donor atoms and the size of the joined chelates formed with them, these biochelators may bind the above metal ions with rather different strength. Furthermore, rate of the ligand exchange reactions in the complexes also has a significant impact on the biological effect of these interactions.

Recently we have studied the interaction between $[(\eta^6\text{-arene})\text{M}(\text{H}_2\text{O})_3]^{2+}$ (M = Ru, Os) cations and ligands with [O,O,O] (citrate, tricarballate, malate, tartarate), [O,O,N] (serine, isoserine), [O,O,S] (tiolactate) and [O,N,S] (cysteine, methionine, S-methyl-cysteine) donor sets.

This contribution summarizes the results of a detailed solution study obtained by the combined use of pH-potentiometry, ¹H NMR and ESI-TOF-MS methods together with the synthesis and solid state characterization of the complexes.

References:

- [1] M. Melchart, P.J. Sadler, in: G. Jaouen (Ed.), *Bioorganometallics*, Wiley-VCH, 2006, pp. 39-64.
- [2] P.C.A. Bruijninx, P.J. Sadler, *Adv. Inorg. Chem.*, 2009, Vol. 61, pp. 1-62.
- [3] I. Bratsos, T. Gianferrara, E. Alessio, C.G. Hartinger, M.A. Jakupec, B.K. Keppler, in: E. Alessio (Ed.), *Bioinorganic Medicinal Chemistry*, Wiley-VCH, 2011, pp. 160-164.
- [4] L. Bíró, E. Balogh, P. Buglyó, *J. Organomet. Chem.*, 2013, Vol. 734, pp. 61-68.
- [5] L. Bíró, D. Hüse, A.C. Béneyei, P. Buglyó, *J. Inorg. Biochem.*, 2012, Vol. 116, pp. 116-125.

Acknowledgement: The authors thank the members of the EU COST Action CM1105 for motivating discussions. This work was supported by the European Union and European Social Fund TAMOP-4.2.2/A-11/1/KONV-2012-0043.

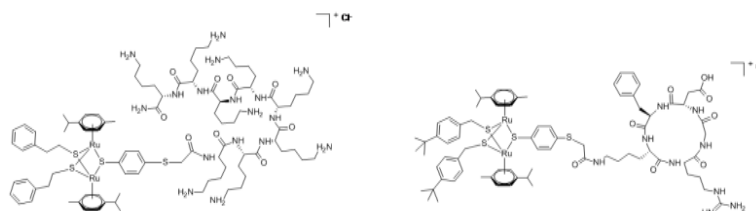
Peptide Conjugates of Dinuclear Arene Ruthenium Trithiolato Complexes

Federico GIANNINI,^{a)} **Marco BARTOLONI,**^{a)} **Lydia E. H. PAUL,**^{a)} **Jean-Louis REYMOND,**^{a)} **Julien FURRER,**^{a)} **Georg SUESS-FINK**^{b)}

a) Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, CH-3012, Berne, Switzerland

b) Institute of Chemistry, University of Neuchâtel, Avenue de Bellevaux 51, CH-2000, Neuchâtel, Switzerland; federico.giannini@dcb.unibe.ch

We have recently synthesized series of highly cytotoxic thiophenolato-bridged dinuclear *p*-cymene ruthenium complexes of the general formula $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\text{SR})_3]^+$ (R being an aliphatic or aromatic substituent), the IC₅₀ values being in the nanomolar range [1]. However, the *in vitro* selectivity between healthy and cancer cells remains low, which could be related to their limited solubility in physiological media.



In order to improve the *in vitro* selectivity towards cancer cells, a new series of ruthenium complexes was obtained by appending selected peptides to one of the thiol groups. The synthesis, characterization and their *in vitro* cytotoxicity towards ovarian cancer cell lines will be presented. The complexes were obtained by conjugating two different thiolato-bridged *p*-cymene Ru-complexes and three selected polypeptides: octaarginine, which is known for its ability to penetrate cell membranes [2], octalysine, and one cyclo-pentapeptide, cyclo-[Lys~Arg~Gly~Asp~Phe], which has been reported to selectively target the $\alpha_v\beta_3$ integrin, overexpressed in many types of cancer cells [3].

References:

- [1] Giannini, F.; Furrer, J.; Ibaio, A.F.; Süß-Fink, G.; Therrien, B.; Zava, O.; Baquie, M.; Dyson P.J.; Štěpnička, P., *J. Biol. Inorg. Chem.* 2012, 17, 951-960.
- [2] Biswas, S.; Desphande, P.P.; Perche, F.; Dodwadkar, N.S.; Sane, S.D.; Torchilin, V.P., *Cancer Letters* 2013, 335, 191-200.
- [3] Lee, M.H.; Kim, J.Y.; Han, J.H.; Bhuniya, S.; Sessler, J.L.; Kang, C.; Kim, J.S., *J. Am. Chem. Soc.* 2012, 134, 12668-12674.

Hydrolytically Stable η^6 -Arene Ruthenium(II) Complexes and Their Evaluation as Anticancer and Antiparasitic Agents

Carsten A. VOCK^{a)}

*a) Institute of Organic Chemistry, Faculty of Chemistry, University of Vienna,
Währinger Str. 38, A-1090 Vienna, Austria; E-Mail: carsten.vock@univie.ac.at*

Besides the well-known Ru(III) complexes KP1019 and NAMI-A – both of which have successfully passed phase I clinical trials as anticancer drugs – η^6 -arene ruthenium(II) complexes have attracted considerable interest during the last decade.^[1] Most of the complexes under investigation contained – and still contain – easily exchangeable (frequently chloro) ligands, which dissociate in aqueous media to form reactive aqua complexes, in which water can be replaced by numerous biomolecules like DNA, proteins etc.

In 2006, we started our work on hydrolytically stable η^6 -arene ruthenium(II) complexes by synthesizing dicationic compounds with three N-coordinated imidazole ligands.^[2] To our surprise, those substances exhibited more interesting cytotoxic properties than similar easily hydrolyzable derivatives. We therefore decided to continue the evaluation of hydrolytically stable ruthenium(II) complexes, their mode of action and potential new applications as a main part of our investigations.

During the presentation, an overview of our successful work in the field of hydrolytically stable ruthenium(II) complexes with highly interesting properties will be presented. Special emphasis will be given on an entirely new field of application for cytotoxic ruthenium compounds, i.e. the use as antiparasitic / anthelmintic agents for the treatment of rare "neglected diseases" occurring in Central Europe, like alveolar echinococcosis^[3] and toxoplasmosis.^[4]

References:

- [1] Nazarov, A.; Hartinger, C. G.; Dyson, P. J., Opening the lid on piano-stool complexes: an account of ruthenium(II)-arene complexes with medicinal applications, *J. Organomet. Chem.* 2014, 751, 251-260.
- [2] Vock, C. A.; Scolaro, C.; Phillips, A. D.; Scopelliti, R.; Sava, G.; Dyson, P. J., Synthesis, characterization and in vitro evaluation of novel ruthenium(II) η^6 -arene imidazole complexes, *J. Med. Chem.* 2006, 49(18), 5552-5561.
- [3] Küster, T.; Lense, N.; Barna, F.; Hemphill, A.; Kindermann, M. K.; Heinicke, J. W.; Vock, C. A., A new promising application for highly cytotoxic metal compounds: η^6 -areneruthenium(II) phosphite complexes for the treatment of alveolar echinococcosis, *J. Med. Chem.* 2012, 55(9), 4178-4188.
- [4] Barna, F.; Debache, K.; Vock, C. A.; Küster, T.; Hemphill, A., In vitro effects of novel ruthenium complexes in *Neospora caninum* and *Toxoplasma gondii* tachyzoites, *Antimicrob. Agents Chemother.* 2013, 57(11), 5747-5754.

Investigating the interaction of hexaruthenium assemblies with proteins

Lydia PAUL,^{a)} **Bruno THERRIEN,**^{b)} **Julien FURRER**^{a)}

a) Department of Chemistry and Biochemistry, University of Berne, Freiestrasse 3, CH-3012 Berne, Switzerland. Email: lydia.paul@dcb.unibe.ch

b) Institute of Chemistry, University of Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel, Switzerland.

Since the 1980s, ruthenium-based drugs have gradually attracted attention, mainly due to their less severe side effects compared to platinum-based drugs. [1-3] In recent years, we have designed different hexacationic hexaruthenium assemblies that can encapsulate planar and bioactive molecules, making them a potential new class of drug delivery vectors. [4] Previous studies conducted within our group have shown that the assemblies 1-3 interact rapidly with amino acids and rather weakly with deoxyguanosine-5'-monophosphate and deoxyadenosine-5'-monophosphate. [5-7] In line with these previous investigations, we here report the interaction between the assemblies shown in Chart 1 and human serum albumin, transferrin, myoglobin, ubiquitin and Cytochrome C.

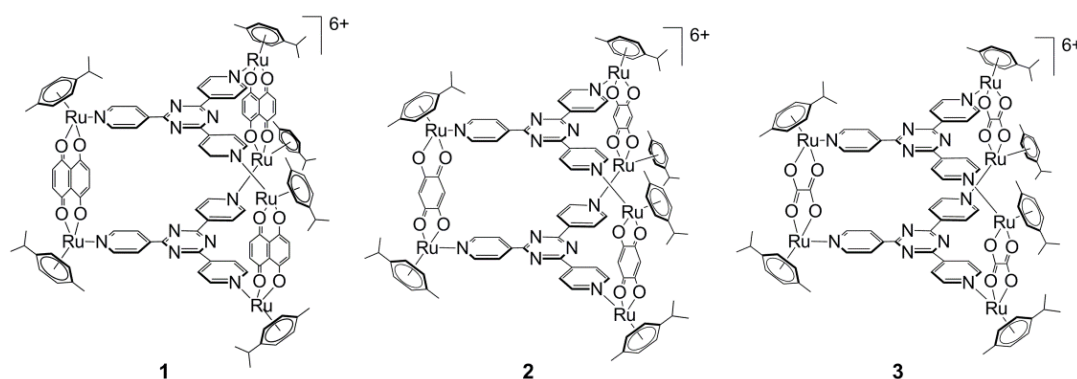


Chart 1: Structure of the hexaruthenium assemblies

References:

- [1] Clarke, M.J., *Met. Ions Biol. Syst.*, 1980, 11, 231-283.
- [2] Rosenberg, B.; van Camp, L.; Grimley, E.B.; Thomson, A.J., *J. Biol. Chem.* 1967, 242, 1347-1352.
- [3] Süss-Fink, G., *Dalton Trans.*, 2010, 39, 1673-1688.
- [4] Therrien, B.; Süss-Fink, G.; Govindaswamy P; Renfrew AK, Dyson PJ (2008) *Angew Chem Int Ed* 47: 3773-3776.
- [5] Paul, L.E.H.; Therrien, B.; Furrer, J., *Inorg. Chem.*, 2012, 51, 1057-1067.
- [6] Paul, L.E.H.; Therrien, B.; Furrer, J., *J. Biol. Inorg. Chem.*, 2012, 17, 1053-1062.
- [7] Paul, L.E.H.; Therrien, B.; Furrer, J., *J. Organomet. Chem.*, 2013, 734, 45-52.

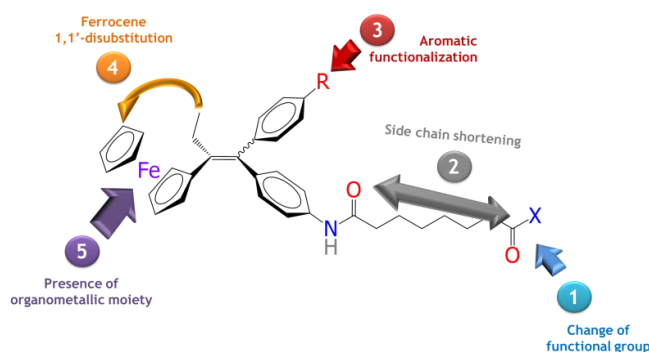
Targeting Triple Negative Breast Cancer Cells with New Efficient Organometallic FcTAM-SAHA Constructs

José de Jesús CAZARES-MARINERO, Siden TOP, Anne VESSIERES, Gérard JAOUEN

*Institut Parisien de Chimie Moléculaire, UMR CNRS 8232, Université Pierre et Marie Curie, Chimie ParisTech, 11 rue Pierre et Marie Curie, Paris 75231 Paris cedex 05, France.
siden.top@upmc.fr*

Pursuing the exploration on the anticancer activities of organometallic tamoxifen derivatives, we have prepared a new family of hybrid compounds based on the combination of key structural motifs of Ferrocifen (FcTAM) and Vorinostat (SAHA). These compounds were tested against triple negative MDA-MB-231 breast cancer cells, which are a subtype of aggressive cancer lacking estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Interestingly, FcTAM-SAHA hybrid showed good activity on MDA-MB-231 cells ($IC_{50} = 0.70 \mu M$), better than FcTAM and SAHA ($IC_{50} = 2.62 \mu M$ and $3.64 \mu M$, respectively).^[1]

A structural modification study of FcTAM-SAHA molecule has shown that hydroxamic acids and primary amides exhibit better cytotoxic effects than carboxylic acids.^[2] Interestingly, the dramatic increase in cytotoxicity due to the presence of a phenol moiety^[3] or by the replacement of a ferrocenyl moiety with a ferrocenophane motif^[4] as seen in ferrocifen was not verified in these hybrids. In all cases, ferrocenic compounds were also much more efficient than organic analogues. We propose that the functionalized side chain may play a fundamental role in the intracellular transport of cytotoxic organometallic moieties to active target sites. With these hindered structures, the redox motif [Fc-ene-phenol] is inhibited but the construct is still active.



References

- [1] Cázares-Marinero, J.J.; Lapierre, M.; Cavaillès, V.; Saint-Fort, R.; Vessièrès, A.; Top, S.; Jaouen, G. Dalton Trans 2013, 42, 15489–15501.
- [2] Cázares-Marinero, J.J.; Top, S.; Jaouen, G. J Organomet Chem 2014, 751, 610–619.
- [3] Cázares-Marinero, J.J.; Top, S.; Vessièrès, A.; Jaouen, G., Dalton Trans 2014, 43, 817–830.
- [4] Cázares-Marinero, J.J.; Buriez, O.; Labbé, E.; Top, S.; Amatore, C.; Jaouen, G. Organometallics 2013, 32, 5926–5934.

Artificial metalloenzymes derived from bovine beta-lactoglobulin for the asymmetric transfer hydrogenation of an aryl ketone

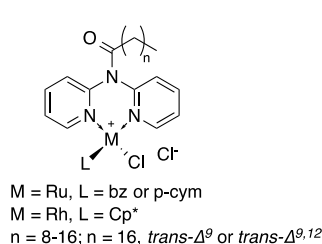
Michèle SALMAIN,^{a)} **Alice CHEVALLEY,**^{a)} **José de Jesus CAZARES-MARINERO,**^{a)}
Mickael V. CHERRIER,^{b)} **Juan C. FONTECILLA-CAMPS**^{b)}

a) Sorbonne Universités, UPMC Univ Paris 06, IPCM, UMR 8232, F-75005 Paris, France;
 michele.salmain@chimie-paristech.fr

b) Metalloproteins unit, IBS, UMR 5075, CEA, CNRS, University Grenoble-Alpes, 38027
 Grenoble, France

Our current research project aims at the design of artificial metalloenzymes operating in environmentally friendly conditions. These hybrid species result from the controlled assembling of synthetic metal cofactors to protein scaffolds. We focused our researches on the design of artificial transfer hydrogenases for the enantioselective reduction of ketones. Since the supramolecular anchoring strategies have provided the most efficient catalytic systems to date, we selected bovine beta-lactoglobulin (bLG) as protein host. bLG displays a 8-stranded, antiparallel beta-barrel folding, forming a calyx lined with hydrophobic residues and binds fatty acids with submicromolar dissociation constants and 1:1 stoichiometry.

We designed and synthesized a large series of bidentate ligands derived from fatty acids by appending a 2,2'-dipyridylamine moiety to their carboxylic acid function. Mononuclear, monocationic, half-sandwich Ru(II) and Rh(III) complexes were then obtained in excellent to quantitative yields from the ligands [1].



Effective association of most of the ligands / complexes to bLG was assessed by various spectroscopic methods and confirmed by protein X-ray crystallography [2]. Eventually, the catalytic activity of the hybrids was tested on a benchmark hydrogenation reaction and the enantiomeric excess reached 32% thanks to the chiral environment brought by the protein.

[1] Chevalley, A.; Cherrier, M. V.; Fontecilla-Camps, J. C.; Ghasemi, M.; Salmain, M. Dalton Trans. 2014, 43, 5482 - 5489.

[2] Cherrier, M. V.; Engilberge, S.; Amara, P.; Chevalley, A.; Salmain, M.; Fontecilla-Car C. Eur. J. Inorg. Chem. 2013, 3596-3600.

NanoSIMS combined with fluorescence microscopy as a tool for subcellular imaging of isotopically labeled platinum-based anticancer drugs

Anton A. LEGIN, ^{a,b)} **Arno SCHINTLMEISTER**, ^{c)} **Michael A. JAKUPEC**, ^{a,b)} **Markus GALANSKI**, ^{a,b)} **Irene LICHTSCHEIDL**, ^{e)} **Michael WAGNER**, ^{c,d)} and **Bernhard K. KEPPLER** ^{a,b)}

a) Institute of Inorganic Chemistry, University of Vienna, Waehringer Str. 42, A-1090, Vienna, Austria, anton.legin@univie.ac.at; b) Research Platform “Translational Cancer Therapy Research”, University of Vienna, Waehringer Strasse 42, A-1090 Vienna, Austria; c) Large-Instrument Facility for Advanced Isotope Research, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria; d) Department of Microbiology and Ecosystem Research, Division of Microbial Ecology, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria; e) Core Facility of Cell Imaging and Ultrastructure Research, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria

Multi-elemental, isotope selective nano-scale secondary ion mass spectrometry (NanoSIMS) proved to be a highly sensitive technique for subcellular imaging of anticancer drugs in cell culture samples [1-3]. NanoSIMS combined with confocal laser-scanning microscopy was used to characterise the subcellular distribution of ¹⁵N-labeled cisplatin in human colon cancer cells. These analyses indicated a predominant cisplatin co-localisation with sulfur-rich structures both in the nucleus and cytoplasm. Furthermore, co-localisation of platinum with phosphorus-rich chromatin regions was observed, which is consistent with its binding affinity to DNA as the generally accepted crucial target of the drug. Application of ¹⁵N-labeled cisplatin and subsequent measurement of the nitrogen isotopic composition and determination of the relative intensities of platinum and nitrogen associated secondary ion signals in different cellular compartments with NanoSIMS suggested partial dissociation of Pt-N bonds during the accumulation process, in particular within nucleoli at elevated cisplatin concentrations. Within the cytoplasm, platinum mainly accumulated in acidic organelles as demonstrated by a direct combination of specific fluorescent staining, confocal laser scanning microscopy and NanoSIMS. Combination with complementary analytical and imaging techniques can aid in identifying and characterising subcellular structures highlighted in elemental distribution patterns measured by NanoSIMS.

References:

- [1] Wedlock, L.E., Kilburn, M.R., Liu, R., Shaw, J.A., et al., Chem Commun 2013, 49, 6944-6946.
- [2] Wedlock, L.E., Kilburn, M.R., Cliff, J.B., Filgueira, L., et al., Metallomics 2011, 3, 917-925.
- [3] Legin, A.A., Schintlmeister, A., Jakupc, M.A., Galanski, M., et al., Chem Sci 2014, in press.

Switching on Anticancer Activity of Transition Metals using modified OO and NO ligands

Patrick C. MCGOWAN,^a Rianne M. LORD,^a Adi NAKO,^a James. J. MANNION,^a Andrew. J. HEBDEN,^a Ben. D. CROSSLEY,^a Max W. MCMULLON^a, Christopher M. PASK,^a Stephanie J. LUCAS,^a Andrea RODRÍGUEZ-BÁRZANO,^a Simon J. ALISON,^b and Roger M. PHILLIPS^b

a) School of Chemistry, University of Leeds, Leeds, UK, LS2 9JT; p.c.mcgowan@leeds.ac.uk

b) Institute of Cancer Therapeutics, Bradford University, Bradford, UK, BD7 1DP

We report the design, synthesis and characterisation of Group 4, 8 and 9 metal complexes.¹⁻³ We include the assessment of cytotoxicity under normoxic and hypoxic environments, measurements of potential DNA damage through a range of Comet assay techniques, assessment of potential DNA binding through melting curve analysis and finally the interference of these complexes on the cell cycle, apoptosis and thioredoxin reductase studies.¹⁻²

We report a library of group 8 and 9 B-ketoiminate complexes to be active against MCF-7 (human breast carcinoma), HT-29 (human colon carcinomas), A2780 (human ovarian carcinomas) and A2780cis (cisplatin resistant human ovarian carcinomas) cell lines, with selected complexes over three times more active than cisplatin against the A2780cis cell line. Complexes have also shown to be highly active under hypoxic conditions, with most complexes increasing with a decrease in O₂ concentration. The enzyme thioredoxin reductase is over expressed in cancer cells and complexes reported herein have the advantage of inhibiting this enzyme, with IC₅₀ values measured in the nanomolar range. The anti-cancer activity of these complexes was further investigated to see whether

activity is due to effects on cellular growth or cell survival. The complexes were found to induce significant cancer cell death by apoptosis with levels induced correlating closely with activity in chemosensitivity studies.

We have also investigated the mechanistic and cytotoxic nature of a series of group 4 β -diketonate coordination complexes and show the ligands are exchangeable on the metal centre.³ When evaluated for the cytotoxicity against human colon adenocarcinoma (HT-29) and human breast adenocarcinoma (MCF-7) cell lines, a general trend of decreasing potency down the group IV metals was observed. This tri β -diketonate hafnium complex (Figure 1) shows potent in vitro cytotoxic activity.³

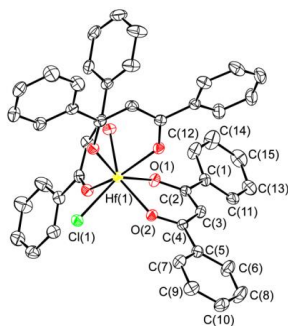


Figure 1

References:

- [1] Z. Almodares, S. J. Lucas, B. D. Crossley, A. M. Basri, C. M. Pask, A. J. Hebden, R. M. Phillips and P. C. McGowan, *Inorg.Chem.*, **2014**, 53(2), 727-773.
- [2] V. Brabec, S. E. Howson, R. A. Kaner, R. M. Lord, J. Malina, R. M. Phillips, Q. M. A. Abdallah, P. C. McGowan, A. Rodger and Peter Scott, *Chem. Sci.*, **2013**, 4, 4407-4416.
- [3] R. M. Lord, A. E. Nako, J. J. Mannion, A. J. Hebden, B. D. Crossley, M. W. McMullon, F. D. Janeway, R. M. Phillips and P. C. McGowan, *ChemMedChem*, DOI: 10.1002/cmdc.201402019.

Dinuclear Arene Ruthenium Trithiolato Complexes with High Anticancer Activity: An *in vitro* and *in vivo* Study

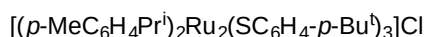
Georg SÜSS-FINK,^{a)} **David STIBAL,**^{a)} **Pavel TOMSIK,**^{b)} **Martina REZACOVA,**^{b)}
Stanislav MICUDA,^{b)} **Stephan HANN**^{c)}

a) University of Neuchâtel, Neuchâtel, Switzerland (georg.suess-fink@unine.ch)

b) Charles University, Faculty of Medicine in Hradec Králové, Czech Republic

c) University of Natural Resources and Life Sciences Vienna, Vienna, Austria

A variety of dinuclear arene ruthenium trithiolato cations of the type $[(\text{arene})_2\text{Ru}_2(\text{SR})_3]^+$ have been synthesized by reaction of the corresponding arene ruthenium dichloride dimer with various thiols and isolated as the chloride salts. All compounds $[(\text{arene})_2\text{Ru}_2(\text{SR})_3]\text{Cl}$ show high anticancer activity *in vitro*, the IC_{50} values for human ovarian cancer cells being in the nanomolar range. The most active complex is the *p*-cymene derivative with *p*-*t*-butylphenylthiolato bridges [1].



in vitro activity for cancer cells:

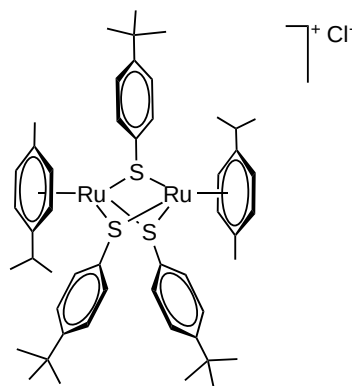
$\text{IC}_{50} = 30 \text{ nM}$ for A2780

$\text{IC}_{50} = 30 \text{ nM}$ for A2780cisR

in vivo activity for tumour-bearing mice:

Therapeutic window: 0.4 - 0.6 mg/kg

Survival prolongation by 8.5 days (average)



An *in vivo* anticancer study with 98 NMRI female mice, inoculated subcutaneously with a solid Ehrlich tumour, showed that doses of 0.4 to 0.6 mg/kg administered twice within 8 days inhibited the tumour growth and prolonged the survival of the mice considerably.

References:

[1] Giannini, F.; Furrer, J.; Ibaó, A.-F.; Süß-Fink, G.; Therrien, B.; Zava, O.; Baquie, M.; Dyson, P. J.; Štěpnička, P., Highly cytotoxic trithiophenolatodiruthenium complexes of the type $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\text{SC}_6\text{H}_4\text{-}p\text{-X})_3]^+$: Synthesis, molecular structure, electrochemistry, cytotoxicity, and glutathione oxidation potential, J. Biol. Inorg. Chem. 2012, 17, 951-960.

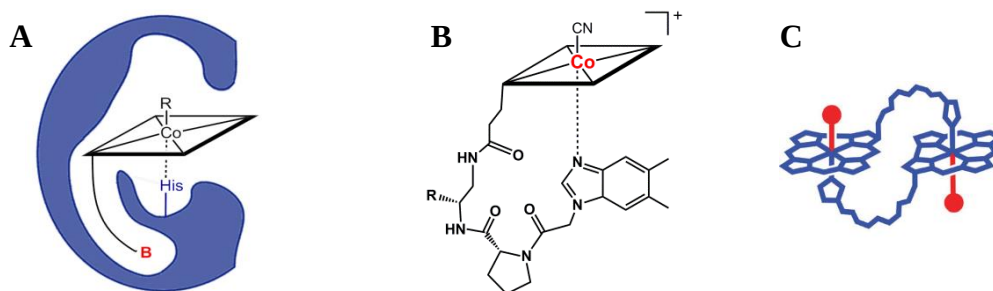
Accessing Modified Properties and Functions of Vitamin B₁₂ through Backbone Alterations

Marjorie SONNAY, ^{a)} Felix ZELDER, Kai ZHOU.

a) marjorie.sonnay@chem.uzh.ch

University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland.

The elaborate structure of Vitamin B₁₂ and its derivatives allows important reversible structural modifications. They can thus act as molecular switches through a reversible coordination of the backbone to the cobalt center (base-on/base-off). Through this interesting feature, the physico-chemical properties of B₁₂ and B₁₂ cofactors can be modified.^[1] B₁₂ dependent enzymes also take advantage of this characteristic by replacing the backbone by a histidine residue, which coordinates to the cobalt (figure A).^[2]



Our group is interested in synthesizing new B₁₂ derivatives (peptide B₁₂), which bear artificial peptide backbones with modular redox and coordination properties. Those analogs brought important insights in various domains, and our recent research advancements will be presented. Some biomimetic cobalamins are good potential enzymatic inhibitors (figure B)^[1] while others allow a better understanding of the cofactor activation in catalytic cycles. Furthermore, a different peptidic backbone yields an interesting intermolecular coordination, leading to a dimeric structure (figure C).^[3]

References:

- [1] Zelder, F.; Zhou, K.; Sonnay, M., Peptide B12: emerging trends at the interface of inorganic chemistry, chemical biology and medicine. Dalton Transactions 2013, 42, 854-862.
- [2] Drennan, C. L.; Huang, S.; Drummond, J. T.; Matthews, R. G.; Ludwig, M. L., How a protein binds B12: a 3.0 Å X-ray structure of B12-binding domains of methionine synthase. Science 1994, 266, 1669-1674.
- [3] Zhou, K.; Zelder, F., "Intra base off/inter base on" coordination: self-assembly of a dimeric vitamin B12 derivative with a versatile tail. Chemical Communications 2011, 47(43), 11999-12001.

