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2023

18-21 September

International Symposium Bioorganometallic Chemistry

Technische Universität Braunschweig

BOOK OF ABSTRACTS

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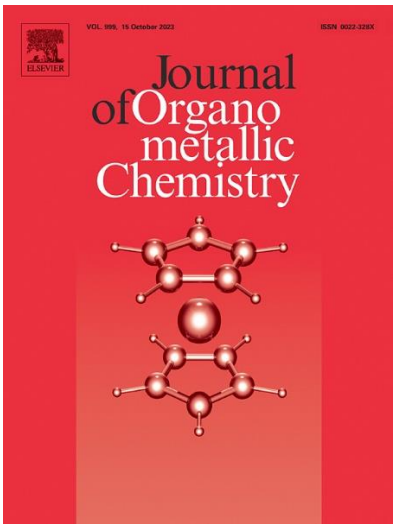

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Infos for Participants

Welcome to the **International Symposium on Bioorganometallic Chemistry 2023** (ISBOMC′23) at Technische Universität Braunschweig (18-21 September 2023)!

ISBOMC’23 will be the next event in a series of meetings, which started in Paris in 2002 and continued in Zurich, Milan, Missoula, Bochum, Toronto, Vienna, Moscow, York, where the to date last “traditional” in-person ISBOMC had been held in 2019, followed by the first online conference in 2021 (digital ISBOMC’21, Braunschweig) and the “First International Symposium on Bioorganometallic Chemistry – 20 years after” in Paris in 2022.

Venue

Technische Universität Braunschweig, Pockelsstr. 4, 38106 Braunschweig

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Conference Dinner (optional):

Altstadtrathaus (Old Town Hall) Altstadtmarkt 7, 38100 Braunschweig

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Entrance and reception: **19:00**, Welcoming and dinner buffet: **19:30**

Special Issue

All participants are invited to contribute to the ISBOMC23 special issue of the *Journal of Organometallic Chemistry