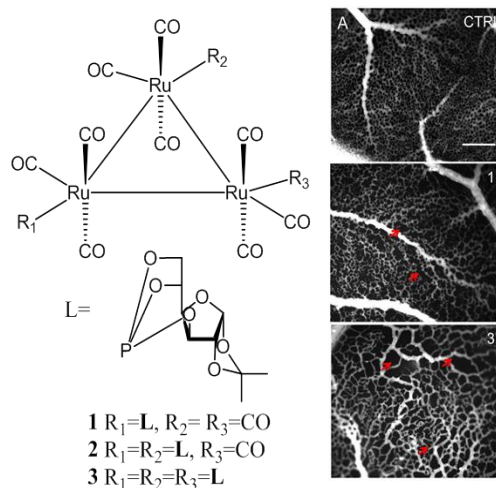
Ruthenium and Osmium clusters: anticancer and anti-angiogenic activity.

Alexey A. NAZAROV^{a)}

*a) Department of Chemistry, M.V.Lomonosov Moscow State University, Leninskie Gory,
119991, Moscow, Russia, alexey.nazarov@me.com*

The research in metal-based anticancer compounds has traditionally focused on platinum-based compounds, however, in recent years there has been much of interest in the development of ruthenium-based anticancer compounds that found to be less cytotoxic towards cancer cells and operate via distinguish different mechanisms to platinum drugs. Two Ru(III) compound (NAMI-A, KP1019) are presently in clinical trials. The organometallic ruthenium(II) complexes (RAPTA) showed strong anti-metastatic and anti-angiogenic effects. In this presentation synthesys of new triruthenium and triosmium -carbonyl clusters derivatized with glucose-modified bicyclopophosphite and evaluation of these compounds as anticancer and anti-angiogenic agents will be discussed. Biological activity was found depend on the number of bicyclopophosphite ligands, and could be tuned for either anticancer or specific anti-angiogenic activity. A good inhibition of angiogenesis was observed in the in vivo chicken chorioallantoic membrane (CAM) model.

The authors are grateful for financial support from Russian Foundation for Basic Research (project no. 13-03-00513_a, 14-03-01101-a and 13-03-12460)



Reference:

[1] Nazarov, A. A.; Baquié, M.; Nowak-Sliwinska, P.; Zava, O.; van Beijnum, J. R.; Groessl, M.; Chisholm, D. M.; Ahmadi, Z.; McIndoe, J. S.; Griffioen, A. W.; van den Bergh, H.; Dyson, P. J., Synthesis and characterization of a new class of anti-angiogenic agents based on ruthenium clusters, *Sci. Rep.* 2013, 3, Article Number 1485.

8-Hydroxyquinolines as Bioactive Ligand Systems in the Preparation of Multi-modal Anticancer Drugs

Mario KUBANIK,^{a)} Hannah HOLTKAMP,^{a)} Lukas K. FILAK,^{a)} Stephen M. F. JAMIESON,^{b)} Wolfgang KANDIOLLER,^{c)} Bernhard K. KEPPLER,^{c)} Christian G. HARTINGER^{a)}

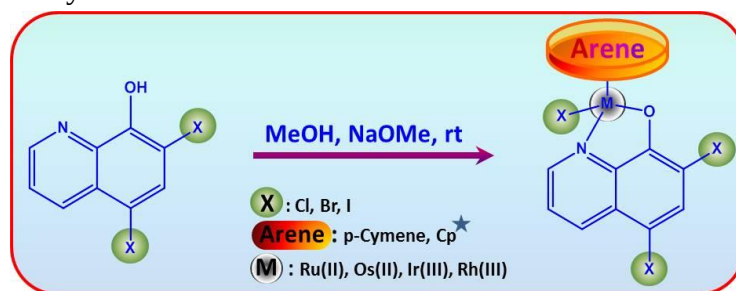
a) University of Auckland, School of Chemical Sciences, Private Bag 92019, Auckland 1142, New Zealand. Email: mkub368@aucklanduni.ac.nz

b) Auckland Cancer Society Research Centre, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

c) University of Vienna, Institute of Inorganic Chemistry, Waehringer Str. 42, A-1090 Vienna, Austria

Quinolines are heterocyclic nitrogen containing aromatic double ring structures with a broad spectrum of pharmacological properties, such as anti-inflammatory,^[1] antimalarial,^[2] anticancer^[3] and antifungal^[4] activity. The complexation of those bioactive chelators to a biologically-active metal centre can result in increased solubility, enhanced cellular uptake of the ligands as well as synergistic effects (“multi-targeted” compounds) and different modes of action.

We report the synthesis of 8-hydroxyquinoline-based metal complexes (M = Ru(II), Os(II), Ir(III) and Rh(III)). All compounds were characterized by determination of the melting point, elemental analysis, NMR, MS and UV/Vis spectroscopy. The biological activity of selected substances was established on cancer cell lines and the behavior towards small biomolecules was studied with NMR spectroscopy and capillary electrophoretic methods. Furthermore the solid state structure of several complexes (Ru(II), Os(II) and Ir(III)) were determined by X-ray diffraction analysis.



References:

- [1] Mukherjee, S.; Pal, M., Medicinal chemistry of quinolines as emerging anti-inflammatory agents: An overview. *Curr Med Chem*, 2013, 20, 4386-4410.
- [2] Kaur, K.; Jain, M.; Reddy, R.; Jain, R., Quinolines and structurally related heterocycles as antimalarials. *Eur J Med Chem*, 2010, 45 (8), 3245-3264.
- [3] Solomon, R.; Lee, H., Quinoline as a Privileged Scaffold in Cancer Drug Discovery. *Curr Med Chem*, 2011, 18 (10), 1488-1508.
- [4] Musiol, R.; Serda, M.; Hensel-Bielowka, S.; Planski, J., Quinoline-Based Antifungals. *Curr Med Chem*, 2010, 17 (18), 1960-1973.

TARGET-ORIENTED ORGANOMETALLIC AND COORDINATION COMPOUNDS WITH PROTECTIVE 2,6-DIALKYLPHENOL GROUP

Elena MILAEVA

*Moscow State Lomonosov University, Lenin Hill, 1-3, Moscow, 119991, Russia
milaeva@org.chem.msu.ru*

A novel approach to the construction of polytopic agents which combine both the biomimetic of the natural antioxidant α -tocopherol and biogenic Fe, Mn, Cu, Co, Zn or cytotoxic Sn, Sb, Au has been proposed for a design of physiologically active substances. This presentation will focus on a synthesis and on the study in vitro, ex vivo and in vivo activities in the cellular processes that are suggested as biomolecular targets responsible for the cellular redox and proliferative status disbalance.

The multifactor antioxidative, antiproliferative activities and neuroprotective potential assay of compounds has been performed by using DPPH, CUPRAC-tests, liposome system and enzymatic methods (xanthine oxidase, lipoxygenase, glutathione reductase, thioredoxine reductase, tubulin); the model reactions of fatty acids peroxidation; ex vivo lipid peroxidation in mitochondria isolated from Wistar rat brain and liver, in vitro lipid peroxidation in rat and fish liver homogenates. The in vivo study was performed for the hit compounds.

The financial support of Russian Science Foundation (14-13-00483) is gratefully acknowledged.

References:

- [1] Shpakovsky, D.B., Banti, C.N., Mukhatova, E.M., Gracheva, Yu.A., Osipova, V.P., Berberova, N.T., Albov, D.V., Antonenko, T.A., Aslanov, L.A., Milaeva, E.R., Hadjikakou S.K., Synthesis, antiradical activity and in vitro cytotoxicity of novel organotin complexes based on 2,6-di-tert-butyl-4-mercaptophenol. Dalton Trans., 2014, Vol.43, pp. 6880–6890.
- [2] Milaeva, E.R., Shpakovsky, D.B., Gracheva, Yu.A., Orlova, S.I., Maduar, V.V., Tarasevich, B.N., Meleshonkova, N.N., Dubova, L.G., Shevtsova, E.F., Metal complexes with functionalised 2,2'-dipicolylamine ligand containing an antioxidant 2,6-di-tert-butylphenol moiety: synthesis and biological studies, Dalton Trans., 2013, Vol.42, 6817–6828.
- [3] Shpakovsky, D.B., Banti, C.N., Beaulieu-Houle, G., Kourkoumelis, N., Manoli, M., Manos, M.J., Tasiopoulos, A.J., Hadjikakou, S.K., Milaeva, E.R., Charalabopoulos, K., Bakas, T., Butler, I.S., Hadjiliadis, N., Synthesis, structural characterization and in vitro inhibitory studies against human breast cancer of the bis-(2,6-di-tert-butylphenol)tin(IV) dichloride and its complexes. Dalton Trans., 2012, Vol. 41, pp. 14568-14582.
- [4] E.R. Milaeva. Metal-Based Antioxidants - Potential Therapeutic Candidates for Prevention the Oxidative Stress-Related Carcinogenesis. Current Topics in Med. Chem., 2011, Vol.11, pp. 2703-2713.

A Fluorescent Probe for Investigating the Activation of Anticancer Platinum(IV) Prodrugs based on Cisplatin scaffold

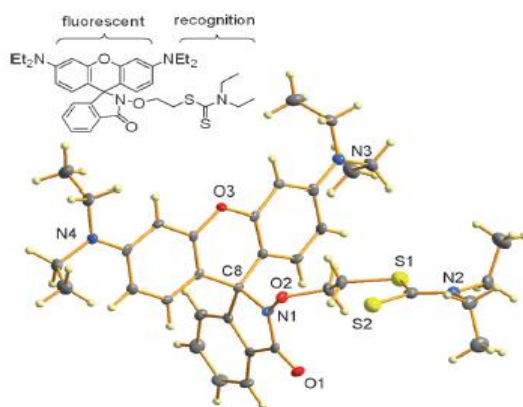
Diego MONTAGNER,^{1,2} Siew Qi YAP,¹ Wee Han ANG^{1*}

¹ *Department of Chemistry, National University of Singapore, 3 Science Drive, Singapore*

² *School of Chemistry, NUI Galway, Ireland; E-mail: diego.montagner@nuigalway.ie*

Following the discovery of its potent antitumoral activity in 1965, the inorganic drug cisplatin has become one of the most important anticancer agents used in the clinic.¹ After this, others Pt(II) based complexes are used as anticancer agents (i.e. carboplatin, oxaliplatin).² In this abstract we present a fluorescent turn-on probe rationally designed for the study of anticancer Pt complexes within live cells. This probe (Rho-DDTC, figure) was custom-built for the detection of Pt(II) drugs such as cisplatin and demonstrate using confocal microscopy the localization of Pt(IV) prodrugs in cancer cells in vitro after cell entry and intracellular reduction.³

The probe is compatible with biological conditions and designed to specific towards Pt(II) complexes containing the diam(m)ineplatinum(II) pharmacophore such as cisplatin. The probe is also able to distinguish between Pt(IV) prodrug complexes and their Pt(II) products. We showed for several Pt(IV) prodrugs, including satraplatin, that reduction occurred after cell entry and the Pt(II) products accumulate with the cytoplasm. In summary, Rho-DDTC is a versatile tool to study localization of clinically important Pt(II) anticancer drugs and the activation of their Pt(IV) prodrug congeners within live cells.



[1] B. Rosenberg, L. Van Camp, T. Krigas, *Nature* 1965, 205, 698-699; (b) B. Rosenberg, L. Van Camp, J. E. Trosko, V. H. Mansour, *Nature* **1969**, 222, 385-386.

[2] L. Kelland, *Nat. Rev. Cancer* 2007, 7, 573-584; (b) D. Wang, S. J. Lippard, *Nat. Rev. Drug Discover.* **2005**, 4, 307-320

[3] D. Montagner, S.Q. Yap, W.H. Ang, *Angew. Chem. Int. Ed.* **2013**, 125, 12001-12005.

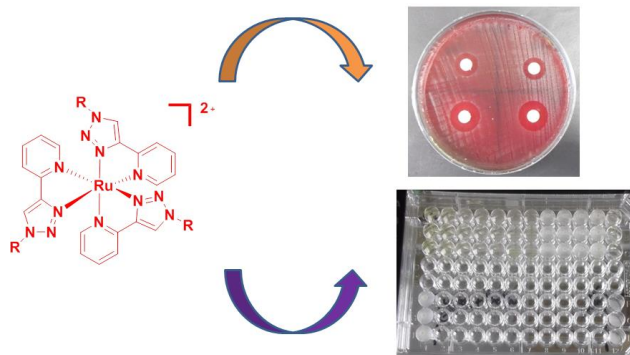
Ruthenium-pyridyl-1,2,3-triazole complexes: Metalloantimicrobials against drug resistant bacteria

Sreedhar K. VELLAS^{a&b} **Lyall R. HANTON,**^a **Heather J. L. BROOKS,**^b
James D. CROWLEY^a

a) Department of Chemistry, University of Otago, P.O.box 56, Dunedin, New Zealand

*b) Department of Microbiology and Immunology, University of Otago, New Zealand;
presenting author e-mail:svellas@chemistry.otago.ac.nz*

The rapid emergence of drug resistant bacterial strains emphasizes the need to develop new classes of antimicrobials. Metal complexes offer a different steric and electronic profile when compared to traditional organic antimicrobials which could be useful for the generation of new and more effective drugs. The use of ruthenium polypyridyl complexes as antibacterial agents was first reported by Dwyer¹ in 1952 and this area has been reinvigorated recently by Keene.² We have previously exploited the copper catalyzed azide alkyne cycloaddition (CuAAC) "click" reaction to generate pyridyl-1,2,3-triazole ligand systems, complexed them to iron(II) and examined their antifungal activity.³ Inspired by Dwyer and Keene's work we have used our "click" ligands to synthesize a series of mononuclear ruthenium complexes with varying lipophilicities. Preliminary investigations have revealed that these ruthenium complexes were bactericidal against different multidrug resistant bacterial strains.



References:

- [1] Dwyer, F.P.; Gyarfas, E.C.; Rogers, W.P.; Koch, J.H., Biological activity of complex ions. *Nature*, 1952, 170, 190-1.
- [2] Li, F.; Mulyana, Y.; Feterl, M.; Warner, J.M.; Collins, J.G.; Keene, F.R., The antimicrobial activity of inert oligonuclear polypyridyl ruthenium(II) complexes against pathogenic bacteria including MRSA. *Dalton Transactions*. 2011, 40, 5032-5038.
- [3] Vellas, S.K.; Lewis, J.E.M.; Shankar, M.; Sagatova, A.; Tyndall, J.D.A.; Monk, B.C.; Fitchett, C.M.; Hanton, L.R.; Crowley, J.D., $[\text{Fe}_2\text{L}_3]^{4+}$ cylinders derived from bis(bidentate) 2-pyridyl-1,2,3-triazole "click" ligands. Synthesis and exploration of biological activity. *Molecules* 2013, 18, 6383-6407.

Leading-edge gold(III) derivatives in targeted anticancer therapy: in vivo acute toxicity investigation and global gene expression analysis of treatment-induced response in two human breast cancer cell lines

Chiara NARDON,^{a)} **Angelina BOCCARELLI**,^{b)} **Fabiana LANOTTE**,^{c)} **Mauro COLUCCIA**,^{b)} **Dolores FREGONA**^{a)}

a) Dept. of Chemical Sciences, University of Padova, Via F. Marzolo 1, Padova 35131, Italy

b) Dept. of Pharmacy, c) Dept. of Computer Science, University of Bari "Aldo Moro", Via Orabona 4, Bari 70125, Italy; E-mail chiara.nardon@unipd.it

With more than one hundred different subtypes [1], cancer is the most lethal disease, after cardiovascular pathologies, with tremendous psychological and economic relapses in our culture and society. Since the serendipitous discover of the cytotoxic effects of cis-dichlorodiamine platinum(II) (named cisplatin) in 1965 [2], an ever-developing era has arose for anticancer compounds. Starting from the chemical properties of Pt(II) and the severe toxicological profile of cisplatin, in the last decade we have designed and biologically studied a new library of dithiocarbamate complexes with promising antitumor activity and reduced toxicity compared to the reference drug[3]. Among all the studied potential drugs, the Au(III)-based complexes AuL12 and AuD8 proved to be particularly interesting due to a good chemotherapeutic index [4], in terms of toxicity/activity ratio. Acute toxicity has been recently evaluated for the peptidomimetic AuD8 in 80 mice by two administration routes (i.v. and oral) taking into account different doses, much higher than those used in chemotherapy, recording outstanding results. No death nor alterations or gross anatomical findings in the main organs and tissues were observed at necropsy. In combination with cell cycle analysis, global gene expression modifications induced by AuL12 and AuD8 have been thoroughly investigated in MCF7 and MDA-MB-231 human breast cancer cell lines. The percentage of differentially expressed genes after AuL12 treatment was higher than that after AuD8 treatment for both MCF7 (9% and 5%, respectively) and MDA cells (9% and 6%, respectively). Distinct pathway maps significantly enriched in MCF7 and MDA cells were identified through functional analysis, thus providing a global view of the changes occurring in the intracellular networks upon metallodrug perturbation.

References:

- [1] Hanahan, D.; Weinberg, R.A.; Hallmarks of Cancer: the next generation. *Cell* 2011, 144, 646-674.
- [2] Rosenberg, B.; Van Camp, L.; Krigas, T.; Inhibition of Cell Division in *Escherichia coli* by Electrolysis Products from a Platinum Electrode, *Nature* 1965, 205 (4972), 698-699.
- [3] Nagy E.M.; Ronconi, L.; Nardon, C.; Fregona D.; Noble metal-dithiocarbamates precious allies in the fight against cancer. *Mini-Reviews in Medicinal Chemistry* 2012, 12(12),1216-1229.
- [4] Nardon, C.; Boscutti, G.; Fregona, D.; Beyond platinum: gold complexes as anticancer agents. *Anticancer Research* 2014, 34 (1), 487-492.

Insights into the chemical biology of rhodium(I) N-heterocyclic carbene complexes as anticancer agents.

Luciano OEHNINGER,^{a)} Sarah SPRECKELMEYER,^{a)} Pavlo HOLENYA,^{b)} Nadine L. KÜSTER,^{c)} Aram PROKOP,^{c)} Stefan WÖLFL,^{b)} Ingo OTT^{a)}

a) Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, Beethovenstr. 55, D-38106 Braunschweig, Germany.

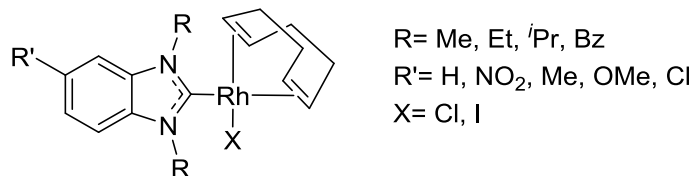
b) Institute of Pharmacy and Molecular Biotechnology, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 364, D-69120 Heidelberg, Germany.

c) Department of Paediatric Oncology, Childrens Hospital Cologne, Amsterdamer Strasse 59, D-50735 Cologne, Germany.

l.oehninger@tu-bs.de

The anticancer properties of rhodium-based organometallic complexes have been widely studied for some decades. A high number of these compounds contain a Cp*Rh(III) fragment, which has been coordinated to diverse organic fragments with remarkable biological results.[1] In the last years, an increasing number of reports were published about Rh(I) derivatives, which showed good activity in vitro against various cancer cell lines.[2]

N-heterocyclic carbene (NHC) moieties are interesting ligands, which could form stable bioactive Rh(I) complexes. To understand the influence of the ligands on the biological activity of these derivatives, a large series of rhodium complexes was synthesized varying the NHC, as well as the halido ligands.[3] Pronounced antiproliferative effects were noted for all complexes, along with moderate inhibitory activity of thioredoxin reductase and efficient binding to biomolecules (DNA and albumin). Biodistribution studies confirmed the transport of rhodium into the nuclei. DNA fragmentation and changes in the mitochondrial membrane potential were observed, indicating the induction of apoptosis. ELISA microarrays were performed for selected complexes showing over- and down-regulation for a large number of proteins. The signaling induced by the rhodium derivatives involved, among others, cytotoxic stress, growth arrest and cell detachment.



References:

- [1] Geldmacher Y., Oleszak, M., Sheldrick W.S., *Inorg. Chim. Acta* 2012, 393, 84– 102.
- [2] Li Y., Kock C.d., Smith P.J., Guzgay H, Hendricks D.T., Naran K., Mizrahi V., Warner D.F., Chibale K., Smith G.S, *Organometallics* 2013, 32, 141-150.
- [3] Oehninger, L., Küster, L. N., Schmidt, C., Muñoz-Castro, A., Prokop, A., Ott I., *Chem. Eur. J.* 2013, 19, 17871–17880.

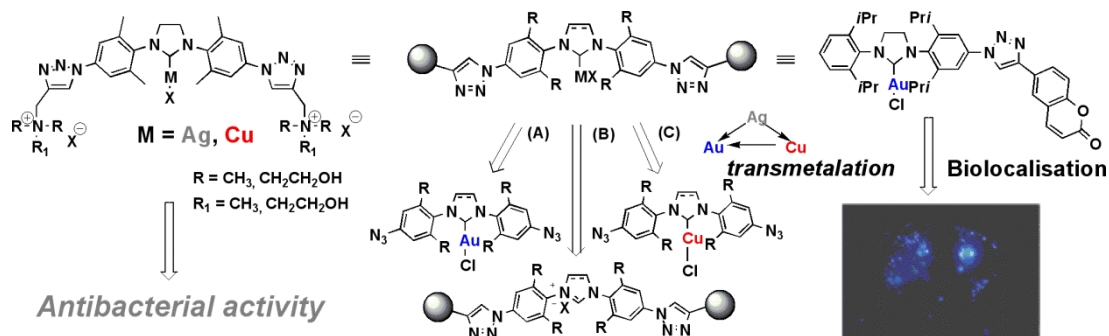
Azide-alkyne functionalisation of coinage metal-NHC complexes: efficient methods for the generation of biorelevant organometallics

Federico CISNETTI,^{a)} Clémentine GIBARD,^{a)} Houssein IBRAHIM,^{a)} Arnaud GAUTIER^{a)}

a) Institut de Chimie de Clermont-Ferrand - UMR CNRS 6296, Université Blaise Pascal, 63171 Aubière, France. federico.cisnetti@univ-bpclermont.fr

In this communication, we demonstrate the interest of efficient and modular synthetic methods to build libraries of organometallic compounds for bioactivity studies. Quite surprisingly, azide-alkyne 'click' chemistry has seldom been used with metal N-heterocyclic carbenes complexes. Starting from azide-tagged NHC precursors "post-fonctionnalisation" (Huisgen, CuAAC and SPAAC, routes A and C) and "pre-fonctionnalisation" (CuAAC, route B) were performed to access diversified architectures.^[1]

Two selected applications will be presented. An "auto-click" strategy using a Cu^I-NHC as catalyst and substrate allows a rapid access to sets of Cu^I and Au^I-NHCs for a specific biological purpose: e.g. the localization in cancer cells of a fluorescent derivative.^[1b] 2) Water-soluble prefunctionalised Ag^I- and Cu^I-NHC complexes bearing cationic pendants have shown antibacterial properties in classical assays and have been included in a library of metal-NHC complexes for the high throughput assessment of antibiofilm activity.^[2]



References:

- [1] (a) Gibard, C.; Avignant, D.; Cisnetti, F.; Gautier, A. CuAAC Functionalization of Azide-Tagged Copper(I)-NHCs Acting as Catalyst and Substrate, *Organometallics*, 2012, 31, 7902-7908. (b) Ibrahim, H.; Gibard, C.; Hesling, C.; Guillot, R.; Morel, L.; Gautier, A.; Cisnetti, F., 'Auto-click' functionalization for diversified copper(I) and gold(I) NHCs *Dalton Trans*, 2014, 63, 6981-6989.
- [2] Bernardi, T.; Badel, S.; Mayer, P.; Groelly, J.; de Frémont, P.; Jacques, B.; Braunstein, P.; Teyssot, M.-L.; Gaulier, C.; Cisnetti, F.; Gautier, A.; Roland, S., High-Throughput Screening of Metal-N-Heterocyclic Carbene Complexes against Biofilm Formation by Pathogenic Bacteria, *ChemMedChem*, 2014, doi: 10.1002/cmdc.201402012

Organometal Coordination by Purines: Semi-chelate Bonding of Modified Guanine and Isocaffeine with Bis(diorganylphosphino)ferrocenylcopper

Wolfgang KAIM

*Institut für Anorganische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70550
Stuttgart, Germany; e-mail: kaim@iac.uni-stuttgart.de*

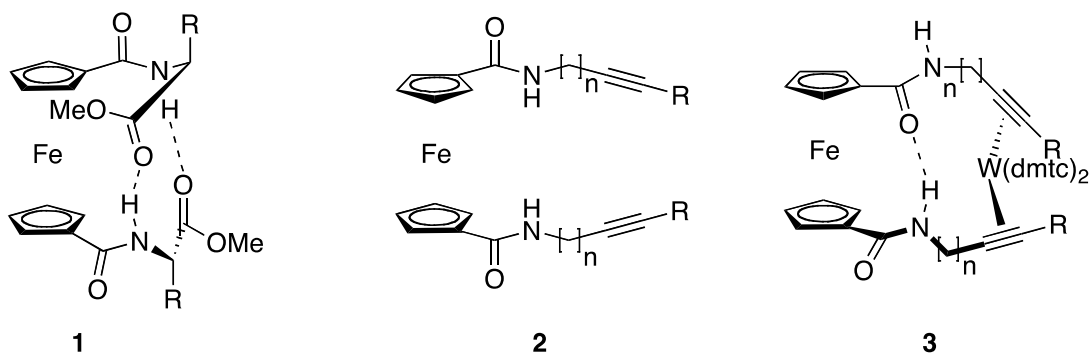
The $[(\text{dopf})\text{Cu}]^+$ complex fragment ($\text{dopf} = 1,1'$ -bis(diorganylphosphino)ferrocene) binds to the bidentate $\text{O}=\text{C}-\text{C}=\text{N}$ function provided by the isocaffeine and guanine heterocyclic systems in a variable “semi-chelate” coordination arrangement. Crystal structures reveal that the normal strong bond between copper and nitrogen is complemented by a weak, sometimes barely noticeable interaction of the oxygen atom with Cu^+ . While the ferrocene oxidation behaviour is conventional and not much different from that of related complexes of $[(\text{dopf})\text{Cu}]^+$ with lumazines or alloxazines, the structural variability of the purine ligands is unique and its implications will be discussed.

A 1,1'-Ferrocenedialkynyldiamide Adopts a van Staveren Conformation Upon Coordination of Both Alkynes to Tungsten

Timothy P. CURRAN, Allison P. LAWRENCE, Taylor S. MURTAUGH, Woojung JI, and Niranjana POKHAREL

*Department of Chemistry, Trinity College, 300 Summit Street, Hartford, CT 06106 USA;
timothy.curran@trincoll.edu*

In solution, peptide derivatives of 1,1'-ferrocenedicarboxylic acid (general structure **1**) generally adopt the Herrick conformation^{1,2}, in which two intramolecular hydrogen bonds form between the amino acid residues closest to the Cp rings. We report here the discovery of a new solution conformation for amide derivatives of 1,1'-ferrocenedicarboxylic acid that is mediated by tungsten-alkyne coordination. Ferrocenedialkynyldiamides having the general structure **2** have been prepared. Neither of the two NH protons in these species participates in an intramolecular hydrogen bond. However, when these dialkynyldiamides are reacted with $W(CO)_3(dmtc)_2$ they form cyclic tungsten bis-alkyne complexes having the general structure **3**. Unlike other cyclic tungsten bis-alkyne complexes that have been studied in our laboratory^{3,4}, which are conformationally flexible, one of these derivatives adopts a single solution conformation in which only one of the amide NH protons participates in an intramolecular hydrogen bond and the other one does not. This is the van Staveren conformation that was postulated in earlier work.² Details concerning the preparation and analysis of these species, along with information about how this finding could be used to constrain peptide conformation using both the ferrocene and tungsten bis-alkyne features will be presented.



References:

- [1] Herrick, R. S.; Jarret, R. M.; Curran, T. P.; Dragoli, D. R.; Flaherty, M. B.; Lindyberg, S. E.; Slate, R. A.; Thornton, L. C., *Tetrahedron Lett.* **1996**, 37, 5289-5292.
- [2] Kirin, S. I.; Schatzschneider, U.; Koster, S. D.; Siebler, D.; Metzler-Nolte, N., *Inorg. Chim. Acta* **2009**, 362, 894-906.
- [3] Curran, T. P.; Yoon, R. S. H.; Volk, B. R., *J. Organomet. Chem.* **2004**, 689, 4837-4847.
- [4] Curran, T. P.; Lesser, A. B.; Yoon, R. S. H., *J. Organomet. Chem.* **2007**, 692, 1243-1254.

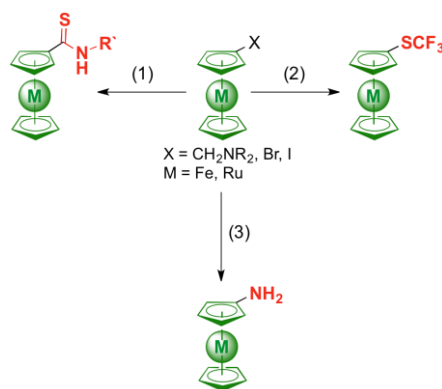
Facile Synthesis and Biological Activity of Metallocene Derivatives

**Jeannine HESS,^{a)} Malay PATRA,^{a)} Anna LEONIDOVA,^{a)} Vanessa PIERROZ,^{a,b)}
Stefano FERRARI,^{b)} Gilles GASSER^{a)}**

a) Department of Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland; jeannine.hess@chem.uzh.ch

b) Institute of Molecular Cancer Research, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland.

Small pharmacophores can play a crucial role for drug uptake, intracellular localization and can therefore influence the bioactivity. In recent years, new pharmacologically relevant metallocenes have been extensively studied as promising drug candidates. Hence the synthetic modification of metallocenes is a crucial tool for the design of such organometallic compounds. Three simple and useful synthetic pathways to prepare metallocene derivatives have been lately reported by our group: (1)^[1] a single-step three-component condensation for the efficient syntheses of various metallocenyl thioamides; (2)^[2] a novel synthetic procedure for trifluoromethylthio-substituted metallocenes, which does not require the use of toxic mercury(II)-based reagents; (3)^[3,4] an improved synthesis of aminometallocene, which meets the basic green chemistry specifications.



References:

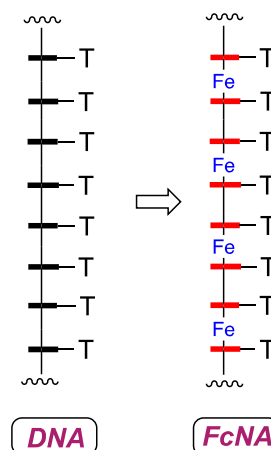
- [1] Patra, M.; Hess, J.; Konatschnig, S.; Spingler, B.; Gasser, G., Synthesis of Ferrocenyl and Ruthenocenyl Thioamide Derivatives Using a Single-Step Three-Component Reaction. *Organometallics* 2013, 32 (20), 6098-6105.
- [2] Hess, J.; Konatschnig, S.; Morard, S.; Pierroz, V.; Ferrari, S.; Spingler, B.; Gasser, G., Novel, Mercury-Free Synthetic Pathway for Trifluoromethylthio-Substituted Metallocenes. *Inorg. Chem.* 2014, 53 (7), 3662-3667.
- [3] Leonidova, A.; Joshi, T.; Nipkow, D.; Frei, A.; Penner, J.-E.; Konatschnig, S.; Patra, M.; Gasser, G., An Environmentally Benign and Cost-Effective Synthesis of Aminoferrocene and Aminoruthenocene. *Organometallics* 2013, 32 (6), 2037-2040.
- [4] Gasser, G.; Leonidova, A.; Joshi, T.; Nipkow, D.; Frei, A.; Penner, J.-E.; Konatschnig, S.; Patra, M., Eur. Pat. Appl. 2013, EP13157319.

Organometallic Mimics of Nucleic Acids and Nucleosides

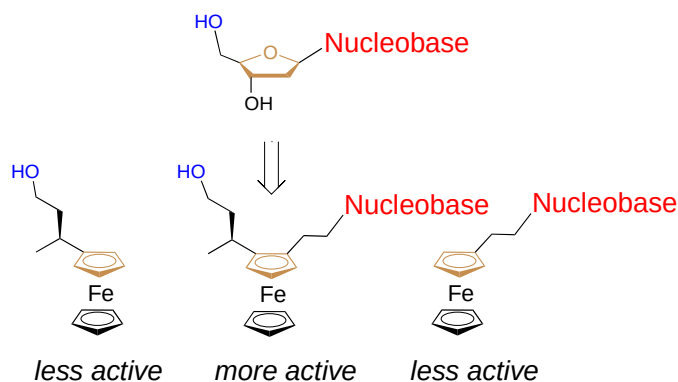
James H. R. TUCKER^{a)}

*a) University of Birmingham, School of Chemistry, Edgbaston, Birmingham, UK, B15 2TT
j.tucker@bham.ac.uk*

As part of our interest in bioorganometallic nucleic acid chemistry,[1] we recently reported the synthesis of an organometallic version of a nucleic acid called *ferrocene nucleic acid* (FcNA), in which the 5-membered sugar ring in DNA is replaced with a cyclopentadienyl unit and every other phosphate in the backbone is replaced with an iron atom.[2] In this presentation, progress in optimizing the synthesis of FcNA will be described, as well as new versions and conjugates containing other nucleobases. Preliminary findings on the electrochemical behavior of these oligomers and their binding behavior towards other nucleic acids will also be presented.



We have also recently discovered that versions of the monomeric components of FcNA present interesting biological activities. These so-called *ferronucleosides* give submicromolar



IC₅₀ activities in certain cancer cell lines and also display promising antiviral activities.[3] The synthesis of and biological studies on these chiral organometallic nucleoside analogues (with nucleobases T and A) will be presented, along with various control compounds. These studies point to a mode of action in which nucleic acid synthesis is adversely affected.

References:

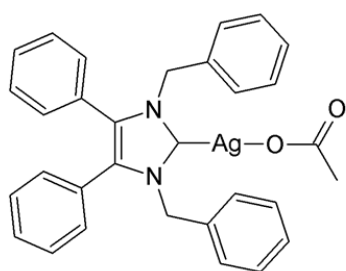
- [1] Duprey, J.L.H.A.; Tucker, J.H.R., Metal-Carbon Bonds in Biopolymer Conjugates: Bioorganometallic Nucleic Acid Chemistry. *Chem. Lett.* 2014, 43, 153-163
- [2] Nguyen, H.V.; Zhao, Z.Y.; Sallustrau, A.; Horswell, S.L.; Male, L.; Mulas, A.; Tucker, J.H.R., A ferrocene Nucleic Acid Oligomer as an Organometallic Structural Mimic of DNA. *Chem. Commun.* 2012, 48, 12165-12167.
- [3] Nguyen, H.V.; Sallustrau, A.; Balzarini, J.; Bedford, M.R.; Eden, J.C.; Georgousi, N.; Hodges, N.J.; Kedge, J.; Mehellou, Y.; Tselepis, C.; Tucker, J.H.R., Organometallic Nucleoside Analogues with Ferrocenyl Linker Groups: Synthesis and Cancer Cell Line Studies, *J. Med. Chem.*, 2014, 57, under revision.

Synthesis and Biological Evaluation of Novel Carbene-Metal Complexes as Potential Antibiotics and Anticancer Drugs

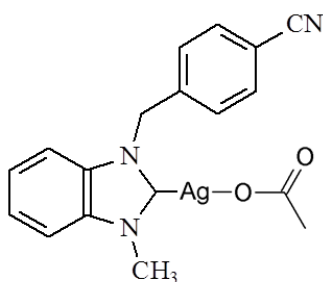
Matthias TACKE

*UCD School of Chemistry and Chemical Biology, University College Dublin
Belfield, Dublin 4, Ireland; matthias.tacke@ucd.ie*

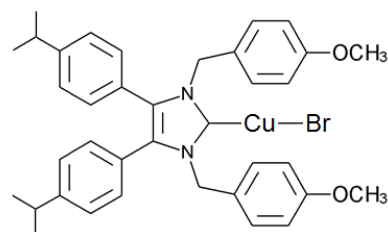
The synthesis of N-heterocyclic carbene (NHC) silver(I) acetate complexes with varying lipophilic benzyl-substituents at the 1 and 3 positions of the (benz)imidazole ring was achieved by reaction of silver(I) acetate with the corresponding (benz)imidazolium halide salts [1,2]. These NHC-silver(I) acetate derivatives exhibit interesting structural motifs in the solid state and prove to be soluble and stable in biological media. Some derivatives like SBC3 [2] show strong antibacterial activity against Gram-negative and Gram-positive bacteria [3], while others are cytotoxic. Here, NHC-silver(I) acetate complexes were found to have IC₅₀ values as low as 1.2 micromolar against the human renal cancer cell line Caki-1 and (1-methyl-3-(p-cyanobenzyl) benzimidazole-2-ylidene) silver(I) acetate has become the anticancer lead structure SBC1. The synthesis and biological evaluation of SBC1 and novel Ag, Au, Ru and Cu complexes like WBC4 will be communicated.



SBC3



SBC1



WBC4

Acknowledgments: This project was funded by UCD and IRCSET.

References:

- [1] Patil, S.; Dietrich, K.; Deally, A.; Gleeson, B.; Müller-Bunz, H.; Paradisi, F.; Tacke, M., Synthesis, Cytotoxicity and Antibacterial Studies of Novel Symmetrically and Nonsymmetrically 4-(Methoxycarbonyl)benzyl-Substituted N-Heterocyclic Carbene – Silver Acetate Complexes. *Helv. Chim. Acta*, **2010**, 93, 2347-2364.
- [2] Patil, S.; Deally, A.; Gleeson, B.; Müller-Bunz, H.; Paradisi, F.; Tacke, M., Novel Benzyl-Substituted N-Heterocyclic Carbene–Silver Acetate Complexes: Synthesis, Cytotoxicity and Antibacterial Studies. *Metallomics*, **2011**, 3, 74-88.
- [3] Sharkey, M.A.; O’Gara, J.P.; Gordon, S.V.; Hackenberg, F.; Healy, C.; Paradisi, F.; Patil, S.; Schaible, B.; Tacke, M., Investigations into the Antibacterial Activity of the Silver-Based Antibiotic Drug Candidate SBC3. *Antibiotics*, **2012**, 1, 25-28.

Platinum(IV) compounds featuring one or two axial ferrocene bearing ligands: Synthesis, characterization, and cytotoxicity

Jelena BANFIC,^{a)} Anton A. LEGIN,^{a)} Michael A. JAKUPEC,^{a)} ,^{b)} Markus GALANSKI,^{a)} and Bernhard K. KEPPLER^{a),b)}

a) University of Vienna, Institute of Inorganic Chemistry, Währinger Str. 42, 1090 Vienna; e-mail: jelena.banfic@univie.ac.at

b) Research Platform “Translational Cancer Therapy Research”, Währinger Str. 42, 1090 Vienna, Austria

Until today, three platinum(II) drugs, namely cisplatin, carboplatin, and oxaliplatin, have gained worldwide market approval as chemotherapeutic drugs. Not only design of novel platinum(II) agents, but also that of platinum(IV) compounds received more attention, since they offer several advantages: (i) kinetical inertness and hence possibility of oral administration, (ii) enabling a better fine-tuning of pharmacological properties due to variation of six instead of four coordination sites, and (iii) acting as prodrug due to reduction inside the tumor tissue.[1] Additionally, also compounds bearing other transition metals, have shown interesting cytotoxic profiles or are even being investigated in clinical trials.[2] Amongst them, ferrocenyl-bearing molecules have shown remarkable cytotoxic activity in vitro as well as in vivo. [3] In order to combine cytotoxic activity of both platinum(IV) and ferrocenyl compounds, the aim of this project was to design the first anticancer platinum(IV) complexes bearing ferrocenyl moieties. Five different ferrocenyl precursors containing either an amine or an alcohol group were synthesized and coupled to a platinum(IV) precursors bearing either one or two carboxylic acid groups. All synthesized compounds were characterized by ESI-MS, elemental analysis, and multinuclear NMR spectroscopy. Promising IC₅₀ values in the low micromolar range could be found in CH1 and SW480 human carcinoma cells. It has to be kept in mind that platinum(IV) agents act as prodrugs and have to be activated by reduction inside the tumor tissue before taking its antiproliferative effect.

References:

- [1] Galanski, M.; Jakupiec, M. A.; Keppler B. K., Update of the preclinical situation of anticancer platinum complexes: novel design strategies and innovative analytical approaches. *Curr. Med. Chem.* 2005, 12, 2075-2094.
- [2] Barry, N. P.; Sadler, P. J., Exploration of the medical periodic table: towards new targets *Chem. Commun.* 2013, 49, 5106-5131.
- [3] Ornelas, C., Application of ferrocene and its derivatives in cancer research. *New. J. Chem.* 2011, 35, 1973-1985.

Acknowledgements

The authors are indebted to the FFG – Austrian Research Promotion Agency (811591) and to the FWF (Austrian Science Fund) and COST CM1105.

Peptidomimetics derived from ferrocene mono- and diamines

^{a)} **Monika KOVAČEVIĆ**, ^{a)} **Mojca ČAKIĆ SEMENČIĆ**, ^{b)} **Ivan KODRIN**, ^{c)} **Sunčica ROCA**, ^{d)} **Anton MEDEN**, ^{a)} **Lidija BARIŠIĆ**

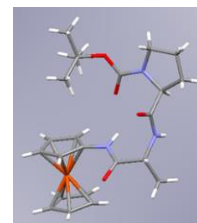
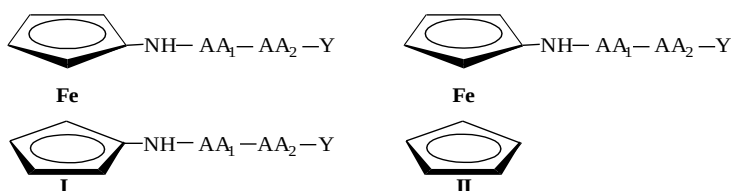
*a) Faculty of Food Technology and Biotechnology, Pierottijeva 6, 10000 Zagreb, Croatia,
lbaris@pbf.hr*

b) Faculty of Science, Horvatovac 102A, 10000 Zagreb, Croatia

c) Rudjer Boskovic Institute, Bijenička 54, 10000 Zagreb, Croatia

d) Faculty of Chemistry and Chemical Technology, Askerceva 5, 1000 Ljubljana, Slovenia

Ferrocene-peptide conjugates present useful and efficient bioorganometallic constraint designed to induce chirally organized structures through intramolecular hydrogen bonding as a prerequisite for 3D structure formation and function of biological systems. As opposed to well-documented peptides derived from ferrocene-1,1'-dicarboxylic acid (Fcda) and 1'-aminoferrocene-1-carboxylic acid (Fca) [1], only two representatives of peptides I derived from ferrocene-1,1'-diamine were reported [2]. We have established a facile and efficient synthetic route for preparation of peptides I which does not include unstable Fcda synthon. Recently, we have showed that introduction of minimum-sized peptide chain on aminoferrocene II led to the formation of a β -turn-like structure originating from intrachain hydrogen-bonding [3].



Herein, we present the synthesis of peptides I and II bearing homo- and heterochiral Ala-Pro sequences followed by extensive studies of their conformational preferences in solution as well as in solid state.

References:

- [1] Metzler-Nolte, N., The Bioorganometallic Chemistry of Ferrocene. In *Ferrocenes: Ligands, Materials and Biomolecules*, Štepička, P., Eds. John Wiley & Sons Ltd: Chichester, 2008; Vol. 13, pp 499-639.
- [2] Chowdhury, S.; Mahmoud, K. A.; Schatte, G.; Kraatz, H.-B., *Org. Biomol. Chem.* 2005, 3, 3018-3023. (b) Djaković, S.; Siebler, D.; Čakić Semenčić, M.; Heinze, K.; Rapić, V., *Organometallics* 2008, 27, 1447-1453.
- [3] Kovač, V.; Čakić Semenčić, M.; Kodrin, I.; Roca, S.; Rapić, V. *Tetrahedron* 2013, 69, 10497-10506.

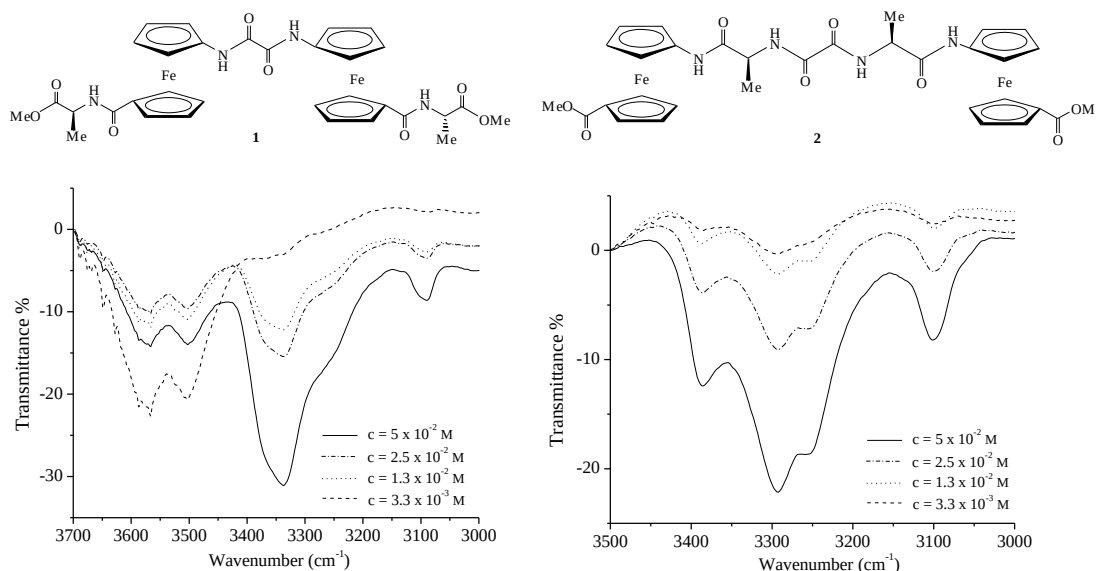
Oxalamide-bridged ferrocenes

^{a)} **Veronika KOVAČ**, ^{b)} **Ivan KODRIN**, ^{a)} **Lidija BARIŠIĆ**

*a) Faculty of Food Technology and Biotechnology, Pierottijeva 6, 10000 Zagreb, Croatia,
lbaris@pbf.hr*

b) Faculty of Science, Horvatovac 102A, 10000 Zagreb, Croatia

A retropeptides, prepared by insertion of an oxalamide unit into the peptide chains, have been considered as peptidomimetics due to their proteolytic stability and bioavailability in comparison with their natural equivalents [1]. Besides their potential as a peptidomimetics, oxalamides are well suited in the design of gelling systems [2]. Herein, we present preparation and conformational analysis of an oxalamide bridged ferrocenes **1** and **2** stabilized through inter- and intramolecular hydrogen-bonding.



References:

- [1] (a) Fletcher, M. D.; Campbell, M. M. *Chem. Rev.* 1998, 98, 763–795., (b) Chorev, M.; Goodman, M. *Trends Biotechnol.* 1995, 13, 438–445., (c) Chorev, M.; Goodman, M. *Acc. Chem. Res.* 1993, 26, 266–273., (d) Ceretti, S.; Luppi, G.; De Pol, S.; Formaggio, F.; Crisma, M.; Toniolo, C.; Tomasini, C. *Eur. J. Org. Chem.* 2004, 4188–4196.
- [2] (a) Frkanec, L.; Žinić, M., *Chem. Commun.* 2010, 46, 522–537. (b) Makarević, J.; Jokić, M.; Frkanec, L.; Čaplar, V.; Šijaković Vujičić, N.; Žinić, M., *Beilstein J. Org. Chem.* 2010, 6, 945–959.

Half-sandwich type $[\text{Ru}(\eta^6\text{-p-cym})(\text{H}_2\text{O})_3]^{2+}$ complexes of short multihistidine containing oligopeptides

Zsolt BIHARI, ^{a)} **Zoltán NAGY**, ^{b)} **Péter BUGLYÓ** ^{a)}

^{a)} University of Debrecen, Faculty of Science and Technology, Department of Inorganic and Analytical Chemistry, Egyetem tér 1, H-4032, Debrecen, Hungary.

^{b)} University of Debrecen, Faculty of Science and Technology, Department of Colloid and Environmental Chemistry, Egyetem tér 1, H-4032, Debrecen, Hungary.

E-mail: bihari.zsolt@science.unideb.hu

In continuation of our recent work highlighting the interaction between half-sandwich type ruthenium complexes with potential antiproliferative activity and various small ligands with biological relevance [1-5], the complex formation between $[\text{Ru}(\eta^6\text{-p-cym})(\text{H}_2\text{O})_3]^{2+}$ and short oligopeptides containing histidine amino acids at various positions in the peptide chain - Ac-HAHH-NH₂ and Ac-HAHAH-NH₂ was studied to model the metal ion binding via the surface histidine residues of h.m.m. serum components, albumin and transferrin. In the metal ion – oligopeptide systems the rather slow reactions prevented the characterization of the complex formation processes using pH-potentiometry. Mass spectrometric, NMR and UV-Vis results support the presence of various complexes with different protonation degree in solution. This contribution will also summarize the results obtained for the selectivity of the various imidazole nitrogens within one oligopeptide ligand.

Acknowledgement

The authors thank members of the EU COST Action CM1105 for motivating discussions. The research was supported by the EU and co-financed by the European Social Fund under the project ENVIKUT (TÁMOP-4.2.2.A-11/1/KONV-2012-0043) and Richter Gedeon Talentum Foundation.

References

- [1] P. Buglyó, E. Farkas, Dalton Trans., 2009, 8063-8070.
- [2] L. Bíró, E. Farkas, P. Buglyó, Dalton Trans., 2010, 39, 10272-10278.
- [3] L. Bíró, E. Farkas and P. Buglyó, Dalton Trans., 2012, 41, 285-291.
- [4] L. Bíró, D. Hüse, A. C. Bényei, P. Buglyó, J. Inorg. Biochem., 2012, 116 116-125.
- [5] L. Bíró, A. Godó, Zs. Bihari, E. Garribba, P. Buglyó, Eur. J. Inorg. Chem., 2013, 3090-3100.

Effect of the strongly coordinating side-chain on the $[(\eta^6\text{-p-cym})\text{Ru}(\text{H}_2\text{O})_3]^{2+}$ binding strengths of amino acids

Linda BÍRÓ,^{a)} Edina BALOGH,^{a)} János PATALENSZKI,^{a)} Attila C. BÉNYEI,^{b)} Péter BUGLYÓ^{a)}

a) Department of Inorganic and Analytical Chemistry, Faculty of Science and Technology, University of Debrecen, H-4032 Debrecen, Hungary; e-mail: linda.biro@science.unideb.hu

b) Laboratory for X-ray Diffraction, Faculty of Science and Technology, University of Debrecen, H-4032, Debrecen, Hungary

Much of the current interest in compounds with potential anticancer activity tends to the half-sandwich type, organometallic Ru(II) complexes with $[(\eta^6\text{-p-cym})\text{Ru}(\text{XY})\text{Z}]$ stoichiometry [1-3]. The *in vivo* effectiveness of these complexes depends on their interaction with the high as well as the low molecular mass serum components.

Among them, amino acids with typical $[\text{NH}_2, \text{COO}^-]$ coordination play an important role in metal ion binding. It was found previously that alanine with no donor atom in the side-chain is not capable of preventing the metal ion from hydrolysis [4]. In order to explore the role of the strongly coordinating side-chain of amino acids in metal ion binding a comparative study has been carried out. Recently citrate with $[\text{COO}^-, \text{COO}^-, \text{O}^-]$ binding set proved to be a very efficient $[(\eta^6\text{-p-cym})\text{Ru}(\text{H}_2\text{O})_3]^{2+}$ binder supporting therefore the key role of the alcoholic -OH [5]. Similar binding motif is available for serine and isoserine by replacing one carboxylate to an NH_2 group. While with ser the $[\text{NH}_2, \text{COO}^-, \text{O}^-]$ binding set would result in (5+6) membered joined chelates, with ise (6+5) may occur [4]. To gain a deeper insight into the effect of the coordinating side-chain with different donor atoms on the stability of the complexes, methionine and S-methylcysteine - that are capable of forming $[\text{NH}_2, \text{COO}^-, \text{S}^-]$ joined chelates - were also studied.

This contribution summarizes the solid state structures and the results of a detailed solution study obtained by combined use of pH-potentiometry, ^1H NMR and ESI-TOF-MS methods.

References:

- [1] M. Melchart, P.J. Sadler, in: G. Jaouen (Ed.), *Bioorganometallics*, Wiley-VCH, 2006, pp. 39-64.
- [2] P.C.A. Bruijninx, P.J. Sadler, *Adv. Inorg. Chem.*, 2009, Vol. 61, pp. 1-62.
- [3] I. Bratsos, T. Gianferrara, E. Alessio, C.G. Hartinger, M.A. Jakupec, B.K. Keppler, in: E. Alessio (Ed.), *Bioinorganic Medicinal Chemistry*, Wiley-VCH, 2011, pp. 160-164.
- [4] L. Bíró, E. Balogh, P. Buglyó, *J. Organomet. Chem.*, 2013, Vol. 734, pp. 61-68.
- [5] L. Bíró, D. Hüse, A.C. Béneyei, P. Buglyó, *J. Inorg. Biochem.*, 2012, Vol. 116, pp. 116-125.

Acknowledgement: The authors thank the members of the EU COST Action CM1105 for motivating discussions. This work was supported by the European Union and European Social Fund TAMOP-4.2.2/A-11/1/KONV-2012-0043.

Alternative cell culture models for preclinical drug screening

Ekaterina BRYNZAK,^a Erik KLAPPROTH,^a Irene LICHTSCHEIDL,^b Robert TRONDL,^a Michael A. JAKUPEC,^a Bernhard K. KEPPLER^a

a) Institute of Inorganic Chemistry, University of Vienna, Waehringer Str. 42, A-1090, Vienna, Austria, ekaterina.brynzak@univie.ac.at;

b) Core Facility of Cell Imaging and Ultrastructure Research, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria

Despite the enormous number of new synthesized substances being successful in preclinical tests, only very few succeed in clinical trials. One reason for this discrepancy is the incompleteness of in vitro drug test models [1]. In this study we investigated the anticancer activity of clinically approved, investigational and experimental drugs based on platinum, gallium, ruthenium and lanthanum in different cell culture models such as monolayers, multicellular spheroids, as well as invasion and metastasis models.

As hypoxic and necrotic regions with low pH and oxygen level are known to be one of the main characteristics of native solid tumors, which (together with the increased distance from blood vessels) affect drug penetration and may cause drug resistance ([2,3], we used two different spheroid models. While spheroids with a diameter of ~450 µm have both a necrotic and hypoxic core, neither a hypoxic nor a necrotic core could be detected in spheroids of ~200 µm. In general, most of the compounds showed lower activity in both spheroid models than in monolayers. Some compounds however, showed similar or even higher activity in spheroid models, which may be explained by different processing of the drug within the spheroid.

We further investigated the anti-invasive activity of ruthenium, osmium and gallium based complexes in both a monolayer based trans-well assay and a spheroid based invasion assay. Corresponding to the cytotoxicity test, most compounds caused significant inhibition of invasiveness in monolayers, whereas only a few showed similar activity in the spheroid model.

Taken together, our results demonstrate the advantages of spheroid based assays and underline the necessity of using different experimental models for reliable preclinical investigations.

References:

- [1] Henning Karlssona; Mårten Fryknäsa; Rolf Larssona; Peter Nygrenb; Loss of cancer drug activity in colon cancer HCT-116 cells during spheroid formation in a new 3-D spheroid cell culture system, *Exp Cell Res.* 2012 Aug 1; 318(13):1577-85.
- [2] Michael Hockel; Peter Vaupel, Tumor Hypoxia: Definitions and Current Clinical, Biologic, and Molecular Aspects, *J Natl Cancer Inst.* 2001 Feb 21; 93(4):266-76.
- [3] Teicher BA, Hypoxia and drug resistance, *Cancer Metastasis Rev* 1994, 13:139-168.

Anthranilic and 3-hydroxyanthranilic acids can affect oxidative stress level in the brain by interactions with iron

Vladimir CHOBOT, ^{a)} Franz HADACEK, ^{b)} Lenka KUBICOVA ^{a)}

a) Department of Molecular Systems Biology, Faculty of Life Sciences, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria; E-Mail: vladimir.chobot@univie.ac.at

b) Albrecht-von-Haller Institut, Plant Biochemistry, Georg-August-Universität Göttingen, Justus-von-Liebig-Weg 11, D-37077 Göttingen, Germany

Iron is an essential element in living organisms. It is an important co-factor of many enzymes participating in electron transfer reactions. In cells, iron forms various coordination complexes not only with proteins, but with low weight compounds as well. This “poorly liganded” iron may enter in pathogenesis of degenerative diseases by reactive oxygen species (ROS) production. High concentrations of ROS cause apoptosis but low concentrations are indispensable for maintaining of the redox homeostasis as an important component of cell signalling.

During the last decades, the intermediates of the kynurenine pathway have been identified as possible key substances in certain physiological and pathophysiological processes in the brain. We focused on two compounds on this pathway – anthranilic and 3-hydroxyanthranilic acids, specifically on their ability to interact with iron ion catalysed ROS production. The ultimate activities of these acids depended on the coordination complexes formation with iron as well as on the chemical milieu; anthranilic acid showed antioxidant effects whereas 3-hydroxyanthranilic acid demonstrated both antioxidant and pro-oxidant activities.

Acknowledgments

This research was supported by the Austrian Science Fund (FWF), grant P24630-B21.

Discovery and Investigation of Anticancer Ruthenium Arene Schiff-Base Complexes via Water-Promoted Combinatorial Three-Component Assembly

Mun Juinn CHOW,^{a) b)} **Cynthia LICONA,**^{c) d)} **Giorgia PASTORIN,**^{b)} **Christian GAIDDON,**^{c)} **Wee Han ANG**^{a)}

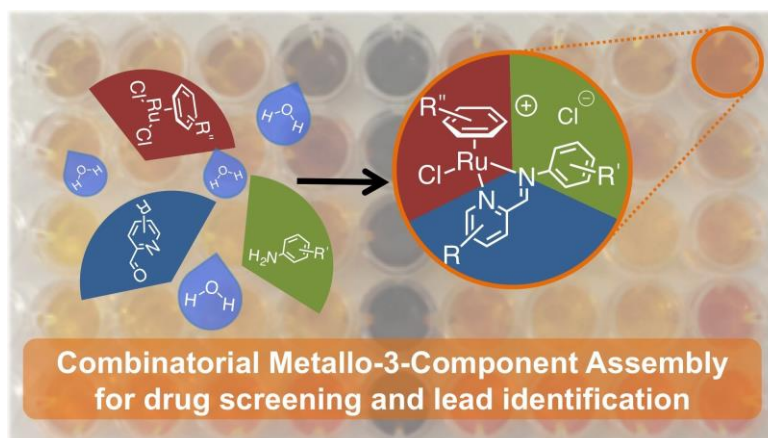
a) Department of Chemistry, National University of Singapore, 3 Science Drive 3, 117543 Singapore; a0037979@nus.edu.sg

b) NUS Graduate School of Integrative Sciences and Engineering, Singapore

c) U1113 INSERM, 3 Avenue Molière, Strasbourg 67200, France

d) 4Université de Strasbourg, Strasbourg, France

The ability to adopt different geometries gives metal scaffolds a greater structural diversity compared to their organic counterpart, and makes them a viable alternative for drug design. Multicomponent Reactions, Combinatorial Coordination Chemistry and High-throughput Screening are useful techniques in drug discovery but they are seldom used for metal-based drug design. We demonstrate their effective use in metal-based drug design through the optimization and validation of a new combinatorial, three-component reaction for the library-synthesis of 442 Ru-Arene Schiff-base (RAS) complexes. These RAS complexes were synthesized using commercially available starting materials in a one-pot, on-a-plate format with a H₂O/DMSO solvent system. The library of RAS complexes was then screened for their anticancer activity and several cytotoxic lead compounds were identified. Several of the lead compounds displayed low micromolar IC₅₀ values in ovarian cancers (A2780, A2780cis), breast cancer (MCF7) and colorectal cancers (HCT116, SW480). The absence of p53 activation in HCT116 or change in activity between p53^{+/+} and p53^{-/-} human foreskin cells (BJwt, BJshp53) suggests the lead compounds may act independently of the p53 tumor suppressor gene frequently mutated in cancer.



Complexes of Rh(III)(η^5 -Cp^{*}) with N/O-donor bidentate ligands: solution equilibrium and interaction with human serum albumin

Orsolya DÖMÖTÖR,^{a)} **Gabriella KISS,**^{a)} **János P. MÉSZÁROS,**^{a)} **Wolfgang KANDIOLLER,**^{b)} **Bernhard K. KEPPLER,**^{b)} **Éva A. ENYEDY**^{a)}

a) Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7. H-6720 Szeged, Hungary; domotor.o@chem.u-szeged.hu

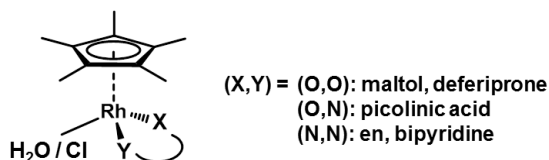
b) Institute of Inorganic Chemistry, University of Vienna, Währinger Str. 42, A-1090 Vienna, Austria

Recently, the interest in metal based anticancer research shows a pronounced shift towards compounds possessing cytotoxic effect different from platinum based compounds. The most promising candidates in this field are Ru(III)-based complexes KP1019 and NAMI-A, which have been investigated in clinical trials with promising results. At the same time there are clear evidences that the active form contains the reduced metal ion, hence half sandwich Ru(II)-arene complexes are extensively investigated. Os(II), Rh(III), Ir(III) complexes are isoelectronic with Ru(II); and introducing of η^6 -arene or η^5 -arenyl ligands in the coordination sphere improve a several orders of magnitude higher ligand exchange rate, which is a prerequisite of efficacy for this type of complexes [1].

Here we report the solution equilibrium studies on four [Rh(III)(η^5 -Cp^{*})]²⁺ complexes formed with (O,O) and (N,N) ligands. These studies were performed using pH-potentiometry, UV-Vis spectrophotometry and ¹H NMR spectroscopy.

Further interesting question is the exploration of possible transport mechanisms in blood serum. The most abundant transporter in blood serum is albumin that has an extraordinary capacity to transport a wide variety of compounds. Therefore spectrofluorometry, capillary electrophoresis, ¹H NMR and ultrafiltration–UV-Vis techniques were used to get a deeper insight into the nature and strength of the interaction of complexes with (O,O) and (N,O) donors towards human serum albumin.

Financial support by the OTKA 103905 and TÁMOP 4.2.4. A/2-11-1-2012-0001 is gratefully acknowledged.



References:

[1] Geldmacher, Y.; Oleszak, M.; Sheldrick, W.S., Rhodium(III) and iridium(III) complexes as anticancer agents. *Inorg. Chim. Acta* 2012, 393 84–102.

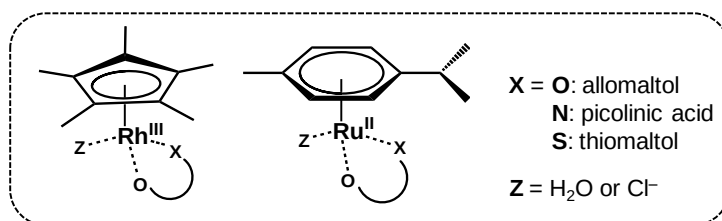
Solution equilibria of analogous Rh(III)(η^5 -Cp^{*}) and Ru(II)(η^6 -p-cymene) complexes formed with various bidentate ligands

Éva A. ENYEDY,^{a)} **Orsolya DÖMÖTÖR,**^{a)} **Wolfgang KANDIOLLER,**^{b)} **Bernhard K. KEPPLER**^{b)}

a) Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7. H-6720 Szeged, Hungary; enyedy@chem.u-szeged.hu

b) Institute of Inorganic Chemistry, University of Vienna, Währinger Str. 42, A-1090 Vienna, Austria

Serious side effects and resistance against antitumor platinum derivatives led to extensive investigation of non-platinum compounds such as Ru, Rh, Ga etc. Development of novel organometallic Ru(II) and Rh(III) compounds with potential antitumor activity also attracts attention. The characterization of the potentially active complexes in aqueous solution can provide sufficient information on the possible biotransformation processes of metal-containing drug candidates in the biological fluids. As a continuation of our former studies on (allo)maltolato complexes of [Rh(III)(η^5 -Cp^{*})]²⁺ [1] here we present the solution equilibria on complexes formed with various (O,X) bidentate ligands investigated by pH-potentiometry, ¹H NMR and UV-visible spectrophotometry. Speciation of these rhodium complexes is compared to analogous [Ru(II)(η^6 -p-cymene)]²⁺ compounds [2,3].



Financial support by OTKA PD103905 and TÁMOP 4.2.4. A/2-11-1-2012-0001 „National Excellence Program" is gratefully acknowledged.

References:

- [1] Dömötör, O.; Aicher, S.; Schmidlehner, M.; Novak, M.S.; Roller, A.; Jakupec, M.A.; Kandioller, W.; Hartinger, C.G.; Keppler, B.K.; Enyedy, É.A., Antitumor Pentamethylcyclopentadienyl Rhodium Complexes of Maltol and Allomaltol: Synthesis, Solution Speciation and Bioactivity. *J. Inorg. Biochem.* 2014, 134 57–65.
- [2] Sija, É.; Hartinger, C.G.; Keppler, B.K.; Kiss, T.; Enyedy, É.A., Solution Equilibrium Studies of Anticancer Ruthenium(II)- η^6 -p-cymene Complexes of Pyridinecarboxylic Acids. *Polyhedron* 2014, 67 51–58.
- [3] Enyedy, É.A.; Sija, É.; Jakusch, T.; Hartinger, C.G.; Kandioller, W.; Keppler, B.K.; Kiss, T.; Solution Equilibria of Anticancer Ruthenium(II)-(η^6 -p-cymene)-Hydroxy(thio)pyr(id)one Complexes: Impact of Sulfur vs. Oxygen Donor Systems on the Speciation and Bioactivity. *J. Inorg. Biochem.* 2013, 127 161–168.

Unfolded Protein Response and Endoplasmic Reticulum Stress Are crucial Modes of Action for Two Thiosemicarbazones

**Lea FLOCKE^{a)}, Robert TRONDL^{a)b)}, Christian R. KOWOL^{a)b)}, Petra HEFFETER^{c)},
Michael A. JAKUPEC^{a)b)}, Walter BERGER^{b)c)}, Bernhard K. KEPPLER^{a)b)}**

a) Institute of Inorganic Chemistry, University of Vienna, Waehringer Strasse 42, A-1090 Vienna, Austria

b) Research Platform "Translational Cancer Therapy Research", University of Vienna, Waehringer Strasse 42, A-1090 Vienna, Austria;

c) Institute of Cancer Research and Comprehensive Cancer Centre, Medical University of Vienna, Vienna, Austria; lea.flocke@univie.ac.at

Triapine (3-AP) is a thiosemicarbazone which is being clinically developed by the cancer therapy evaluation program of the NCI and is well known to inhibit ribonucleotide reductase. It was/is the subject to 36 clinical trials. Fluorescence microscopy studies performed in our institute showed colocalization of 3-AP with the endoplasmic reticulum (ER). When the cell has to cope with an overload of un- and/or misfolded proteins it activates the unfolded protein response (UPR) as part of the endoplasmic reticulum stress (ER stress). Severe ER stress leads to apoptosis induction if the cell cannot handle the misfolded protein burden.¹ In cancer cells a variety of proteins are translated due to enhanced metabolism resulting in elevated levels also of un- and/or misfolded proteins. This makes ER stress a promising target for anticancer therapy. We investigated the potential of Triapine and its dimethylated derivative (3-AP-Me) to induce UPR as well as ER stress and the impact of those mechanisms on their mode of action. Elevated levels of different key factors of both mechanisms were found on the mRNA level in RT qPCR as well as on the protein level in Western blot experiments. E.g., XBPI mRNA is significantly spliced after treatment with 3-AP-Me. This leads to a shorter mRNA, and the resulting frameshift allows translation of the functional transcription factor that activates not only different chaperones but also different genes for protein degradation. EIF2 α is activated via phosphorylation, which leads to a translational block of cap dependent genes and an overexpression of the transcription factor ATF4 which we could show as well. ATF4 activates after translocation to the nucleus not only stress responses and redox reactions but also CHOP. CHOP is a proapoptotic protein which was also shown to be upregulated after treatment with both thiosemicarbazones. MTT assays revealed a significant decrease of cytotoxicity when protein synthesis was inhibited by cycloheximide (CHX), which reduces the protein load to the ER; as well as when translation from ER stress to apoptosis was inhibited by a c-Jun-N-terminal kinase (JNK) inhibitor, which proves the impact of the mentioned mechanisms on the mode of action of 3-AP and 3-AP-Me.²

Acknowledgement. The project was supported by the Johanna Mahlke née Obermann Foundation project no.FA526007.

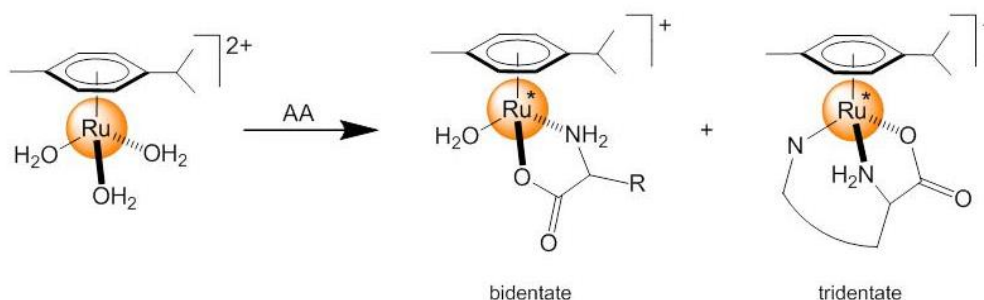
Synthesis, characterization and cytotoxicity of (η^6 -p-cymene)ruthenium(II) complexes of α -amino acids

Folake A. EGBEWANDE,^{a)} Lydia PAUL,^{a)} Bruno THERRIEN,^{b)} Julien FURRER^{a)}

a) Department für Chemie und Biochemie, Universität Bern, CH-3012 Berne, Switzerland,
julien.furrer@dcb.unibe.ch

b) Institut de Chimie, Université de Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel,
Switzerland

Arene ruthenium complexes of α -amino acids, obtained by mixing aqueous solutions of [$(\eta^6$ -p-cymene)RuCl₂]₂ in the presence of AgCF₃SO₃ with various amino acids, have been studied at 37 °C using NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS). Presumably, complexes with the general formula [$(\eta^6$ -p-cymene)Ru(AA)₂]ⁿ⁺ and bridged complexes with the general formula [$((\eta^6$ -p-cymene)Ru)₂(η -AA)₂(m-OH)]⁺ are formed together with the expected bi- and tridentate chelate complexes. All complexes are highly cytotoxic, with IC₅₀ values ranging from 0.16 to 19.8 microM. Interestingly, all complexes exhibit selectivity towards A2780 versus A2780cisR cells, indicating a distinct mechanism of action, different from that of many previously reported cytotoxic ruthenium complexes. No direct correlation between the kinetics of formation and the cytotoxicity could be evidenced, suggesting that other physico-chemical parameters such as the stability and ligand exchange kinetics may play an important role in their biological activity [1].



References:

- [1] Egbewande, F.A.; Paul, L. E. H.; Therrien, B.; Furrer, J., Synthesis, characterization and cytotoxicity of (η^6 -p-cymene)ruthenium(II) complexes of α -amino acids. Eur. J. Inorg. Chem. 2014, 1174-1184.

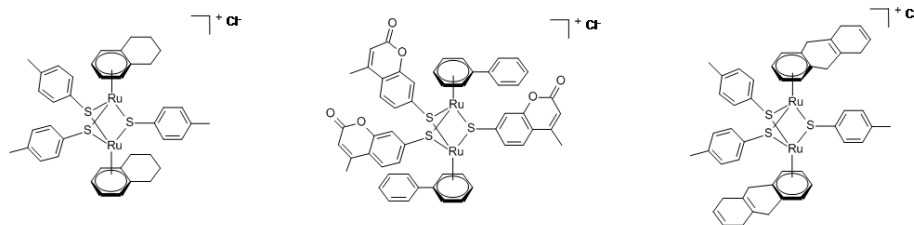
Tuning the *in vitro* cell cytotoxicity of dinuclear arene ruthenium trithiolato complexes: Influence of the arene ligand

Federico GIANNINI,^{a)} **Lennart GEISER,**^{a)} **Lydia E.H. Paul,**^{a)} **Thomas RODER,**^{a)}
Georg SUESS-FINK,^{b)} **Julien FURRER**^{a)}

a) Department of Chemistry and Biochemistry, University of Berne, Freiestrasse 3, CH-3012, Berne, Switzerland

b) Institut of Chemistry, University of Neuchâtel, Avenue de Bellevaux 51, CH-2000, Neuchâtel, Switzerland; frederico.giannini@dcb.unibe.ch

We recently synthesized thiophenolato-bridged *p*-cymene ruthenium complexes of the type $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^t)_2\text{Ru}_2(\text{SR})_3]^+$, which are highly cytotoxic against human ovarian cancer cells, the IC_{50} values being in the nanomolar range [1-3]. Their exact mechanism of action is still unclear, although the cytotoxicity of these complexes could be to a certain extent correlated to the lipophilicity of the corresponding thiophenol ligands [2-3].



In this contribution, the influence of the arene on the *in vitro* cytotoxicity is investigated. For this purpose, a new series of eight thiolato-bridged arene ruthenium complexes bearing 4-methylthiophenolato or 4-methylcoumarin-7-mercapto bridges and biphenyl, 5,8,9,10-tetrahydroanthracene, indane, and 1,2,3,4-tetrahydronaphthalene as arene ligands have been synthesized and studied for their *in vitro* cytotoxicity.

References:

- [1] Giannini, F.; Furrer, J.; Ibaio, A.F.; Süß-Fink, G.; Therrien, B.; Zava, O.; Baquie, M.; Dyson, P.J.; Štěpnička, P., *J. Biol. Inorg. Chem.* 2012, 17, 951-960.
- [2] Giannini, F.; Furrer, J.; Süß-Fink, G.; Clavel, C.M.; Dyson, P.J., *J. Organomet. Chem.* 2013, 744, 41-48.
- [3] Giannini, F.; Paul, L.E.H.; Furrer, J.; Therrien, B.; Süß-Fink, G., *New J. Chem.* 2013, 37, 3503-3511.

Cellular accumulation and redox behavior of novel platinum(IV) compounds

Simone GÖSCHL,^{a)} Hristo VARBANOV,^{a)} Sarah THEINER,^{a)b)} Michael A. JAKUPEC,^{a)b)} Markus GALANSKI,^{a)} Bernhard K. KEPPLER^{a)b)}

a) Institute of Inorganic Chemistry, University of Vienna, Währinger Straße 42, 1090 Vienna – Austria; e-mail: simone.goeschl@univie.ac.at

b) Research Platform "Translational Cancer Therapy Research", Institute of Inorganic Chemistry, University of Vienna, Währinger Straße 42, 1090 Vienna - Austria

Platinum(IV) complexes are an attractive way to overcome the disadvantages of platinum(II)-based chemotherapeutics such as severe side effects or resistances, because they are kinetically more inert to ligand substitution and their higher lipophilicity can improve the cellular uptake.[1][2] The platinum(IV) complexes reported herein have shown activity in vitro in CH1 and SW480 cells in the micromolar range. As platinum(II) biotransformation products are expected to be the active species of the platinum(IV) complexes, the reduction properties of the complexes in the presence of GSH and ascorbic acid were studied with NMR and their behavior under co-incubation with ascorbic acid by using the MTT-based cytotoxicity assay. To get a deeper insight in the accumulation behavior of the compounds cellular uptake studies at 37 °C were performed by using ICP-MS to quantify the amount of platinum in SW480 cells upon exposure to seven different platinum(IV) complexes representing variations in all ligand positions. First results have shown that the lipophilicity of the compounds has not the expected impact on the cellular accumulation. Further uptake experiments at 4 °C were carried out to suppress the active transport into the cells to assess whether the compounds are taken up actively or passively. Three of the compounds with similar structure have shown a strong temperature-dependent accumulation, which can be also found for satraplatin, the most promising platinum(IV) compound in clinical trials.[3] These results lead to the following conclusions: the axial ligands are influencing the lipophilicity but are not the major determinants for cellular accumulation, whereas the equatorial ligands can have a strong influence. It seems that chlorides as equatorial leaving groups are associated with a temperature-dependent accumulation. To determine whether the compounds enter the cells by an energy-dependent process, further uptake studies will be performed in which the glycolysis and the oxidative phosphorylation will be inhibited with 2-deoxyglucose and oligomycin, respectively.

References:

- [1] M. Galanski, MA. Jakupc, BK. Keppler, Current Medicinal Chemistry, 2005, vol. 12, pp. 2075-2094
- [2] S. Dhar, SJ. Lippard in: Enzo Alessio (Editor), Bioinorganic Medicinal Chemistry, 2011, Wiley
- [3] SY. Sharp, PM. Rogers, L.R. Kelland, Clinical Cancer Research, 1995, vol 1, pp. 981-989

New ruthenium(II)-arene complexes with N, O or S containing ligands

^{a)}Stefan NIKOLIĆ, ^{a)}Ivanka IVANOVIĆ, ^{a)}Darko PANTIĆ, ^{a)}Vuk FILIPOVIĆ, ^{b)}Dejan OPSENICA, ^{c)}Siniša RADULOVIĆ, ^{a)}Tibor SABO, ^{a)}Sanja GRGURIĆ-ŠIPKA

a) Faculty of Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia

b) Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Njegoševa 12,

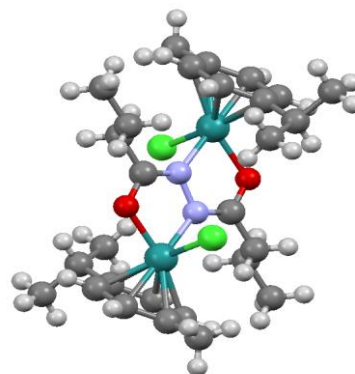
11000 Belgrade, Serbia c) Institute for Oncology and Radiology of Serbia, Pasterova 14, 11000 Belgrade, Serbia; sanjag@chem.bg.ac.rs

Among the great number of non-platinum metal complexes examined for anticancer characteristics up to date, recent attention is focused on ruthenium complexes. Ruthenium complexes are reported to show patterns of antitumor activity and clinical toxicity that are distinct from those of platinum complexes. Because of the ability of ruthenium(II)-arene species to coordinate to different classes of ligands, they are suitable for fine-tuning chemical and pharmaceutical properties.

Ruthenium(II)-arene complexes containing different types of ligands: propyl-, butyl- and caprylic hydrazide (hydrazide with short and long hydrocarbon chain); isonicotinic acid hydrazide (a hydrazide with an aromatic pyridine ring); benzimidazole derivatives; thiourea or guanidine derivatives of chloroquinoline and pyridine-3-imidazole were obtained.

The complexes were characterized by elemental analysis, mass spectrometry, IR and NMR spectroscopies. The structure of some complexes were determined by X-ray crystallography (Figure).

Antiproliferative activity of the complexes with caprylic hydrazide and isonicotinic acid hydrazide, determined for three human cancer cell lines (HeLa, A549 and LS-174) revealed moderate activity. The cytotoxicity of other complexes is under evaluation.



References:

- [1]Noffke, A.L.; Habtemariam, A.; Pizarro, A.M.; Sadler, P.J., Designing organometallic compounds for catalysis and therapy. *Chem. Commun.* 2012, 48, 5219-5246.
- [2]Hartinger, C.G.; Dyson, P.J., Bioorganometallic chemistry-from teaching paradigms to medicinal applications. *Chem. Soc. Rev.* 2009, 38, 391-401.

Comparison of intracellular phosphoprotein stress response of NCI-H526 small cell lung cancer (SCLC) cells to platinum(II) cisplatin and platinum(IV) oxoplatin.

Gerhard HAMILTON^{a)} Barbara RATH^{b)}

a) Ludwig Boltzmann Cluster of Translational Oncology, Vienna, Austria;

gerhard.hamilton@toc.lbg.ac.at

b) Ludwig Boltzmann Cluster of Clinical Oncology, Vienna, Austria

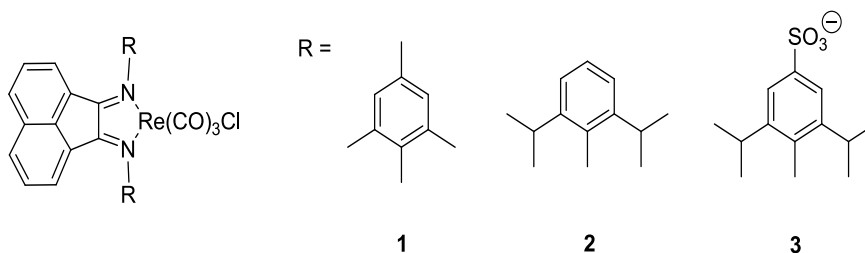
In attempts to develop an orally applicable platinum-based drug, platinum(IV) drugs were formulated which exhibit higher stability in vivo compared to the platinum(II) drug cisplatin. The first such chemotherapeutic agent, namely satraplatin, failed approval. In the present work, we checked the initial cellular stress response of the chemosensitive NCI-H526 small cell lung cancer (SCLC) cells by determination of the relative phosphorylation of 46 specific phosphorylation sites of 38 selected proteins in a six hours response to cisplatin (platinum(II)) or oxoplatin (platinum(IV)), respectively (Proteome Profiler Human Phospho-Kinase Array Kit, R&D, MN, USA). Oxoplatin is considered as prodrug of cisplatin, although several findings point to differences in their intracellular targets and effects. Cisplatin induced hyperphosphorylation of p38 α MAPK and AMPK α 1, whereas oxoplatin treatment resulted in increased phosphorylation of a large number of signaling proteins involved in stress response/drug resistance, comprising JNK, GSK-3 α , AMPK α 1, src kinases, STATs, CHK-2 and especially focal adhesion kinase (FAK), among others. Cisplatin exerts markedly higher cytotoxicity upon four hours short-term exposure in comparison to oxoplatin and, correspondingly, the extensive initial stress response to the platinum(IV) drug oxoplatin is expected to increase clinical drug resistance. Induction of a substantial stress response to any prodrug of a platinum-based compound may likewise limit the effectivity of its subsequently generated active metabolite(s), such contributing to insufficient cytotoxicity of selected derivatized platinum complexes.

Carbon Monoxide Photorelease from new Rhenium Carbonyl Complexes

Elham KIANFAR, Günther KNÖR

*Institute of Inorganic Chemistry, Johannes Kepler University Linz (JKU), Altenberger
Strasse 69, 4040 Linz, Austria; elham.kianfar@jku.at*

Carbon monoxide has come a long way from just being considered as a silent killer and an environmental pollutant to an important molecular messenger involved in several physiological processes. Recently, important progress has been made towards developing photoactive CO-releasing moieties (PhotoCORMs) for possible therapeutic applications [1]. Here, The synthesis and characterization of new rhenium tricarbonyl diimine complexes of the type fac-Re(1,2-diimine)(CO)₃Cl, carrying bis-(phenylimino)acenaphthene ligands (BIAN) **1-3** is reported [2].



Among these novel complexes, a special focus will be given to the deeply coloured water-soluble organometallic rhenium (I) derivative **3**, which offers highly desirable features for potential biomedical and catalytic applications such as light-controlled release of carbon monoxide (PhotoCORMs) [3], and homogenous photocatalytic CO₂ reduction. CO liberated from the irradiated solutions of CORMs **1-3** has been quantified in the headspace gas using FTIR and GC analysis.

References:

- [1] Rimmer, R. D.; Pierri, A. E.; Ford, P. C., Photochemically activated carbon monoxide release for biological targets. Toward developing air-stable PhotoCORMs labilized by visible light. *Coord. Chem. Rev.* 2012, 256, 1509-1519.
- [2] Kianfar, E.; Monkowius, U.; Portenkirchner, E.; Knör, G., Synthesis and characterization of novel Re(BIAN)(CO)₃Cl Derivatives including the first Example of a Water-Soluble Tricarbonyl Rhenium(I) Complex with Bis(imino)acenaphthene Ligands. *Z. Naturforsch.* 2014, in press.
- [3] Kianfar, E.; Monkowius, U.; Knör, G., Synthesis, structure and properties of new rhenium carbonyl complexes including water soluble derivatives as photoactive CO-releasing molecules. *Bioinorg. React. Mechan.* 2013, 9, S1-105.

Metallo-chromones - new complexes inducing oxidative stress and arresting human cancer cells in G2/M phase

Konrad KOWALSKI,^{a)} **Aneta KOCEVA-CHYŁA,**^{b)} **Łukasz SZCZUPAK,**^{a)} **Paweł HIKISZ,**^{b)} **Aleksandra RAJNISZ,**^{c)} **Jolanta SOLECKA,**^{c)} **Bruno THERRIEN**^{d)}

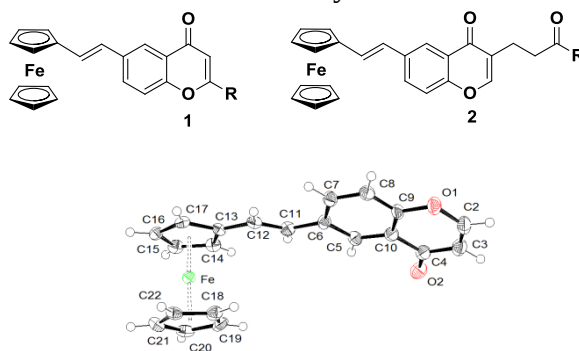
a) Faculty of Chemistry, Department of Organic Chemistry, University of Łódź, Tamka 12, 91-403 Łódź, Poland

b) Department of Thermobiology, Faculty of Biology and Environmental Protection, University of Łódź, Pomorska 141/143, 90-236 Łódź, Poland

c) National Institute of Public Health-National Institute of Hygiene, Chocimska 24, 00-791 Warsaw, Poland

d) Institute of Chemistry, University of Neuchatel, Avenue de Bellevaux 51, CH-2000 Neuchatel, Switzerland

The chromone skeleton is a core structural motif in the flavones family. Due to their biological properties flavones have been in focus of medicinal chemistry for many years. In contrary, valuable biological properties of the ferrocenyl-flavone conjugates have been noticed only recently.¹ We have an on-going programme of study into the biological application of organometallic chromones.² Here we want to report on ferrocenyl-chromones **1** and **2** as a novel anticancer and antibacterial active bioorganometallics (Fig. 1). The mechanism of anticancer activity of **1** and **2** involve oxidative stress induction, DNA scission, and apoptosis induction. Moreover our results show that some compounds of class **2** induce of the HEP-G2, MCF-7 and CCRF-CEM cell cycle arrest in G2/M phase.



Acknowledgements: K.K thanks the National Science Centre in Cracow, Poland (Grant no. DEC-2011/03/B/ST5/01015)

References:

- [1] Monserrat, J.-P.; Tiwari, K. N.; Quentin, L.; Pigeon, P.; Jaouen, G.; Vessi res, A.; Chabot, G. G.; Hillard, E. A., *J. Organomet. Chem.* 2013 (734) 78-85
- [2] Kowalski, K.; Koceva-Chy la, A.; Szczupak,  .; Hikisz, P.; Bernasi nska, J.; Rajnisz, A.; Solecka, J.; Therrien, B., *J. Organomet. Chem.* 2013, (741-742) 153-161

Metallocene-modified uracils: synthesis, anticancer and antibacterial activity

Konrad KOWALSKI,^{a)} **Joanna SKIBA,**^{a)} **Ingo OTT,**^{b)} **Jolanta SOLECKA,**^{c)} **Bruno THERRIEN**^{d)}

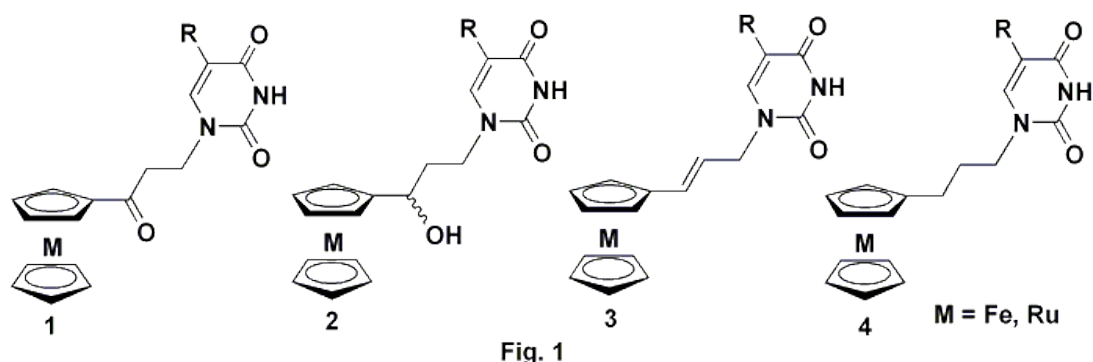
a) Faculty of Chemistry, Department of Organic Chemistry, University of Łódź, Tamka 12, PL-91403 Łódź, Poland, e-mail: kondor15@wp.pl

b) Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, Beethovenstr. 55, D-38106 Braunschweig, Germany

c) National Institute of Public Health-National Institute of Hygiene, Chocimska 24, PL-00791 Warsaw, Poland

d) Institute of Chemistry, University of Neuchatel, Avenue de Bellevaux 51, CH-2000 Neuchatel, Switzerland

Biogenic nucleobases, are an attractive targets for ferrocenyl conjugation. In connection with our previous studies on biologically active ferrocenes, we have started a new project in the chemistry of ferrocenyl-nucleobase conjugates.^{1,2} Herein presentation report on the synthesis, structure, and biological activity of metallocene-uracils **1-4** (Fig. 1).



The synthetic approach towards complexes **1-4** employ a Michael addition reaction as a key step.² Biological evaluation results indicated the thymine derivative **3** (**M**=Fe, **R** = CH₃) the most antiproliferative active complex (IC_{50} = 23.8 μ M) against MCF-7 cells and derivative **1** (**M** = Fe, **R** = F) the most active antibacterial agent against Gram-positive methicillin-resistant and vancomycin-resistant *Staphylococcus aureus* strains (MIC = 32 μ g mL⁻¹).²

Acknowledgements: J.S. thanks the National Science Centre in Cracow, Poland (Grant PRELUDIUM no. DEC-2012/05/N/ST5/01055) for financial support.

References:

- [1] Kowalski, K.; Koceva-Chyla, A.; Pieniążek, A.; Bernasińska, J.; Skiba, J.; Rybarczyk-Pirek, A. J.; Jóźwiak, Z., J. Organomet. Chem. 2012 (700) 58-68.
- [2] Kowalski, K.; Skiba, J.; Oehninger, L.; Ott, I.; Solecka, J.; Rajnisz, A.; Therrien, B., Organometallics 2013 (32) 5766-5773.

Metallocarbonyl complexes ($\eta^5\text{-C}_5\text{H}_5$)M(CO) $_n$ ($\eta^1\text{-N-maleimidato}$) (M = Mo, W, Fe, Ru; n = 3, 2) - New Photoactive CO-Releasing Molecules (CO-RMs)

^{a)} **Aleksandra KUBICKA**, ^{a)} **Bogna RUDOLF**, ^{b)} **Ewa PARFIENIUK**, ^{b)} **Emilia FORNAL**

a) Department of Organic Chemistry, University of Lodz, 91-403 Lodz, Poland;

alex.chemi@wp.pl

b) Laboratory of Separation and Spectroscopic Method Applications, Center for Interdisciplinary Research, The John Paul II Catholic University of Lublin, al. Krasnicka 102, 20-718 Lublin, Poland

Over the last 15 years, the interest in the pharmacological activity of exogenous CO has greatly increased, due to its beneficial therapeutic effect. CO-releasing molecules (CORMs) may find the application in the treatment of patients with cardiovascular problems, in suppressing organ graft rejection and protecting tissues from ischemic injury and apoptosis[1]. Control of the amount of CO released from CO-RMs, in order to avoid toxic effects of carbon monoxide, is the main problem in the application of CO as therapeutic agent. The new strategies where CO release is stimulated by light or enzymes offer the possibility to control the location, time and therapeutic dosage of carbon monoxide[2]. The conversion of deoxy-myoglobin (deoxy-Mb) to carbonmonoxy-myoglobin (Mb-CO) UV-vis assay is the principal method used for quantifying the rates of CO release from CO-RMs (Fig. 1). Recently we have developed a new method for monitoring carbon monoxide release from CO-RMs based on LC-MS spectrometry. For many years we have worked on metallocarbonyl complexes of different metals bearing a maleimidato ligand which could be applied as proteins labels (detected by IR spectroscopy) and enzyme inhibitors. Our recent studies have shown that these complexes activated by irradiation could also serve as CO-releasing molecules.

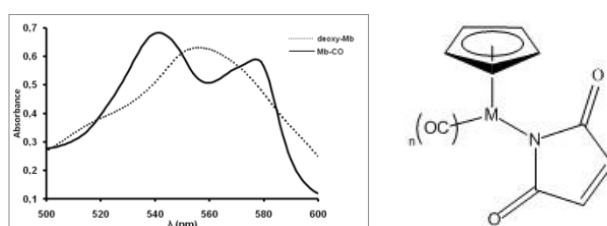


Fig. 1. UV-vis spectra of deoxy-Mb and Mb-CO (left). Structure of metallocarbonyl complexes ($\eta^5\text{-C}_5\text{H}_5$)M(CO) $_n$ ($\eta^1\text{-N-maleimidato}$) (M=Mo, W, Fe, Ru; n=3, 2) (right).

Herein we describe activated-by-visible-light CO-releasing properties of complexes ($\eta^5\text{-C}_5\text{H}_5$)M(CO) $_n$ ($\eta^1\text{-N-maleimidato}$) (M=Mo, W, Fe, Ru; n=3, 2).

References:

- [1] Johnson, T. R.; Mann, B. E.; Clark, J. E.; Foresti, R.; Green, C. J.; Motterlini, R.; *Angew. Chem. Int. Ed.*, 2003, (42), 3722-3729.
- [2] Crespy, D.; Landfester, K.; Schubert, U. S.; Schiller, A.; *Chem. Commun.*, 2010, (46), 6651-6662.

Acknowledgement: The research was funded by NCN grant DEC-2011/03/B/ST5/01480

Is iron–quinolinic acid complex formation a mechanism of neurotoxicity or redox homeostasis modulation?

Lenka KUBICOVA,^{a)} Franz HADACEK,^{b)} Vladimir CHOBOT^{a)}

a) Department of Molecular Systems Biology, Faculty of Life Sciences, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria; E-Mail: lenka.kubicova@univie.ac.at

b) Albrecht-von-Haller Institut, Plant Biochemistry, Georg-August-Universität Göttingen, Justus-von-Liebig-Weg 11, D-37077 Göttingen, Germany

Quinolinic acid (QUIN) is an intermediate of the kynurenine pathway. Several decades ago, QUIN was identified as an endogenous neurotoxin that is able to increase production of cytotoxic reactive oxygen species (ROS). It is generally assumed that coordination complexes of QUIN with iron ions play a key role in the ROS production caused by QUIN.

In cells, iron occurs as iron(II) due to the presence of ascorbic acid and various other reducing agents. The oxidative attack can release iron(II) from its complexes with proteins allowing it to enter new coordination complexes that facilitate ROS formation catalysis. Hydroxyl radicals are the most aggressive products of the Fenton reaction. On the contrary, ROS are known to participate in cell signalling. The cell redox homeostasis is maintained by enzymatic and non-enzymatic systems.

The possible effects of the iron–QUIN complexes on the ROS production were explored by differential pulse voltammetry and the deoxyribose degradation assay. The redox potential of iron was shifted to anodic direction when liganded by QUIN. Equally important, in the deoxyribose degradation assay, QUIN showed pro- or antioxidant activities due to hydrogen peroxide and ascorbic acid concentrations. QUIN did not demonstrate direct ROS scavenging or producing activities. However, it influenced Fe(II)/Fe(III) redox cycling by complex formation with Fe. The results suggest that QUIN may serve as a low-molecular modulator of redox homeostasis.

Acknowledgments

This research was supported by the Austrian Science Fund (FWF), grant P24630-B21.

Microwave Assisted Synthesis of Organometallic Building Blocks

Paul-Steffen KUHN,^{a)} **Melanie SCHMIDLEHNER,**^{a)} **Carmen C. HACKL**^{a)} **Alexander ROLLER,**^{a)} **Wolfgang KANDIOLLER,**^{a), b)} **Bernhard K. KEPPLER**^{a), b)}

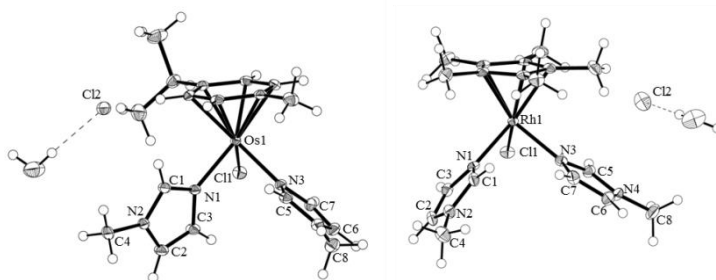
a) Institute of Inorganic Chemistry, University of Vienna, Waehringer Str. 42, A-1090 Vienna, Austria

*b) Research Platform "Translational Cancer Therapy", University of Vienna, Waehringer Str. 42, A-1090 Vienna, Austria
Paul-Steffen.Kuhn@univie.ac.at*

Metal-arene complexes are extensively studied especially for their role in catalysis[1] and medicinal inorganic chemistry, [2] where complexes of the general formula $[M(\text{arene})\text{Cl}_2]_2$ ($M = \text{Ru(II)}, \text{Os(II)}, \text{Rh(III)}, \text{Ir(III)}$; arene = benzene, *p*-cymene, toluene, biphenyl, Cp^*) can act as precursor for the synthesis of different potential metallodrugs. To improve their stability as well as solubility in aqueous media, chlorido ligands can be easily replaced by stronger donor molecules such as *N*-heterocycles.

The previous standard procedure for the substitution of the halide by a *N*-donor ligand included reaction times ranging from several hours to days either at room temperature or reflux.[3] However, the formation of side products is forced under these conditions and the resulting more complicate purification reduces the overall yield.

We have utilized microwave conditions to overcome these drawbacks. The synthesis of 15 organometallic precursors under optimized reaction will be presented. It was possible to reduce the reaction time from hours or days to minutes, accompanied by smaller solvent amounts and - in some cases - with an increased yield.



References:

- [1] Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H.; Chem. Rev. 2012, 112, 5879–5918.
- [2] Yan, Y. K.; Melchart, M.; Habtemariam, A.; Sadler, P. J., Chem. Commun. 2005, 38, 4764-4776.
- [3] Vock, C. A.; Scolaro, C.; Phillips, A. D.; Scopelliti, R.; Sava, G.; Dyson, P. J., J. Med. Chem. 2006, 49, 5552–5561.

Organometallic Carbonyl Complexes - Towards Surface Enhanced Raman Spectroscopy (SERS) Biosensing

Kien Voon KONG,^{a)} Zhiyong LAM,^{b)} Weng Kee LEONG^{b)*} and Malini OLIVO^{a,c)*}

*a) Singapore Bioimaging Consortium, Agency for Science, Technology and Research (A*STAR), Singapore.*

b) Division of Chemistry & Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore. E-mail: lamz0008@e.ntu.edu.sg

c) School of Physics, National University of Ireland Galway, Ireland.

**Corresponding authors: chmlwk@ntu.edu.sg, malini_olivo@sbic.a-star.edu.sg*

Organometallic carbonyl complexes show intense carbonyl (CO) stretching vibrations in the mid-infrared (IR) at 1800-2200 cm^{-1} , a region which is relatively free of interference from other functional groups in the cellular content. This characteristic feature was first utilized by Jaouen and co-workers in the development of a quantitative assay termed carbonyl metalloimmunoassay (CMIA).¹⁻³ We have now extended this concept by coupling such complexes with SERS-active colloids and planar substrates, and employed them for cancer cells and glucose detection, respectively.^{4,5} The unhindered CO stretching vibrations are utilized for qualitative and quantitative detection of the target molecules. In the colloidal platform, organometallic-nanoparticle (OM-NP) conjugates, which are prepared by combining triosmium carbonyl clusters with gold nanoparticles, have been used successfully in SERS live-cell imaging (figure 1A). In the planar substrate platform, a triosmium carbonyl cluster-boronic acid conjugate is used as a secondary carbohydrate probe in a sensitive and selective SERS-based glucose assay (figure 1B).

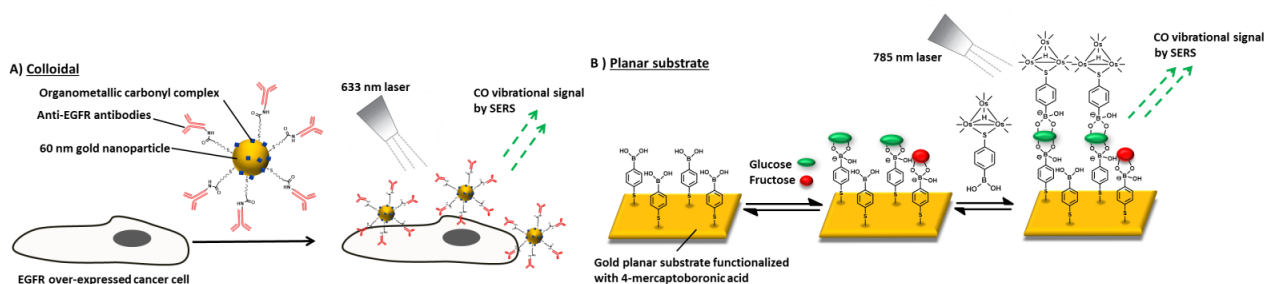


Figure 1. Schematic representations of the use of organometallic carbonyl complexes in SERS applications.

References:

- [1] Jaouen, G.; Vessi res, A.; Top, S.; Ismail, A. A.; Butler, I. S. J. Am. Chem. Soc. 1985, 107, 4778.
- [2] Butler, I. S.; Vessi res, A.; Salmain, M.; Brossier, P.; Jaouen, G. Appl. Spectrosc. 1989, 43, 1497.
- [3] Salmain, M.; Vessi res, A.; Brossier, P.; Butler, I. S.; Jaouen, G. J. Immunol. Methods 1992, 148, 65.
- [4] Kong, K. V.; Lam, Z.; Goh, W. D.; Leong, W. K.; Olivo, M. Angew. Chem. Int. Ed. 2012, 51, 9796.
- [5] Kong, K. V.; Lam, Z.; Lau, W. K. O.; Leong, W. K.; Olivo, M. J. Am. Chem. Soc. 2013, 135, 18028.

Synthesis and Characterization of Osmium based Tamoxifens. Comparison of their antiproliferative effects with those of other members of the metallocifen family (Fe, Ru).

Shirley LEE,^{a,b)} **Siden TOP,**^{a)} **Anne VESSIÈRES,**^{a)} **Gérard JAOUEN,**^{a)} **Weng Kee LEONG**^{b)}

a) Institut Parisien de Chimie Moléculaire, UMR CNRS 8232, Université Pierre et Marie Curie, Chimie ParisTech, 11 rue Pierre et Marie Curie, Paris 75231 Paris cedex 05, France.

b) Division of Chemistry & Biological Chemistry, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore; s110032@e.ntu.edu.sg

There is an increasing interest in the application of organometallic compounds in drug development; a prime example of which is the development of ferrocifens, reported by Jaouen and co-workers, who found that these compounds expressed high antiproliferative activity against both ER+ and ER- breast cancer cells ($IC_{50} \sim 0.5 \mu M$),¹ in contrast to the organic analogue, hydroxytamoxifen, which is only active against ER + cancer cells. In order to gain an insight into the role of the metal, three series of the group 8 metallocifens (Figure 1) were prepared, and their physical properties, chemical reactivities and antiproliferative activities compared.

All the compounds showed no significant differences in their structural and physical properties, but there were great differences in their biological activity. The hydroxymetallocifens (**1c**, **2c**, **3c**) were active against both ER+ and ER- cancer cells, and their activities followed the order: Fe>Ru>Os. While **1a** and **1b**

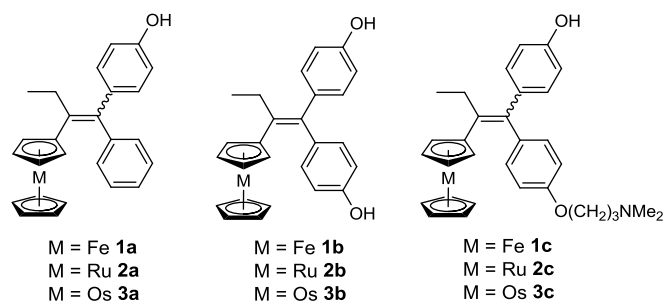


Figure 1. The metallocifens (Fe, Ru, Os) studied.

were active against both cell lines, **2a**, **2b**, **3a** and **3b** showed no activity against the ER- cancer cells but exhibited proliferative effects against the ER+ cancer cells. These suggest that the modes of action for the phenol and amine chain derivatives are different and probably ascribable to differences in chemical reactivity. Detailed chemical/biological reactivity studies are underway, as are synchronon imaging with the heavier ruthenium/osmium analogues.

References:

- [1] a) A. Nguyen, A. Vessièrès, E. A. Hillard, S. Top, P. Pigeon, G. Jaouen, *Chimia*. **2007**, 61, 716; b) S. Top, A. Vessièrès, C. Cabestaing, I. Laios, G. Leclercq, C. Provot, G. Jaouen, *J. Organomet. Chem.* **2001**, 637-639, 500; c) S. Top, A. Vessièrès, G. Leclercq, J. Quivy, J. Tang, J. Vaissermann, M. Huché, G. Jaouen, *Chem Eur J.* **2003**, 9, 5223; d) E. A. Hillard, P. Pigeon, A. Vessieres, C. Amatore, G. Jaouen, *Dalton Trans.* **2007**, 5073.

The impact of leaving group variation on the chemical properties and anticancer activity of molybdenocenes

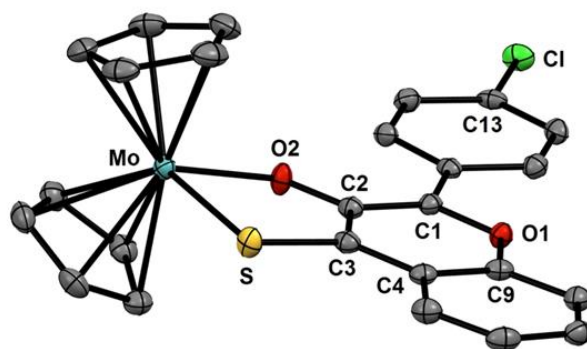
Marlene REIKERSDORFER,^{a,b} Michael JAKUPEC,^{a,b} Michael S. MALAREK,^a
Wolfgang KANDIOLLER,^{a,b} Bernhard K. KEPPLER^{a,b}

a) Institute of Inorganic Chemistry, University of Vienna, Waehringer Str.42, 1090 Vienna, Austria.

b) Research Platform "Translational Cancer Therapy Research", University of Vienna, Waehringer Str. 42, 1090 Vienna, Austria

michael.malarek@univie.ac.at.

In order to reduce the broad spectrum of severe side effects caused by cisplatin, carboplatin, and oxaliplatin, complexes with other metal centers have been investigated as chemotherapeutic agents. In 1979, Köpf and Köpf-Maier tested a group of metallocenes of the general formula Cp_2MX_2 ($\text{M} = \text{Ti}, \text{V}, \text{Nb}, \text{Mo}$; $\text{X} = \text{halides and pseudo-halides}$) on a variety of tumor cells and revealed that these compounds exhibited antitumor activity with less toxic effects than cisplatin.[1] The Cp rings of the molybdenocene dichloride possesses a good hydrolytic stability, however, in aqueous solution the labile chloride ligands are rapidly replaced by water molecules. By substituting these chloride ligands with biologically active ligands, favorable effects such as stabilization of ligand geometries, acquired redox-activity, increased solubility, enhanced cellular uptake, different mode of action and synergistic effects on bioactivity are to be expected. In this work, we substituted the chlorido leaving groups with various bioactive *O,O*-, *S,O*-, and *N,O*-chelating moieties including: picolinic acid, (thio)pyrones, naphthoquinones and (thio)flavones derivatives and analyzed the impact on their stabilities, HSA interaction, redox potential and anticancer activity.



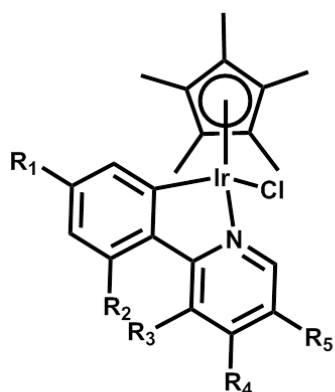
References:

- [1] Köpf, H., Köpf-Maier, P., *Angewandte Chemie, Int. Ed. Engl.* 18 (1979), 477.

Contrasting Biological Activity of Iridium(III) Half-Sandwich Complexes Bearing Functionally Diverse 2-Phenylpyridine Ligands

Adam J. MILLETT,^{a)} Isolda ROMERO-CANELÓN,^{a)} Abraha HABTEMARIAM,^{a)} Carlos SANCHEZ-CANO,^{a)} Guy J. CLARKSON^{a)} and Peter J. SADLER^{a)}

*a) Department of Chemistry, University of Warwick, Gibbet Hill, Coventry, UK, CV4 7AL
A.J.Millett@warwick.ac.uk*



$R_{1-5} = -F, -CF_3, -CHO, -NO_2, -OH, -CH_2OH, -OCH_3, -CH_3, -H$

Cyclopentadienyl iridium(III) half-sandwich complexes can exhibit potent anticancer activity in a variety of cancer cell lines. We have shown that their potency increases with hydrophobicity, addition of phenyl substituents on the Cp* ring and by switching from -N,N based chelating ligands to -C,N chelating ligands [1,2]. Here we investigate the contrasting biological activity of a series of iridium(III) half-sandwich complexes containing functionally diverse 2-phenylpyridine ligands.

The antiproliferative activity of these complexes spans a wide range, with IC₅₀ values between 1 - 89 μM in a variety of cancer cell lines, with contrasting activity observed for structural isomers. We have studied correlations between anticancer activity and hydrophobicity, iridium cellular accumulation and distribution. The results indicate a correlation between hydrophobicity and cellular accumulation, and a weak correlation between accumulation and antiproliferative activity. We have shown that the substituent on the chelating ligand significantly affects the phase of cell cycle arrest. Similarly we showed that the induction of apoptosis is dependent on the structure of the complex. Interestingly, these complexes can catalytically oxidise NADH to NAD⁺ and may have a multi-targeting redox mechanism of action [3], although this behaviour does not correlate directly with antiproliferative potency. We are investigating the ability of these complexes to bind to CT-DNA and their interactions with ROS-related enzymes. This work shows how small variations of functionality on the chelating ligand can significantly affect the biological activity of this series of iridium(III) complexes.

We thank the ERC (grant no. 247450), IAS University of Warwick, Science City (AWM/ERDF) for support and COST CM1105 for stimulating discussions.

References:

- [1] Z. Liu, L. Salassa, A. Habtemariam, A. M. Pizarro, G. J. Clarkson, P. J. Sadler. Contrasting Reactivity and Cancer Cell Cytotoxicity of Isoelectronic Organometallic Iridium(III) Complexes. *Inorg. Chem.* 2011, **50**, 5777-5783.
- [2] Z. Liu, L. Salassa, A. Habtemariam, A. M. Pizarro, G. J. Clarkson, P. J. Sadler. Organometallic Iridium(III) Cyclopentadienyl Anticancer Complexes Containing C,N Chelating Ligands. *Organometallics*. 2011, **30**, 4702-4710.
- [3] I. Romero-Canelón, P.J. Sadler. Next-Generation Metal Anticancer Complexes: Multitargeting via Redox Modulation. *Inorg. Chem.* 2013, **52**, 12276-12291.

1,3-Dioxoindan-2-carboxamides as selective O,O-chelating ligands for the development of novel organometallic anticancer drugs

Stephan MOKESCH^a, Wolfgang KANDIOLLER^{a,b}, Bernhard KEPPLER^{a,b}

a) University of Vienna, Institute of Inorganic Chemistry, Währinger Str. 42, 1090 Vienna

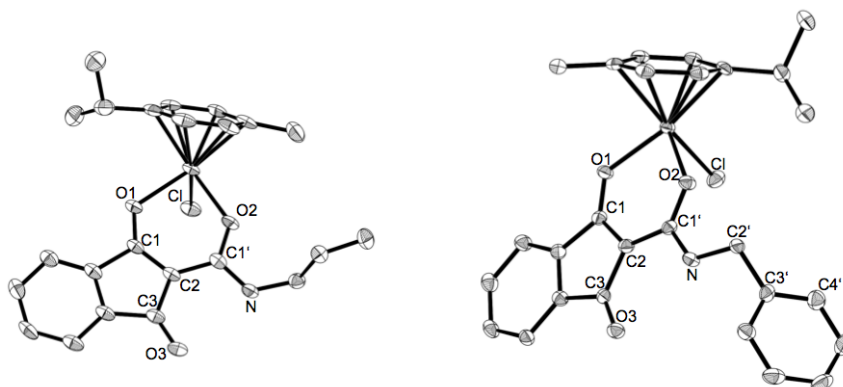
b) Research Platform "Translational Cancer Therapy", University of Vienna,

Waehringer Str. 42, A-1090 Vienna, Austria

stephan.mokesch@univie.ac.at

Platinum-based anticancer drugs are applied in 50% of all cancer therapies; however, the unselective mode of action of these chemotherapeutics results in severe side effects. Apart from the high toxicity, intrinsic and/or acquired resistances are major drawbacks, which induced an expansion of cancer research to other metal centers besides platinum [1]. 1,3-Dioxoindan-2-carboxamides, due to structural similarities to known dual topoisomerase I/II inhibitors, show very promising anticancer activity [2].

The aim of this project was the generation of compounds, which exploit synergistic effects of bioactive ligands being coordinated to cytotoxic transition metal centers. Four differently *N*-alkylated indan-1,3-dione-2-carboxamides and their ‘piano-stool’ configured Ru(II)-cymene and Rh(III)-Cp* complexes were synthesized and characterized *via* 1D and 2D NMR spectroscopy, elemental analysis, and in two cases by X-ray diffraction analysis. By the use of ESI mass spectrometry the complexes were investigated toward their behavior in aqueous systems and their binding preferences towards biomolecules were examined.



References:

- [1] Bergamo, A., Sava, G., Black, A., Approaching tumour therapy beyond platinum drugs: Status of the art and perspectives of ruthenium drug candidates, *J. Inorg. Biochem.* 2012, 106(1), 90-99.
- [2] Jung, J.-K., Ryu, J., Yang, S.-I., Cho, J., Lee, H., Synthesis and in vitro cytotoxicity of 1,3-Dioxoindan-2-carboxylic acid arylamides, *Arch. Pharm. Res.* 2004, 27(10), 997-1000

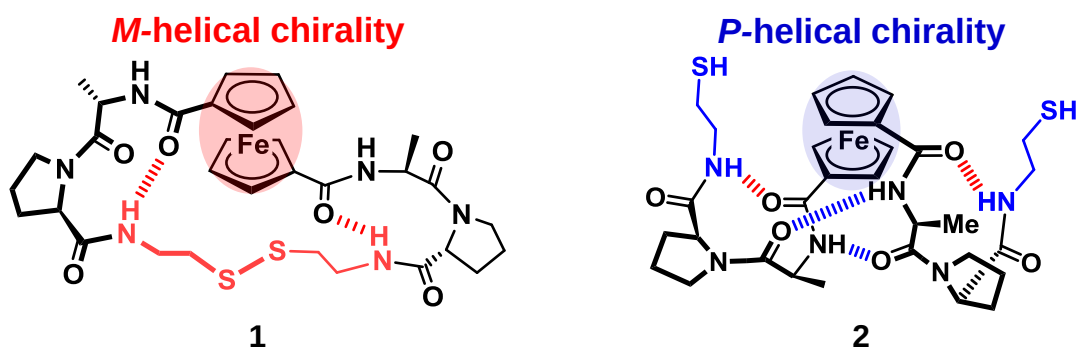
Chirality-Organized Structure of Ferrocene-Dipeptide Conjugate Bearing Disulfide Linkage

Toshiyuki MORIUCHI, Taiki NISHIYAMA, Toshikazu HIRAO

Department of Applied Chemistry, Graduate School of Engineering, Osaka University,
Yamada-oka, Suita, Osaka 565-0871, Japan
e-mail: moriuchi@chem.eng.osaka-u.ac.jp

Ferrocene, which is recognized as one of the most stable organometallic compounds and a most useful one among metallocenes, has drawn much attention in their application to materials based on a reversible redox couple and two rotatory coplanar cyclopentadienyl (Cp) rings. The inter-ring distance of ferrocene is suitable for hydrogen bonding of the attached peptide strands. The utilization of a ferrocene unit as a central reverse-turn unit is considered to be one strategy to study the hydrogen bonding ability of various peptide strands. We have already demonstrated that a combination of the ferrocene scaffold as a central reverse-turn unit with the dipeptide chains (-L-Ala-L-Pro-) induces the chirality-organized structure, resulting in the *P*-helical arrangement of the ferrocenoyl moiety [1]. We herein report the control of chirality-organized structures of ferrocene-dipeptide conjugates bearing disulfide linkage.

Ferrocene-dipeptide conjugates **1** and **2** were synthesized from 1,1'-bis(chlorocarbonyl)-ferrocene and the corresponding dipeptide derivatives (-L-Ala-D-Pro-). The ferrocene-dipeptide conjugate **1** was found to form the *M*-helical arrangement of the ferrocenoyl moiety. On the other hand, the reduction to the thiol **2** resulted in the formation of the *P*-helical arrangement of the ferrocenoyl moiety.



References:

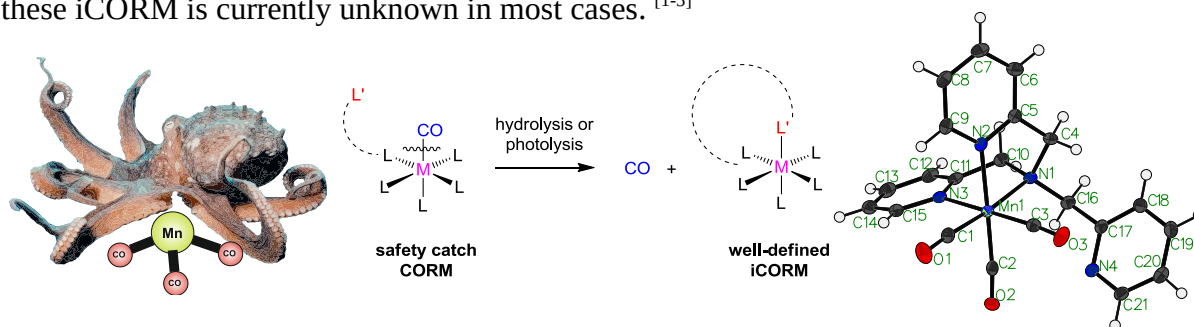
- [1] Moriuchi, T.; Hirao, T. *Acc. Chem. Res.* **2010**, 43, 1040.

Bactericidal $\text{Mn}(\text{CO})_3$ -based CO-releasing molecules (CORMs)

Christoph NAGEL, Ulrich SCHATZSCHNEIDER

*Institut für Anorganische Chemie, Julius-Maximilians-Universität Würzburg,
Am Hubland, D-97074 Würzburg, Germany, christoph.nagel@uni-wuerzburg.de*

Although carbon monoxide is commonly only known as a highly toxic gas, it is now also well-established as an endogenously produced gasotransmitter in higher organisms, including humans. There, it has cytoprotective effects against oxidative stress and acts as a small-molecule messenger on a number of cellular targets. For clinical applications in human medicine, metal carbonyl complexes, which release CO triggered by ligand exchange or photolysis, are promising carrying systems. Studies of the biological activity of these *CO-releasing molecules* (CORMs) face the challenge of the formation of a metal-coligand fragment (called *inactivated CORM* or iCORM) in addition to carbon monoxide. These iCORMs have one or more free coordination sites, which can potentially react with solvent or bio(macro)molecules to form bioactive side-products. Furthermore, the molecular structure of these iCORM is currently unknown in most cases. ^[1-5]



Therefore, we have prepared metal carbonyl complexes with additional free ligand “arms”, which can bind to the coordination site(s) vacated by the CO released via neighbor-group effects. Using tris(2 picolyl)amine (tpa) as a ligand, the reaction with manganese(I) pentacarbonyl bromide lead to $[\text{Mn}(\text{CO})_3(\text{tpa}-\kappa^3\text{N})]^+$, which still contains one non-coordinated pyridyl group. The binding of the free arm following the photoinduced release of CO could be demonstrated by UV/Vis, IR, NMR and DFT studies. Furthermore, preliminary data on the photoactivated bactericidal activity of this CORM will be presented. ^[6]

References:

- [1] R. Motterlini, L. E. Otterbein, *Nature Rev. Drug Discovery* **2010**, 9, 728-743.
- [2] U. Schatzschneider, *Brit. J. Pharmacol.* **2014**, doi: 10.1111/bph.12688.
- [3] J. Niesel, A. Pinto, H.W. Peindy N'Dongo, K. Merz, I. Ott, R. Gust, U. Schatzschneider, *Chem. Commun.* **2008**, 1798-1800.
- [4] H. Pfeiffer, A. Rojas, J. Niesel, U. Schatzschneider, *Dalton Trans.* **2009**, 4292-4298.
- [5] U. Schatzschneider, *Inorg. Chim. Acta* **2011**, 374, 19-23.
- [6] C. Nagel, S. McLean, R. Poole, H. Braunschweig, T. Kramer, U. Schatzschneider, *Dalton Trans.* **2014**, accepted.

Topoisomerase II α targeting activity of half-sandwich ruthenium(II) and rhodium(III) complexes with indan-1,3-dione-derived ligands

Maria S. NOVAK,^{a)} **Stephan MOKESCH,**^{a)} **Wolfgang KANDIOLLER,**^{a,b)}
Michael A. JAKUPEC,^{a,b)} **Bernhard K. KEPPLER**^{a,b)}

a) Institute of Inorganic Chemistry, University of Vienna, Waehringer Strasse 42, A-1090 Vienna, Austria;

b) Research Platform "Translational Cancer Therapy Research", University of Vienna, Waehringer Strasse 42, A-1090 Vienna, Austria; maria.novak@univie.ac.at

Topoisomerase II α is an essential nuclear enzyme that plays a role in every aspect of DNA functionality (replication, transcription, recombination and chromosome condensation) and is the primary target for a number of clinically important cytotoxic drugs [1]. Ruthenium(II) and rhodium(III) compounds bearing indan-1,3-dione-2-carboxamides as bioactive ligand systems exhibit promising anticancer activity, at least partially due to structural similarities with the topoisomerase inhibitor TAS-103 [2]. The cytotoxic potency of novel metal-based indan-1,3-dione-2-carboxamide complexes was tested in human cancer cell lines A549 (non-small lung cancer), CH1 (ovarian carcinoma) and SW480 (colon cancer) by the MTT assay. All compounds show similar activity in the lower micromolar concentration range in all three cell lines. As analogs of TAS-103 they were studied in the DNA relaxation assay for their topoisomerase II α inhibition properties. The capacity of altering the secondary structure of DNA was studied in cell-free experiments using an electrophoretic dsDNA plasmid assay. Ruthenium- and rhodium-based complexes (but not the free ligand) display a high capacity of topoisomerase II α inhibition in the DNA relaxation assay, and only a ruthenium-based complex induces changes in the electrophoretic mobility of the dsDNA plasmid, suggesting a direct interaction with DNA in this singular case. Changes in cell cycle distribution induced by these substances were examined by FACS using propidium iodide staining, revealing an increase of the S-phase fraction after 8 h exposure to the complexes, consistent with topoisomerase inhibition. The results suggest that topoisomerase II α is a target for ruthenium(II)- and rhodium(III)-based indan-1,3-dione-2-carboxamides complexes. In addition, the organometallic complexes show a significantly higher enzyme inhibitory capacity compared to the free ligand. Therefore, ruthenium(II) and rhodium(III) compounds based on indan-1,3-dione-2-carboxamide derivatives are promising candidates for the development of anticancer agents with topoisomerase II α inhibition properties.

References:

- [1] Osheroff N., DNA topoisomerases. *Biochimica et biophysica acta* 1998, 1400, 1-2.
- [2] Fortune J.M., Velea L., Graves D.E., Utsugi T., Yamada Y. and Osheroff N., DNA topoisomerases as targets for the anticancer drug TAS-103: DNA interactions and topoisomerase catalytic inhibition. *Biochemistry* 1999, 38, 15580-15586.

A dual-targeting, apoptosis-inducing organometallic half-sandwich iridium anticancer complex

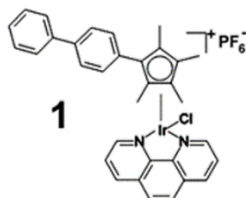
Vojtech NOVOHRADSKY,^{a,b)} **Lenka ZERZANKOVA**,^{a)} **Jana STEPANKOVA**,^{a)} **Anna KISOVA**,^{a)} **Hana KOSTRHUNOVA**,^{a)} **Jana KASPARKOVA**,^{b)} **Peter J. SADLER**,^{c)}
Viktor BRABEC^a

a) Institute of Biophysics, Academy of Sciences of the Czech Republic, v.v.i., Kralovopolska 135, CZ-61265 Brno, Czech Republic. e-mail: novohradskyv@gmail.com

b) Department of Biophysics, Faculty of Science, Palacky University, 17. listopadu 12, CZ-77146 Olomouc, Czech Republic.

c) Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, United Kingdom

The cellular mechanism of action of iridium(III) half-sandwich complex [(η^5 -C₅Me₄C₆H₄C₆H₅)Ir(phen)Cl]PF₆ (**1**) is reported. Complex **1** was used to treat several cell lines, including carcinoma cells cisplatin-sensitive, cisplatin-resistant (with intrinsic and acquired resistance), with wild type p53 status as well as the cells with no intact p53 gene, and nontumorigenic cells. Complex **1** preferentially kills cancer cells over nontumorigenic cells and exhibits no cross-resistance with cisplatin. It appears to retain significant activity in human tumor cell lines that are refractory or poorly responsive to cisplatin, and in contrast to cisplatin it displays a high activity in human tumor cell lines that are characterized by both wild type and mutant p53 gene. The mechanism of cell killing was established through detailed cell-based assays. Complex **1** exhibits dual effects in killing cancer cells causing nuclear DNA damage and mitochondrial dysfunction involving ROS production simultaneously. Flow cytometric studies and impedance-based monitoring of cellular responses to **1** demonstrated that **1** acts more quickly than cisplatin to induce cell death and that **1** is effective apoptosis inducer in particular in early stages of treatment, when the apoptotic effects predominate over the necrosis. Our findings confirm that **1** and its iridium derivatives represent promising candidates for additional pre-clinical studies and new additions to the growing family of nonplatinum metal-based anticancer complexes.^{1, 2}



References:

- [1] V. Novohradsky, Z. Liu, M. Vojtiskova, P. J. Sadler, V. Brabec and J. Kasparkova, Mechanism of cellular accumulation of an iridium(III) pentamethylcyclopentadienyl anticancer complex containing a C,N-chelating ligand. *Metallomics* 2014, 6. 682-690.
- [2] J. M. Hearn, I. Romero-Canelon, B. Qamar, Z. Liu, I. Hands-Portman and P. J. Sadler, Organometallic iridium(III) anticancer complexes with new mechanisms of action: NCI-60 screening, mitochondrial targeting, and apoptosis. *ACS Chem. Biol.* 2013, 8. 1335-1343.

Ruthenium(II) Arene Complexes: Reactions with Biologically Relevant Ligands

Tom SCRASE,^{a)} Sally BOSS,^{a)} Paul BARKER,^{a)} Michael O'NEILL^{a, b)}

a) University of Cambridge, Chemistry Department, Lensfield Road, CB2 1EW

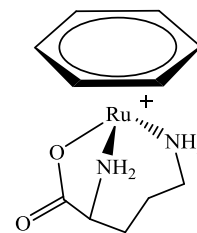
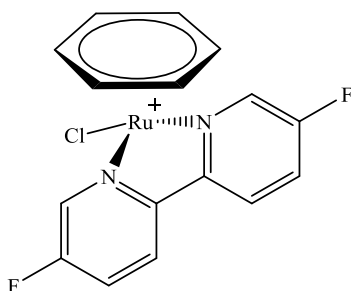
b) mo374@cam.ac.uk

A worldwide survey suggested that in 2008 there were 12.7m new cases of cancer and 7.6 m fatalities due to cancer (13% of total deaths), giving a crude fatality rate of 60%.[1]

Most anti-cancer drugs are organic products, but the advent of cisplatin has led to platinum-based molecules becoming widely used in chemotherapy. There are, however, problems with platinum therapies, and a variety of anti-cancer candidates using different metals are being developed; our work centres on the use of ruthenium (II) in this context.

Although some ruthenium-based molecules have shown promising activities,[2] our understanding of their mode(s) of action is incomplete.[3] Specifically, the binding- or redox-pathways leading to cell death are unclear, hindering the rational improvement of these drugs.

Our broad aim is to pursue a rational course of drug candidate design and improvement involving Ru(II) arenes (examples pictured). We hope to do this by addressing some very simple questions about Ru(II) binding using techniques such as MS and NMR. Questions such as: What biological residues (if any) does ruthenium bind to? Which does it bind to in preference? What is the extent of this preference? Do the binding constants change markedly between conditions (pH, O₂ levels) mimicking cancerous and healthy cells? Is reactivity under kinetic or thermodynamic control? Answering questions such as this is the first step in manipulating the properties of the molecules to rationally improve the performance of drug candidates.



References:

- [1] Cancer Research UK, Cancer Worldwide Key Facts 2013
- [2] Hartinger, C. G. et al, *Chemistry & Biodiversity* 2008, 5 (10), 2140-2155; Hartinger, C. G. et al, *Journal of Inorganic Biochemistry* 2006, 100 (5-6), 891-904. Sava, G. et al, *Anticancer Research* 1999, 19 (2A), 969-972; Bergamo, A. et al, *Journal of Pharmacology and Experimental Therapeutics* 1999, 289 (1), 559-564
- [3] See Kostova, I., *Current Medicinal Chemistry* 2006, 13 (9), 1085-1107

Ferrocenyl taxanes - synthesis and anticancer activities

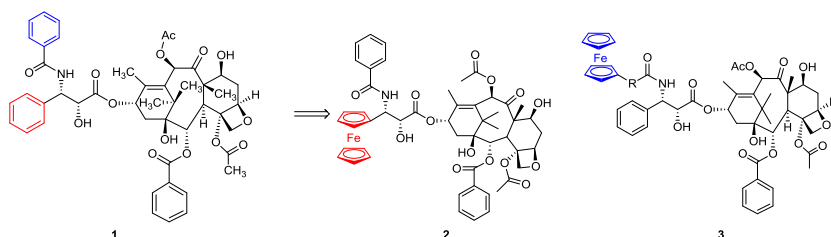
Damian PLAŻUK,^{a)} **Anna WIECZOREK**,^{a)} **Aleksandra ŻAL**,^{b)} **Andrzej BŁAUŻ**,^{b)}
Błażej RYCHLIK^{b)}

a) University of Łódź, Department of Organic Chemistry, ul. Tamka 12, Łódź, 91-403, POLAND; email: damplaz@uni.lodz.pl

b) University of Łódź, Department of Molecular Biophysics, Cytometry Lab, 12/16 Banacha, Łódź, 90-237, POLAND

The antineoplastic agent paclitaxel **1**, promote polymerization of tubulin and stabilize microtubule, which disturb in proliferation of the cells and consequently cause the death of the cancer cells¹. Ferrocen, is redox active, nontoxic and stable in biologically media metallocene, shown only slight cytotoxic activity, whereas when conjugated with biologically active compounds it provides some promising anticancer agents². Continuing our research of cytotoxic ferrocenyl compounds³⁻⁵ we became interested in synthesis of a ferrocenyl analogue of paclitaxel (**Scheme 1**). Some of the synthesized compounds exhibited anticancer activities at submiromolar. In this communication we will disclose a synthesis and biological properties, e.g. anticancer activities, tubulin.

Acknowledgement: The authors are grateful for the financial support of The National Science Centre (Poland) based on the decision no DEC-2012/05/B/ST5/00300



Scheme 1. Paclitaxel and its ferrocenyl analogs

References:

- [1] Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T.; J. Am. Chem. Soc. 1971, 93, 2325-2327
- [2] Vessi res, A. J. Organomet. Chem. 2013, 734, 3-16
- [3] Pla zuk, D.; Rychlik, B.; B lau , A. Domaga a, S.; J. Organomet. Chem. 2012, 715, 102-112
- [4] Pla zuk, D.; Wiecezorek, A.; B lau , A. Rychlik, B. MedChemComm 2012, 3, 4, 498-501
- [5] Pla zuk, D.; Zakrzewski, J.; Salmain, M.; B lau , A.; Rychlik, B.; Strzelczyk, P.; Bujacz, A.; Bujacz, G.; Organometallics 2013, 32, 30, 5774-5783

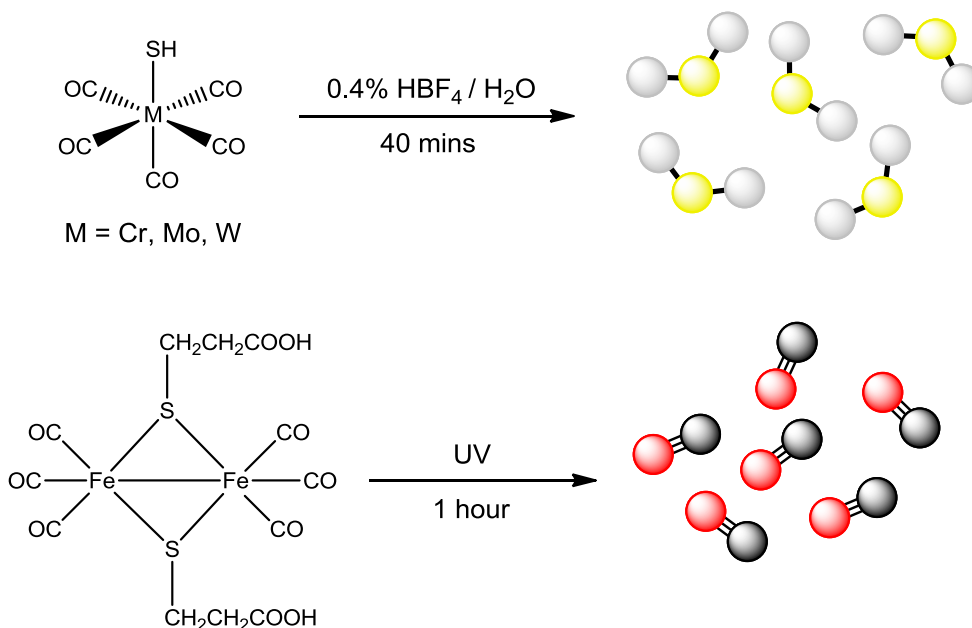
Water Soluble Transition Metal Carbonyl Complexes as H₂S and CO Releasing Molecules

a) Hwa Tiong Calvin POH, b) Wai Yip FAN

a) Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore

b) Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore; calvinpoh@nus.edu.sg

Hydrogen sulfide¹ and carbon monoxide² has been shown to act as signaling molecules³ in biological systems. A class of transition metal carbonyl complexes has been synthesized and characterized. These metal carbonyl complexes are water soluble and have been shown to release their ligands in the form of the two naturally occurring gasotransmitters - hydrogen sulfide and carbon monoxide, in a controlled manner.



References:

- [1] R. Hosoki, N. Matsuki and H. Kimura, *Biochem. Biophys. Res. Commun.*, 1997, 237, 527-531.
- [2] H. Kimura, *Mol. Neurobiol.*, 2002, 26, 13-19; H. Kimura, *Antioxid Redox Signal*, 2010, 12, 1111-1123; D. Boehning and S. H. Snyder, *Annu. Rev. Neurosci.*, 2003, 26, 105-131.
- [3] A. F. Perna, D. Lanza, I. Sepe, I. Raiola, R. Capasso, N. G. De Santo and D. Ingrosso, *Blood Purif*, 2011, 31, 102-106; C. Szabo, *Antioxid Redox Signal*, 2012, 17, 68-80.

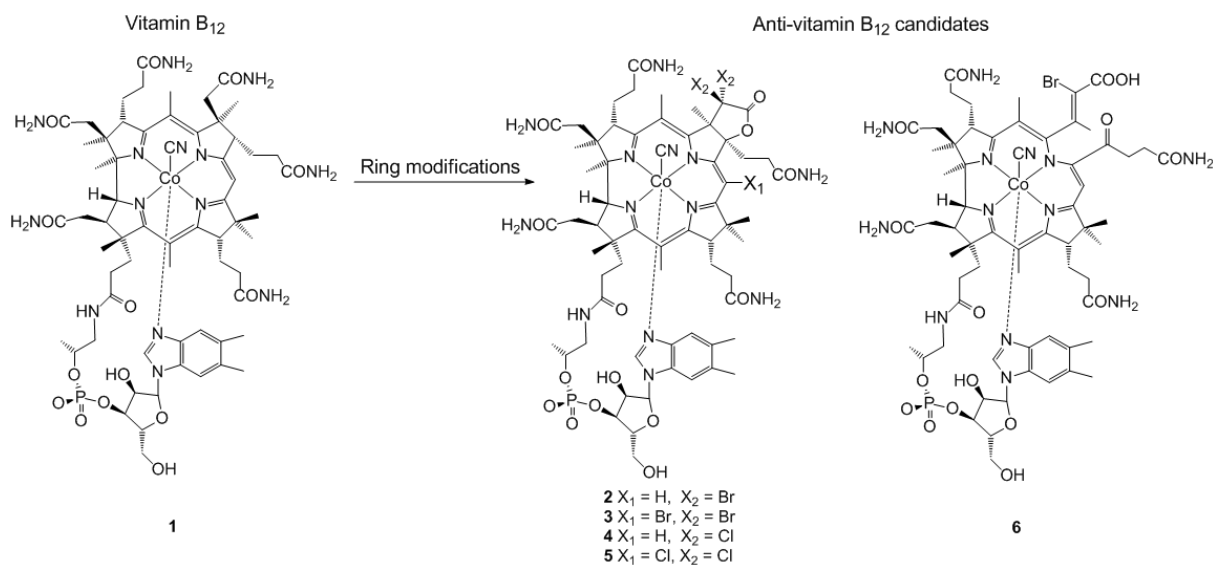
Ring-modified Vitamin B₁₂ Derivatives as Potential B₁₂ Anti-vitamins

Lucas PRIETO,^a René OETTERLI, Bernhard SPINGLER, Felix ZELDER

a) Department of Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland; lucas.prieto@chem.uzh.ch

Vitamin B₁₂ (**1**) is an enzymatic cofactor involved in cell-growth processes in many organisms including humans.^[1] Therefore fast-proliferating cells, like cancer cells, take up increased amounts of this essential nutrient. The design of anti-vitamin B₁₂ derivatives (B₁₂ surrogates with modified catalytic activity) represents a promising approach towards the development of anti-proliferative agents in cancer treatment.

Herein, we present new ring-modified vitamin B₁₂ derivatives (**2**, **3**, **4**, **5**, **6**).^[2,3] Halogenations of the corrin macrocycle modify strongly the electronic properties of this chromophore, which plays an important role in the reactivity of the vitamin within the enzymes. Biological studies with these new derivatives are currently underway.



References:

- [1] Kräutler B.; Arigoni D.; Golding B. T., Vitamin B₁₂ and B₁₂ proteins, Wiley VCH, Weinheim, 1998.
- [2] Oetterli R.; Prieto L.; Spingler B.; Zelder F., Organic Letters, 2013, 15 (18), 4630-4633.
- [3] Prieto L.; Oetterli R.; Spingler B.; Zelder F., in preparation.

Synthesis and biochemical application of magnetic nanoparticles functionalized with metallocarbonyl complexes

Bogna RUDOLF,^{a)} Agnieszka Z. WILCZEWSKA,^{b)} Michele SALMAIN,^{c)} Aleksandra KUBICKA,^{a)} Iwona MISZTALEWSKA^{b)}

*a) Department of Organic Chemistry, University of Lodz, 91-403 Lodz, Poland;
brudolf@chemia.uni.lodz.pl*

b) Institute of Chemistry University of Bialystok, 15-399 Bialystok, Poland;

c) Sorbonne Universités, UPMC Univ Paris 06, IPCM, UMR CNRS 8232, F-75005 Paris, France;

Magnetic nanoparticles are widely employed in a variety of areas including immunoassays, cell separation, targeted transport of drugs, tissue repair, contrast enhancement in magnetic resonance imaging and hyperthermia. Magnetic nanoparticles are easily manipulated using a magnetic field and can be removed from solutions in a matter of minutes. They may be modified with a variety of biological ligands that have the ability to bind to target compounds and separate them from complex biological media. To make possible the surface functionalization of nanoparticles with ligands capable of binding targeted compounds, their surface should be first coated with functional groups.

Metallocarbonyl complexes and their bioconjugates display specific and intense absorption bands in the mid-IR spectral range assigned to the stretching vibrations of the carbonyl ligands which make them useful bioprobes to study biomolecular processes such as hormone-receptor or antigen-antibody interactions.

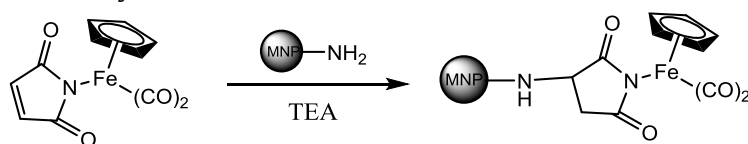


Fig 1. Synthesis of metallocarbonyl-MNP conjugate

Herein we employed the $(\eta^5\text{-cyclopentadienyl})\text{M}(\text{CO})_n(\eta^1\text{-N-maleimidato})$ ($\text{M}=\text{Fe}, \text{Mo}, \text{W}$, $n=2,3$) complexes to introduce IR-active probes onto the surface of magnetic nanoparticles. Labeling was achieved via covalent binding of the complexes to amine and thiol groups on the surface of nanoparticles. We also present the derivatization of metallocarbonyl-labeled magnetic nanoparticles with an antibody to provide IR reporter immunoprobes.

Acknowledgement: The research was funded by NCN grant DEC-2011/03/B/ST5/01480

Synthesis and Structure of Organogold(I) Complex Bearing Uracil Moiety

Yuki SAKAMOTO, Toshiyuki MORIUCHI, Toshikazu HIRAO

*Department of Applied Chemistry, Graduate School of Engineering, Osaka University,
Yamada-oka, Suita, Osaka 565-0871, Japan
e-mail: ysakamoto@chem.eng.osaka-u.ac.jp*

The double helical DNA is comprised of A-T and G-C base pairs, which are mainly controlled by hydrogen bonds and π - π interactions. Utilization of self-assembling properties of nucleobases offers the flexibility of exploiting four different binding motifs. On the other hand, the linear gold(I) compounds possess interesting property which is attractive aurophilic interaction with forming the weak Au-Au bond and exhibiting a unique emission. We have already demonstrated that bioorganometallic compounds composed of the gold(I) complexes and guanine show a unique emission based on the aurophilic interaction through self-assembling of the guanine moiety [1]. We herein report the syntheses and characterization of the gold(I) complexes having a uracil moiety.

The gold(I) complex **1** was prepared by the reaction of chlorophenylisocyanidegold(I) with 6-ethynyl-1-octyluracil. The single crystal X-ray structure determination of the gold(I) complex **1** disclosed the dimer structure through hydrogen bonds between the uracil moieties (**Figure 1**). In the packing structure, the intermolecular Au-Au distance is 3.31 Å, indicating Au-Au interaction in a solid state.

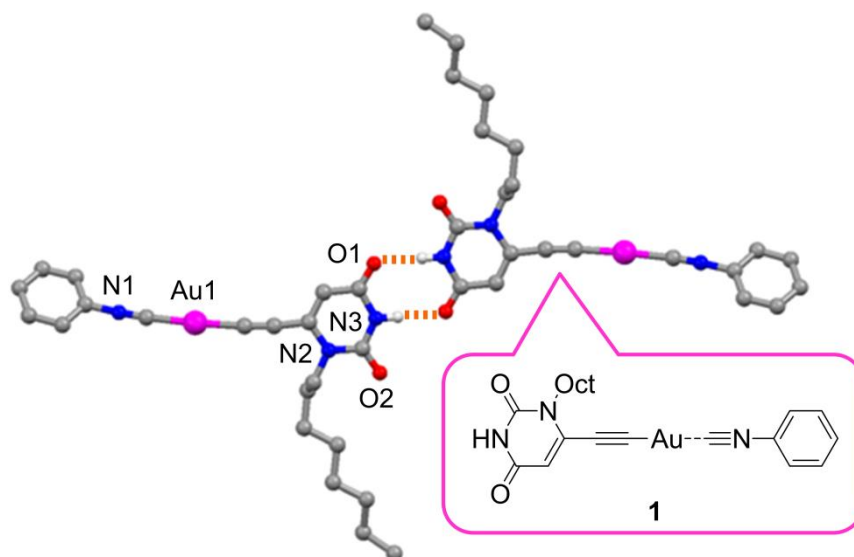


Figure 1 Crystal structure of the gold(I) complex **1**.

References:

- [1] Meng, X.; Moriuchi, T.; Kawahata, M.; Yamaguchi, K.; Hirao, T. *Chem. Commun.* **2011**, 47, 4682.; Meng, X.; Moriuchi, T.; Sakamoto, Y.; Kawahata, M.; Yamaguchi, K.; Hirao, T. *RSC Advances*, **2012**, 2, 4359.

Grafting redox cofactors onto surface-bound peptides using click chemistry

Martin SCHLAGETER,^{a)} **Vanessa TROUILLET**,^{b)} **Annie K. POWELL**,^{a)} **Frank BREITLING**^{b)}

a) Institute of Nanotechnology, Karlsruhe Institute of Technology (KIT)

E-Mail: Martin.Schlageter@kit.edu

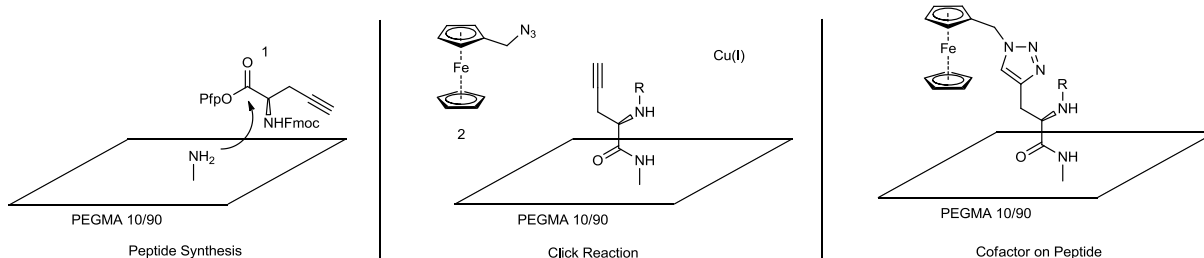
b) Institute of Microsystems Technology, KIT, Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen

Charge separation is a key step in harvesting light, both in nature and technology. It is realized via directional electron tunneling, where an electron travels along a series of redox cofactors in a preferred direction, similar to a diode. Optimizing this process is vital for the development of efficient solar cells. Charge separation performance is influenced by the redox potentials and distances of the cofactors.^[1]

Because peptide chemistry is well established, versatile and provides the possibility of combinatorial synthesis, we decided to arrange redox cofactors using peptides as framework. In order to avoid exposure to harsh reaction conditions and reduce the required substance amount, we aim for the post-synthetic grafting of the cofactors onto peptides (Graph).

The particle-based peptide synthesis by Breitling et al.^[2] allows for the parallel synthesis of a large number of different Amino acid sequences and thus to screen efficiently for performing peptide-based diodes. This method requires amino acids in 10 g amounts with N-Fmoc protection and OPfp activation.

We present the post-synthetic grafting of Azidomethylferrocene **2** onto a surface-bound peptide containing L-Propargylglycine **1** using click chemistry and the characterization via X-ray Photoelectron spectroscopy.



References:

- [1] Noy, D.; Moser, C. C.; Dutton, P. L.; Design and engineering of photosynthetic light-harvesting and electron transfer using length, time, and energy scales. *Biochim Biophys Acta* 2006, 1757 (2), 90-105.
- [2] Breitling, F.; Felgenhauer, T.; Nesterov, A.; Lindenstruth, V.; Stadler, V.; Bischoff, F. R., Particle-Based Synthesis of Peptide Arrays. *ChemBioChem* 2009, 10 (5), 803-808.

Influence of *N*-heterocycles on stability and solubility of novel (thio)maltol-derived metal arene complexes: Synthesis, characterization and cytotoxicity

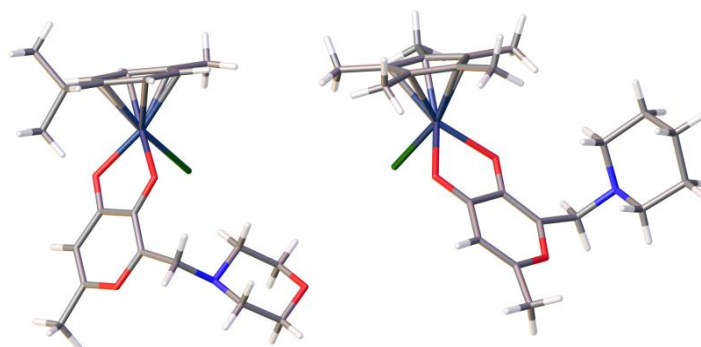
Melanie SCHMIDLEHNER,^{a)} **Verena PICHLER,**^{a)} **Alexander ROLLER,**^{a)} **Michael A. JAKUPEC,**^{a,b)} **Wolfgang KANDIOLLER,**^{a,b)} **Bernhard K. KEPPLER**^{a,b)}

a) Institute of Inorganic Chemistry, University of Vienna, Waehringer Str.42, 1090 Vienna, Austria.

*b) Research Platform “Translational Cancer Therapy Research”, University of Vienna, Waehringer Str. 42, 1090 Vienna, Austria
melanie.schmidlehner@univie.ac.at.*

Due to their advantageous properties like bioavailability, favorable toxicity profile and high affinity towards metal ions, pyrones are a promising ligand system for the development of novel metallodrugs. This intensively studied compound class can be easily converted to their corresponding thiopyrones. Thiopyrone-based Ru(II)-arene complexes provide an increased stability under physiological conditions and a different biomolecule interaction profile compared to the pyrone analogues. In addition, these compounds exhibit promising cytotoxicity *in vitro*[1,2] and are currently investigated *in vivo*.

The (thio)pyrone library was expanded by modifying the scaffold *via* Mannich reaction utilizing morpholine, *N*-methylpiperazine and piperidine. Due to the emerging interest in Rh(III) and Os(II) complexes the series was expanded to the analogous Rh(III)-Cp* and Os(II)-arene derivatives. All synthesized compounds were characterized by standard analytical methods and if possible by X-ray diffraction analysis. In addition the stability in aqueous solution was studied via ¹H NMR spectroscopy and the cytotoxicity was investigated by means of the colorimetric MTT assay.



References:

- [1] Kandioller, W., Kurzwernhart, A., Hanif, M., Meier, S.M., Henke, H., Keppler, B. K., Hartinger, C.G., Pyrone derivatives and metals: From natural products to metal-based drugs. *J. Organometal. Chem.* **2011**, 696, 999-1010.
- [2] Kandioller, W., Hartinger, C.G., Nararov, A.A., Kuznetsov, M.L., John, R., Bartel, C., Jakupiec, M.A., Arion, V.B., Keppler, B.K., From Pyrone to Thiopyrone Ligands - Rendering Maltol-Derived Ruthenium(II)-Arene Complexes That Are Anticancer Active in Vitro. *Organometallics* **2009**, 28, 4249-4251.

Platinum(IV)- conjugated polyamidoamine (PAMAM) dendrimers: synthesis and characterisation

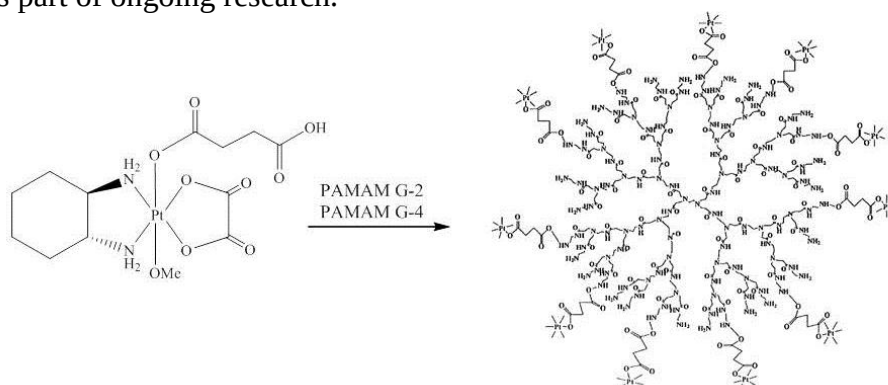
Nadine SOMMERFELD,^a Markus GALANSKI,^a and Bernhard K. KEPPLER^{a,b}

a) University of Vienna, Institute of Inorganic Chemistry, Währinger Str. 42, 1090 Vienna

b) Research platform “Translational Cancer Therapy Research”, Währinger Str. 42, 1090 Vienna, Austria

e-mail: nadine.sommerfeld@univie.ac.at

It is widely accepted that Pt(IV) complexes act as prodrugs, which have to be reduced to the corresponding Pt(II) analogues before displaying their anticancer potential (‘activation by reduction’).^[1] Nevertheless, the inefficient delivery of the complexes into the cell is one of the main drawbacks of Pt-based therapy. The loss of axial ligands during the reduction process provides a promising opportunity for drug targeting strategies. Dendrimers are known for their well-defined nanosized architectures, multivalency, and narrow polydispersity; of them, polyamidoamines (PAMAM) are shown to be the most well-characterised dendrimer family.^[2] Their non-toxic, water soluble properties and the high concentration of peripheral end-groups make PAMAM dendrimers well-suited as innovative scaffolds for drug delivery. Here, we report for the first time on the synthesis and characterisation of Pt(IV)-functionalised PAMAM dendrimers. An unsymmetrically carboxylated Pt(IV) analogue of oxaliplatin was coupled to low generation cationic polyamidoamines with an amino-terminated surface. One- and two-dimensional NMR spectroscopy measurements were used to characterise the intermediates and drug-polymer conjugates. Platinum loading was determined by ICP MS. Evaluation of anti-proliferative properties by means of MTT colorimetric assay in human cancer cell lines as well as the synthesis of different loaded polymers is part of ongoing research.



Acknowledgements

The authors are indebted to the FFG – Austrian Research Promotion Agency (811591) and to the FWF (Austrian Science Fund) and COST CM1105.

References

- [1] Galanski, M., Jakupiec, M. A., Keppler, B. K., *Curr. Med. Chem.* 2005, 12, 2075-2094.
- [2] Govender, P.; Therrien, B.; Smith, G., S.; *Eur. J. Inorg. Chem.* 2012, 2853–286.

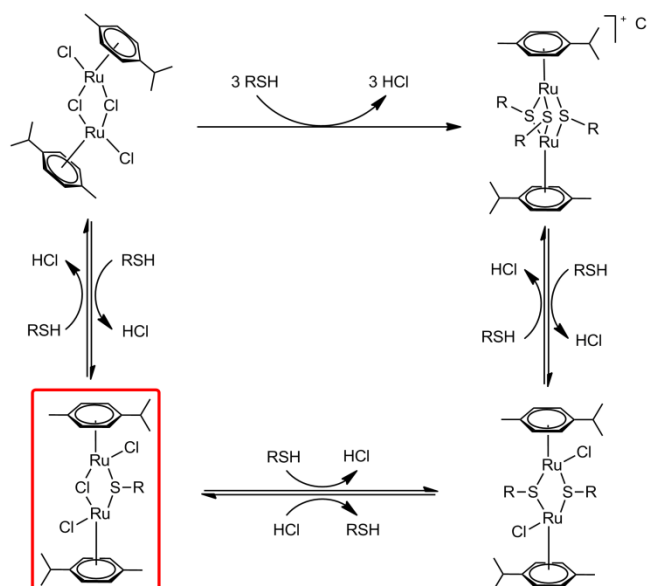
Monothiolato-Bridged Dinuclear Arene Ruthenium Complexes: The Missing Link in the Reaction of Arene Ruthenium Dichloride Dimers with Thiols

David STÍBAL,^{a)} **Bruno THERRIEN,**^{a)} **Georg SÜSS-FINK,**^{a)} **Federico GIANNINI,**^{b)}
Lydia PAUL,^{b)} **Julien FURRER**^{b)}

a) Institut de Chimie, Université de Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel, Switzerland.

b) Department für Chemie und Biochemie, Universität Bern, 3012 Berne, Switzerland

The reaction of p-cymene ruthenium dichloride dimer with thiols is well known to give the cationic trithiolato complexes $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2(\mu\text{-SR})_3]^+$ or the intermediary dithiolato complexes $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{Pr}^i)_2\text{Ru}_2\text{Cl}_2(\mu\text{-SR})_2]$, depending on the reaction conditions [1]. We have recently observed the formation of previously unknown monothiolato complexes of the general formula $[(\eta^6\text{-}p\text{-MeC}_6\text{H}_4\text{-Pr}^i)_2\text{Ru}_2\text{Cl}_3(\mu\text{-SR})]$ which represent the missing link in the stepwise formation of the trithiolato complexes.



Four complexes of this type have been successfully synthesized and evaluated for their activity against human ovarian cancer (A2780) cells. Their catalytic activity in the oxidation of glutathione was also studied. Our results provide insight into the structure-activity relationship of thiolato-bridged arene ruthenium complexes.

References:

[1] Ibao, A.-F.; Gras, M.; Therrien, B.; Süß-Fink, G.; Zava, O.; Dyson, P.J.; Eur. J. Inorg. Chem. 2012, 1531-1535.

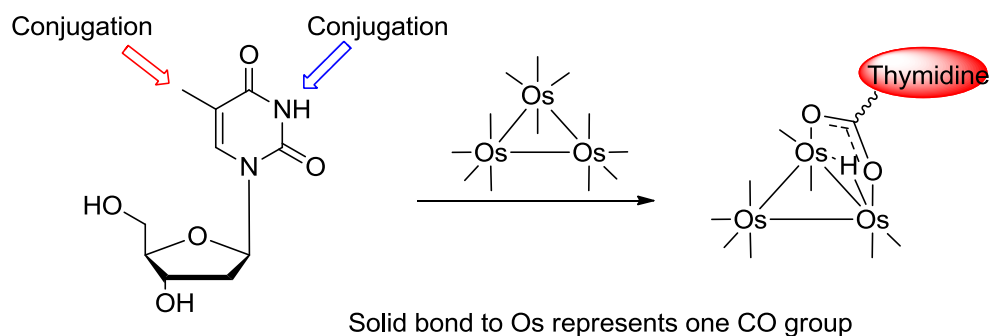
Conjugation of Triosmium Carbonyl Clusters to Nucleosides

Weng Kee, LEONG, ^{a)} Yu Qian, TAN^{a)}

a) Division of Chemistry and Biological Chemistry, Nanyang Technological University, 21 Nanyang Link, Singapore 637371. E-mail : yqtan5@e.ntu.edu.sg

Our group has demonstrated that osmium carbonyl clusters can act as both anti-cancer and bioimaging agents. Some of the more well-known clusters, such as $\text{Os}_3(\text{CO})_{10}(\text{NCCH}_3)_2$, have been shown to exhibit good cytotoxicity against breast cancer cell lines,^[1] while others can also be used for direct cell imaging in the mid-IR, or as conjugates with SERS-active surfaces, in bioimaging and bioassays.^[2,3] A very important requirement is, therefore, the construction of the organometallic cluster bioconjugates.

Oligonucleotides and their derivatives have been widely used as anti-cancer agents and markers of cell proliferation due to their ability to accumulate in rapidly dividing cells. In this work, we have demonstrated the synthesis of such conjugates through direct reaction of triosmium carbonyl clusters with nucleoside derivatives, as well as via click chemistry, utilizing 5-ethynyl-deoxyuridine. The effect of these conjugates on cell proliferation in MDA-MB-231 and MCF-7 cells have been assessed in comparison with the non-conjugated derivatives.



References:

- [1] Kong, K.V.; Leong, W.K.; Ng, S.P.; Nguyen, T.H.; Lim, L.H.K., Osmium Carbonyl Clusters : A New Class of Apoptosis Inducing Agents, *ChemMedChem* 2008, 3, 1269-75
- [2] Kong, K.V.; Chew, W.; Lim, L.H.K.; Fan, W.Y.; Leong, W.K., Bioimaging in the mid-Infrared using an Organometallic Carbonyl Tag, *Bioconjugate Chemistry* 2007, 18, 1370-4
- [3] Kong, K.V.; Lam, Z.; Goh, W.D.; Leong, W.K.; Olivo, M., Metal Carbonyl-Gold Nanoparticle Conjugates for Live Cell SERS Imaging, *Angew. Chem. Int. Ed.* 2012, 51, 9796-9.

Tracking of platinum(IV)-based anticancer drugs in mice tissues by ICP-MS and LA-ICP-MS

Sarah THEINER^{a,b}, Hristo P. VARBANOV^a, Alexander E. EGGER^d, Petra HEFFETER^{b,c}, Walter BERGER^{b,c}, Markus GALANSKI^a, Bernhard K. KEPPLER^{a,b}

a) Institute of Inorganic Chemistry, University of Vienna, Waehringer Strasse 42, 1090 Vienna, Austria; sarah.theiner@univie.ac.at

b) Research Platform 'Translational Cancer Therapy Research', University of Vienna, Austria

c) Department of Medicine I, Institute of Cancer Research, Medical University of Vienna, Borschkegasse 8a, 1090 Vienna, Austria

d) ADSI – Austrian Drug Screening Institute GmbH, Innrain 66a, 6020 Innsbruck, Austria

The rational development of novel drugs requires fundamental knowledge about their activity and pharmacokinetic behavior in terms of absorption and distribution. In this context, the accumulation pattern of drugs in the organism can give information on tissue-specific pharmacology or toxicology and can have a major influence on the therapeutic efficacy and adverse side effects. In the case of metal-based anticancer drugs, inductively coupled plasma-mass spectrometry (ICP-MS) serves as ideal analytical tool to track the metal in the organism. In addition, laser ablation hyphenated to ICP-MS (LA-ICP-MS) has emerged as promising imaging technique in the medicinal sector to study the distribution of metal-based chemotherapeutics in biological tissues due to its outstanding capability of spatial resolution power down to the micrometer scale.

In this study, the anticancer activity of two novel platinum(IV)-based anticancer drug candidates, as well as satraplatin was evaluated after i.p. or p.o treatment of mice (using the CT-26 model) with the respective compound. Mice tissues (including tumor, kidney and liver), serum and blood pellet were digested using microwave-assisted acid digestion followed by quantification of platinum by means of ICP-MS.

Despite similar physicochemical properties, the quantitative accumulation of the novel Pt(IV)-based compounds in mice tissues differed significantly. After oral administration both Pt(IV) complexes displayed similar in vivo anticancer activity, whereas satraplatin turned out to be inactive on the CT-26 model. In addition, a quantitative bioimaging LA-ICP-MS technique was applied to tumor and kidney of mice, allowing spatially-resolved determination of platinum concentrations within the histological structures of these organs. The suitability of the quantitative platinum accumulation in mice tissue samples and the serum platinum levels for the prediction of the in vivo anticancer activity of platinum complexes was assessed. Moreover, the intratissue distribution pattern of platinum was correlated to the respective histological image and related to the anticancer activity of the platinum (IV) compound.

NOVEL PHOTOACTIVATABLE MANGANESE-BASED CO-RELEASING MOLECULES WITH BENZIMIDAZOLE LIGANDS

^{a)} Serpil DEMİR, ^{a)} İsmail ÖZDEMİR, ^{b)} Ulrich SCHATZSCHNEIDER,

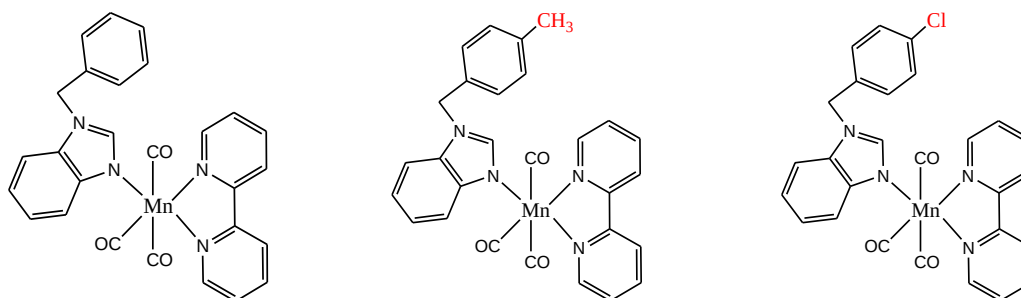
^{c)} Elvan ÜSTÜN

a) Department of Chemistry, İnönü University, 44280 Malatya TÜRKİYE

*b) Institut für Anorganische Chemie, Julius-Maximilians-Universität Würzburg, Am Hubland
D-97074 Würzburg GERMANY*

*c) Department of Chemistry, Ordu University, 52200, Ordu TÜRKİYE
elvanustun77@gmail.com*

Metal carbonyl complexes are the systems of choice to exploit the beneficial effects of CO for therapeutic applications in medicine [1]. Also, photoactivatable CO-releasing molecules (PhotoCORMs) are important aspects of these researches [2]. Benzimidazoles are bioactive compounds with established anti-inflammatory and anti-hypertensive action [3]. Therefore, we decided to combine these two kinds of bioactive molecules and synthesized the three hybrid systems shown below to explore the synergistic potential of their activity.



All molecules synthesized were fully characterized by NMR, IR, MS and elemental analysis. Currently, we are investigating the long-term stability, electronic absorption spectra, and CO-release properties of these complexes. This work was supported by "The Scientific and Technological Research Council of Turkey (TÜBİTAK) within project 112T320.

References:

- [1] Johnson, T.R.; Mann, B.E.; Clark, J.E.; Foresti, R., Green, C.J.; Motterlini, R., Metal Carbonyls: A New Class of Pharmaceuticals?, *Angew. Chem. Int. Ed.* 2003, 42, 3722-3729.
- [2] Schatzschneider, U., PhotoCORMs: Light-triggered Release of Carbon Monoxide from the Coordination Sphere of Transition Metal Complexes for Biological Applications, *Inorg. Chim. Acta* 2011, 374, 19-21.
- [3] Schlenk, M.; Ott, I.; Gust, R., Cobalt-Alkyne Complexes with Imidazoline Ligands as Estrogenic Carriers: Synthesis and Pharmacological Investigations, *J. Med. Chem.* 2008, 51, 7318-7322.

A novel class of bis- and tris-chelate diam(m)inebis(dicarboxylato)platinum(IV) complexes as potential anticancer prodrugs

Hristo P. VARBANOV^{a)}, Simone GÖSCHL^{a)}, Petra HEFFETER^{b)c)}, Sarah THEINER^{a)c)}, Alexander ROLLER^{a)}, Frank JENSEN^{d)}, Michael A. JAKUPEC^{a)c)}, Walter BERGER^{b)c)}, Markus GALANSKI^{a)}, Bernhard K. KEPPLER^{a)c)}

a) University of Vienna, Institute of Inorganic Chemistry, Waehringer Strasse 42, A-1090 Vienna, Austria; hristo.varbanov@univie.ac.at

b) Comprehensive Cancer Center and Department of Medicine I, Institute of Cancer Research, Medical University of Vienna, Borschkegasse 8a, 1090 Vienna, Austria

c) Research Platform "Translational Cancer Therapy Research", University of Vienna, Waehringer Strasse 42, 1090 Vienna, Austria

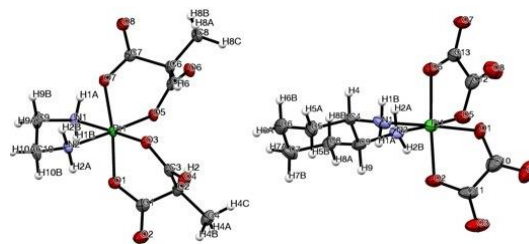
d) University of Aarhus, Department of Chemistry, Langelandgade 140, 8000 Aarhus C, Denmark

Platinum(IV) complexes are promising candidates for novel metal-based anticancer drugs, capable to overcome several problems associated with classical platinum-based chemotherapy. Their physicochemical properties, retained cytotoxicity and diverse possibilities for derivatization offer a variety of opportunities for development of an effective and safe prodrug for oral application. Nevertheless, it is still a challenge to design a platinum(IV) compound, featuring a coordination sphere, ensuring optimal pharmacokinetic behavior.

A novel class of platinum(IV) complexes of the type $[\text{Pt}(\text{Am})(\text{R}(\text{COO})_2)_2]$, where Am is a chelating diamine or two monodentate am(m)ine ligands and $\text{R}(\text{COO})_2$ is a chelating dicarboxylato moiety, was developed. For this purpose, the reaction between the corresponding tetrahydroxido platinum(IV) precursors and various dicarboxylic acids (*i.e.*, oxalic, malonic, 3-methylmalonic and cyclobutanedicarboxylic acid) in aqueous media was utilized. All new compounds were fully characterized employing 1D and 2D NMR techniques, ESI-MS, FTIR spectroscopy, elemental analysis, TGA and X-ray diffraction. Their *in vitro* cytotoxicity was determined in a panel of human tumor cell lines (CH1, SW480 and A549) by means of the MTT colorimetric assay. Furthermore, the lipophilicity and redox properties of the novel complexes were examined in order to better understand their pharmacological behavior. Animal experiments, conducted with the most promising drug candidate in the series revealed pronounced anticancer and especially antileukemic activity combined with a low systemic toxicity.

Acknowledgements

The authors are thankful to the University of Vienna, FWF, FFG and COST CM1105 for the financial support.



Anticancer Activities and Tubulin Interactions of Ferrocenyl Analogs of Plinabulin

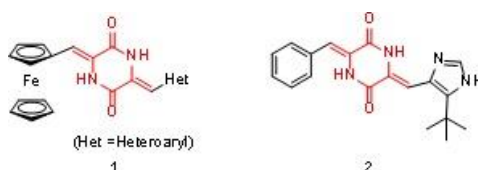
^{a)} Anna WIECZOREK, ^{a)} Damian PLAŻUK, ^{a)} Janusz ZAKRZEWSKI, ^{b)} Błażej RYCHLIK

a) University of Łódź, Department of Organic Chemistry, Tamka 12, 91-403 Łódź, POLAND

b) University of Łódź, Department of Molecular Biophysics, 12/16 Banacha, 90-237, POLAND

aniwie9@wp.pl

Ferrocene is a redox-active metallocene which is stable in biological media. It has shown only slight cytotoxic activity, itself while its conjugated with biologically active compounds provide some promising cytotoxic agents. We have recently become interested in the synthesis of ferrocenyl piperazine-2,5-diones **1**, structurally related to the promising cytotoxic compound, Plinabulin (NPI-2358) **2**, being currently under phase 2 of clinical trials as a vascular disrupting agent (VDA)^[1].



We will present synthetic route and a short overview biological properties, e.g. cytotoxicity and tubulin affinity of the prepared compounds.

Acknowledgment: The authors are grateful for the financial support of The National Science Centre (Poland) grant UMO-2011/01/B/ST5/03933

References:

[1] Millward, M.; Mainwaring, P.; Mita, A.; Federico, K.; Lloyd, G.K.; Reddinger, N.; Nawrocki, S.; Mita, M.; Sear, M.A.; Phase 1 study of novel vascular disrupting agent plinabulin (NPI-2358) and docetaxel, *Investigational New Drugs*, 2012, 30, 1065-1073.

New class of gold complexes - synthesis, structure and anticancer activities

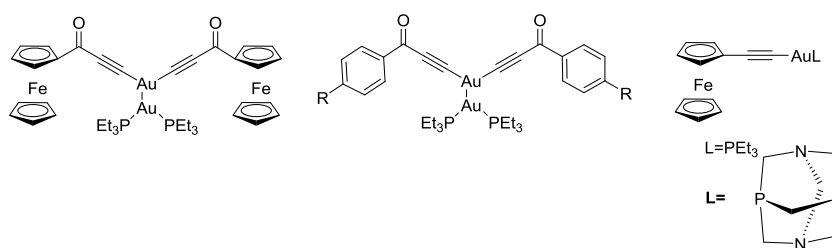
Aleksandra ŻAL,^{a)} **Damian PLAŻUK,**^{b)} **Błażej RYCHLIK,**^{a)} **Janusz ZAKRZEWSKI,**^{b)}
Grzegorz BARTOSZ,^{a)} **Anna MAKAL,**^{c)} **Krzysztof WOŹNIAK**^{c)}

a) University of Łódź, Department of Molecular Biophysics, Cytometry Lab, 12/16 Banacha, Łódź, 90-237, POLAND, email: azal@biol.uni.lodz.pl

b) University of Łódź, Department of Organic Chemistry, ul. Tamka 12, Łódź, 91-403, POLAND

c) Warsaw University, Department of Chemistry, ul. Pasteura 1, Warszawa, 02-093, POLAND

The most common problem related to the anti-cancer therapy is multidrug resistance (MDR) mediated by ATP-binding cassette transporters. Consequently, the use of chemotherapeutics is ineffective and leads to the reduction in the sensitivity of tumor cells towards the above mentioned agents. Metal complexes, such as platinum or ruthenium compounds, have been used in anti-cancer therapy. Their mechanism of action is more or less known. However, scientists are still looking for a new organometallic compounds. A promising group of such compounds includes molecules containing a gold atom in their structure. Studies have shown that gold is more active than other metals used so far in terms of multidrug resistance. We prepared new class of gold(I)-complexes (**Scheme 1**). Our results have shown that this compounds sensitizes tumor cells overexpressing ABC transporters. In this communication we will disclose a synthesis and cytotoxic activities of this compounds on wild type SW620 human colorectal adenocarcinoma cells and selectants obtained by a long-term culture with a group of anticancer drugs and on MDCKII cells transfected with human ABCG2 and ABCB1 genes.



Scheme 1. An example of synthesized gold(I) complexes

Acknowledgment: The study was performed within the POIG project 01.01.02-10-005/08 TESTOPLEK supported by the EU through the European Regional Development Fund.

Theobromine derived platinum(II) carbene complexes with multiple anti-cancer activities

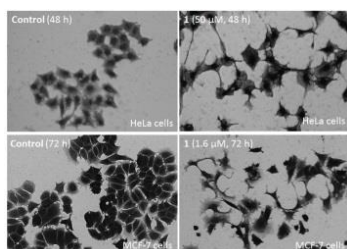
Jing-Jing ZHANG,^{a)} **Chi-Ming Che,**^{b)} **Ingo OTT**^{a)}

a) Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, Beethovenstrasse 55, 38106 Braunschweig, Germany

b) State Key Laboratory of Synthetic Chemistry, Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, and Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, China; behappyday333@gmail.com

Inhibition of angiogenesis¹ and differentiation of cancer cells² has displayed promising anti-cancer results in clinical trials. In combination with the traditional tumor therapies like chemotherapy, these treatments might achieve much more anti-cancer efficiency. However, administration of more than one kind of anti-cancer drugs highly increases the risk of fatal side effects. Herein, we introduced theobromine and corresponding derivatives into cytotoxic cyclometalated platinum(II) moieties. Several compounds like caffeine³ containing a core structure of theobromine have displayed anti-angiogenic properties. It was expected that inducing anti-angiogenic properties into cytotoxic species might result in multiple anti-tumor properties. First results showed that the cytotoxic organometallic platinum(II) complex [Pt^{II}(terpy)(1,3,7,9-tetramethylxanthine-8-ylidene)](PF₆)₂ (**1**) (terpy = 2,2':6',2''-terpyridine) displayed anti-angiogenic effects at sub-cytotoxic concentrations. Most interestingly, it also induced differentiation-like morphological changes in human cervical epithelial carcinoma (HeLa) and breast adenocarcinoma (MCF-7) cells (Figure 1). Moreover, the inhibition of the tumor-relevant enzyme thioredoxin reductase (TrxR) as well as the cellular platinum accumulation was investigated.

Figure 1: Complex **1** induces differentiation-like morphological changes in HeLa and MCF-7 cells.



References:

- [1] A. Vacca, M. Bruno, A. Boccarelli, M. Coluccia, D. Ribatti, A. Bergamo, S. Garbisa, L. Sartor, G. Sava, *Brit. J. Cancer* 2002, 86, 993-998.
- [2] D. Nowak, D. Stewart, H. P. Koeffler, *Blood* 2009, 113, 3655-3665.
- [3] C.-H. Yeh, Y.-F. Liao, C.-Y. Chang, J.-N. Tsai, Y.-H. Wang, C.-C. Cheng, C.-C. Wen, Y.-H. Chen, *Drug Chem. Toxicol.* 2012, 35, 361-365.

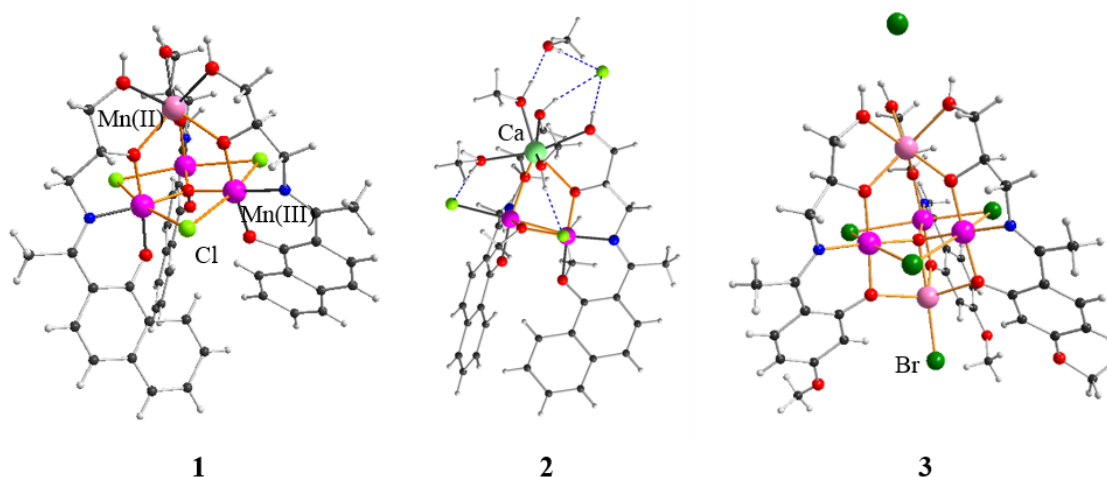
Model Systems for the OEC in Photosystem II

Nadine ZILIAN, ^{a)} Christopher E. ANSON, ^{a)} Valeriu MEREACRE, ^{a)} Annie K. POWELL ^{a)}

*a) KIT, Institute of Inorganic Chemistry, Engesserstrasse 15, 76131 Karlsruhe
email: Nadine.Zilian@kit.edu*

The oxygen evolving center (OEC) of Photosystem II catalyses water oxidation and O₂ formation and is therefore an important part of the photosynthesis process in green plants and cyanobacteria. The core of the OEC contains a [Mn₄CaO_n] cluster embedded in a large protein matrix.[1] The large protein matrix complicates direct studies of the OEC. Therefore biomimetic manganese oxide clusters incorporating calcium(II) are needed to provide better insight into reactivity and spectroscopic properties. However, synthesizing model coordination clusters which contain both manganese and calcium ions is not straightforward.

In order to produce such biomimetic clusters, we have chosen new Schiff base ligands constructed from aromatic carbonyl and aliphatic amino ligands as a means of steering the composition and electronic details of the target molecules. Thus using condensation reactions of 1-hydroxy-2-acetonaphthone (HL₁) or 2'-hydroxy-4'-methoxy-acetophenone (HL₂) with 3-amino-1,2-propanediol and supplying manganese and calcium salts compounds **1**, **2** and **3** were obtained. The complexes were characterized by single crystal X-ray analysis and SQUID measurements.



References:

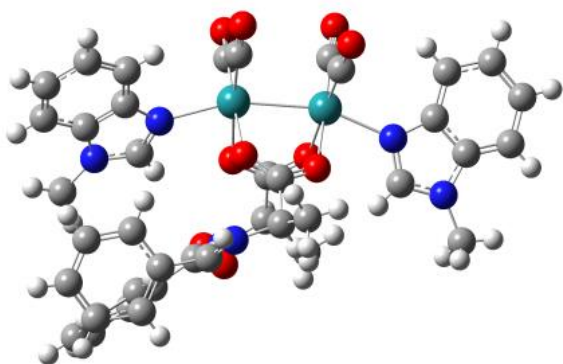
[1] Umena, Y.; Kawakami, K.; Shen, J., Crystal structure of oxygen-evolving photosystem II at a resolution of 1.9Å. *Nature* 2011, 473 (7345), 55-60.

Synthesis, and X-ray and DFT Structural Studies of some Ruthenium-Carbonyl-Azole Compounds

Gabriella TAMASI, Renzo CINI

Department of Biotechnologies Chemistry and Pharmacy, University of Siena, Via Alcide De Gasperi 2, I-53100 Siena, Italy. tamasi@unisi.it

Beside the versatile properties of ruthenium for synthetic chemistry and catalysis, this metal has a number of easily accessible oxidation states (Ru^{II} , Ru^{III} , Ru^{IV}) that can play important roles under physiological conditions [1,2]. In fact, ruthenium complexes are considered promising *anti*-cancer agents, and their cytotoxic activity, *anti*-cancer properties, transport of drugs in the living tissues, membrane crossing, etc. depends on the metal oxidation status. Ruthenium^{II/III} complexes have usually good stability and kinetic inertness at amounts that guarantee transportation, red-ox processes, and subsequently interaction with target biomolecules. The choice of $\text{Ru}(\text{CO})_x$ -core is based on: (i) the presence of carbonyl ligands favors low oxidation status, avoiding the need for reduction to Ru^{II} *in vivo*; (ii) the *trans* effects/influences by carbonyl could modulate the release of other ligands, that could be either pharmaceutical molecules by themselves, and/or just chlorido anions; (iii) the *core* might slowly release low amounts of carbon monoxide that can facilitate apoptosis in cancer cells. The reaction of $[\text{Ru}^{\text{II}}_2(\text{CO})_6\text{Cl}_2]$, with azoles affords complexes that contain the $\text{Ru}(\text{CO})_x$ -unit. The complexes presented in this work contain imidazole (IM), N-methyl-imidazole (MIM), 1-methyl-benzimidazole (MBI), 5,6-dimethyl-benzimidazole (DMBI) in the *pseudo*-octahedral coordination sphere and two chlorido ligands. The compounds have appreciable solubility in water (up to ca 1 g/L) at 25°C and in alcohol. In case water is 10% v/v or higher, significant dissociation of the Ru-N bond occurs, and a series of reactions may take place afterward,



depending on the experimental conditions. Even some release of carbonyl might occur. Thus, complexes of the type *cis,trans,cis*- $[\text{Ru}^{\text{II}}(\text{CO})_2\text{Cl}_2(\text{MBI})_2]$, *cis,trans*- $[\text{Ru}^{\text{II}}\text{Cl}(\text{CO})(\text{MBI})_2(\mu\text{-Cl})]_2$, *cis*- $[\text{Ru}^{\text{I}}(\text{CO})_2(\text{MBI})(\mu\text{-AL})]_2$ (AL, N-benzoyl-L-alanine) were obtained. The complexes were characterized via single crystal XRD, DFT and spectroscopic methods.

References:

- [1] Ang, H.W.; Dyson, P.J. *Eur. J. Inorg. Chem.* 2006, 4003-4018.
- [2] Hartinger, C.G.; Zorbas-Seifried, S.; Jakupec, M.A.; Kynast, B.; Zorbas, H.; Keppler, B.K. *J. Inorg. Biochem.* 2006, 100, 891-904.

Acknowledgment: The authors thank A.Carpini and S.Draghi for their work during internships for Tesi di Laurea.

Author Index

Abbott	Geoffrey	KL3
Alberto	Roger	KL1
Alison	Simon J.	O16
Ang	Wee Han	O22, P08
Anson	Christopher E.	P49
Balogh	Edina	O09, P05
Banfić	Jelena	P01
Barišić	Lidija	P02, P03
Barker	Paul	P32
Bartoloni	Marco	O10
Bartosz	Grzegorz	P47
Bényei	Attila Cs.	O09, P05
Benz	Michael	KL1
Berger	Walter	P11, P43, P45
Bihari	Zsolt	O09, P04
Bíró	Linda	O09, P05
Blauž	Andrzej	P33
Boccarelli	Angelina	O24
Boss	Sally	P32
Braband	Henrik	KL1
Brabec	Viktor	P31
Breitling	Frank	P38
Brooks	Heather J. L.	O23
Brynzak	Ekaterina	P06
Buglyó	Péter	O09, P04, P05
Čakić Semenčić	Mojca	P02
Cazares-Marinero	Jóse de Jesús	O13, O14
Cini	Renzo	P50
Che	Chi-Ming	P48
Cherrier	Mickael V.	O14
Chevalley	Alice	O14
Chobot	Vladimir	P07, P21
Chow	Mun Juinn	P08
Cisnetti	Federico	O26

Clarkson	Guy J.	P26
Coluccia	Mauro	O24
Crossley	Ben D.	O16
Crowley	James D.	O23
Curran	Timothy P.	O28
Das	Sangeetha	O02
Demir	Serpil	P44
Dömötör	Orsolya	P09, P10
Dyson	Paul J.	PL1
Efremenko	Irena	KL3
Egbewande	Folake A.	P12
Egger	Alexander E.	P43
Enyedy	Éva A.	P09, P10
Fan	Wai Yip	P34
Felber	Michael	KL1
Ferrari	Stefano	O29
Filak	Lukas K.	O20
Filipović	Vuk	P15
Flocke	Lea	P11
Fontecilla-Camps	Juan C.	O14
Fornal	Emilia	P20
Fregona	Dolores	O24
Furrer	Julien	O10, O12, P12, P13, P41
Gaiddon	Christian	P08
Galanski	Markus	O15, P01, P14, P40, P43, P45
Gasser	Gilles	O01, O29
Gautier	Arnaud	O26
Geiser	Lennart	P13
Giannini	Federico	O10, P13, P41
Gibard	Clémentine	O26
Göschl	Simone	P14, P45
Grgurić-Šipka	Sanja	P15
Habtemariam	Abraha	O03, P26
Hackl	Carmen M.	P22

Hadacek	Franz	P07, P21
Hamilton	Gerhard	P16
Hann	Stephan	O17
Hanton	Lyall R.	O23
Hartinger	Christian G.	O20
Hebden	Andrew J.	O16
Heffeter	Petra	P11, P43, P45
Hess	Jeannine	O29
Hikisz	Paweł	P18
Hirao	Toshikazu	KL4, P28, P37
Hisaeda	Yoshio	O07
Holenya	Pavlo	O25
Holtkamp	Hannah	O20
Hüse	Dániel	O09
Ibrahim	Houssein	O26
Imstepf	Sebastian	KL1
Ingram	Katrin	O01
Ivanović	Ivanka	P15
Jakupec	Michael A.	O15, P01, P06, P11, P14, P25, P30, P39, P45
Jamieson	Stephen M. F.	O20
Jaouen	Gérard	KL2, O13, P24
Jarosz	Maciej	O06
Jensen	Frank	P45
Ji	Woojung	O28
Kaim	Wolfgang	O27
Kaiser	Manuel	O04
Kandioller	Wolfgang	O20, P09, P10, P22, P25, P27, P30, P39
Kasparkova	Jana	P31
Keiser	Jennifer	O01
Keppler	Bernhard K.	O15, O20, P01, P06, P09, P10, P11, P14, P22, P25, P27, P30, P39, P40, P43, P45
Kianfar	Elham	P17
Kisova	Anna	P31
Kiss	Gabriella	P09
Klapproth	Erik	P06

Knör	Günther	O04, P17
Koceva-Chyla	Aneta	P18
Kodrin	Ivan	P02, P03
Kong	Kien Voon	P23
Kostrhunova	Hana	P31
Kovač	Veronika	P03
Kovačević	Monika	P02
Kowalski	Konrad	P18, P19
Kowol	Christian R.	P11
Kraatz	Heinz-Bernhard	PL3
Kubanik	Mario	O20
Kubicka	Aleksandra	P20, P36
Kubicova	Lenka	P07, P21
Kudinov	Alexander R.	O05
Kuhn	Paul-Steffen	P22
Küster	Nadine L.	O25
Lam	Zhiyong	P23
Lanotte	Fabiana	O24
Lawrence	Allison P.	O28
Lee	Shirley	P24
Legat	Joanna	O06
Legin	Anton A.	O15, P01
Leong	Weng Kee	P23, P24, P42
Leonidova	Anna	O29
Lichtscheidl	Irene	O15, P06
Licona	Cynthia	P08
Lord	Rianne M.	O16
Lucas	Stephanie J.	O16
Makal	Anna	P47
Malarek	Michael S.	P25
Mannion	James J.	O16
Matczuk	Magdalena	O06
Matthias	Tacke	O31
McGowan	Patrick C.	O16
McMullon	Max W.	O16
Meden	Anton	P02
Mereacre	Valeriu	P49

Mészáros	János P.	P09
Metzler-Nolte	Nils	PL2
Micuda	Stanislav	O17
Milaeva	Elena	O21
Millett	Adam J.	P26
Misztalewska	Iwona	P36
Mitra	Raja	O02
Mokesch	Stephan	P27, P30
Montagner	Diego	O22
Moriuchi	Toshiyuki	P28, P37
Murtaugh	Taylor S.	O28
Nagel	Christoph	P29
Nagy	Zoltán	P04
Nako	Adi	O16
Nardon	Chiara	O24
Nazarov	Alexey A.	O19
Nikolić	Stefan	P15
Nishiyama	Taiki	P28
Novak	Maria S.	P30
Novikov	Valentin V.	O05
Novohradsky	Vojtech	P31
Oehninger	Luciano	O25
Oetterli	René	P35
Olivo	Malini	P23
O'Neill	Michael	P32
Opsenica	Dejan	P15
Ott	Ingo	O25, P19, P48
Özdemir	Ismail	P44
Pantić	Darko	P15
Parfieniuk	Ewa	P20
Pask	Christopher M.	O16
Pastorin	Giorgia	P08
Patalenszki	János	O09, P05
Patra	Malay	O01, O29
Paul	Lydia E. H.	O10, O12, P12, P13, P41
Pawlak	Katarzyna	O06
Perekalin	Dmitry S.	O05

Phillips	Roger M.	O16
Pichler	Verena	P39
Pierroz	Vanessa	O29
Plažuk	Damian	P33, P46, P47
Poh	Hwa Tiong Calvin	P34
Pokharel	Niranjana	O28
Powell	Annie K.	P38, P49
Prieto	Lucas	P35
Prokop	Aram	O25
Przadka	Monika	O06
Radulović	Siniša	P15
Rajnisz	Aleksandra	P18
Rath	Barbara	P16
Reikersdorfer	Marlene	P25
Reymond	Jean-Louis	O10
Rezacova	Martina	O17
Roca	Sunčica	P02
Roder	Thomas	P13
Rodríguez-Bárzano	Andrea	O16
Roller	Alexander	P22, P39, P45
Romero-Caneón	Isolda	O03, P26
Rosenberg	Edward	KL3
Ross	Alexander J. B.	KL3
Rudolf	Bogna	P20, P36
Rychlik	Błażej	P33, P46, P47
Sabo	Tibor	P15
Sadler	Peter J.	O03, P26, P31
Sakamoto	Yuki	P37
Salmain	Michèle	O14, P36
Samuelson	Ashoka	O02
Sanchez-Cano	Carlos	P26
Schatzschneider	Ulrich	O08, P29, P44
Schintmeister	Arno	O15
Schlageter	Martin	P38
Schmidlehner	Melanie	P22, P39
Scrase	Tom	P32
Sharmin	Ayesha	KL3

Shimakoshi	Hisashi	O07
Skiba	Joanna	P19
Soldevilla-Barreda	Joan	O03
Solecka	Jolanta	P18, P19
Sommerfeld	Nadine	P40
Sonnay	Marjorie	O18
Spingler	Bernhard	P35
Spreckelmeyer	Sarah	O25
Stepankova	Jana	P31
Stibal	David	O17, P41
Süss-Fink	Georg	O10, O17, P13, P41
Szczupak	Łukasz	P18
Tacke	Matthias	O31
Tamasi	Gabriella	P50
Tan	Yu Qian	P42
Terwilliger	Michelle	KL3
Theiner	Sarah	P14, P43, P45
Therrien	Bruno	O12, P12, P18, P19, P41
Timerbaev	Andrei	O06
Tomsik	Pavel	O17
Top	Siden	O13, P24
Trondl	Robert	P06, P11

Trouillet	Vanessa	P38
Tucker	James H. R.	O30
Ursillo	Samer	KL1
Üstün	Elvan	P44
Varbanov	Hristo P.	P14, P43, P45
Vellas	Sreedhar K.	O23
Vessieres	Anne	O13, P24
Vock	Carsten	O11
Wagner	Michael	O15
Wieczorek	Anna	P33, P46
Wilczewska	Agnieszka Z.	P36
Wölfl	Stefan	O25
Woźniak	Krzysztof	P47
Yap	Siew Qi	O22
Zakrzewski	Janusz	P46, P47
Żal	Aleksandra	P33, P47
Zelder	Felix	O18, P35
Zerzankova	Lenka	P31
Zhang	Jing-Jing	P48
Zhou	Kai	O18
Zilian	Nadine	P49

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

NOTES

[illegible]

NOTES

[illegible]

NOTES

[illegible]

2014 Roundtable 2nd Edition



"In many fields, relatively small groups of individuals set many standards and much of the 'style.' The *Organometallics* Roundtable is an attempt to reach out and engage our readership regarding a variety of fundamental issues facing organometallic chemistry today. These range from 'where the action is' scientifically, to 'best practices' in research and education."



ACS Publications
Most Trusted. Most Cited. Most Read.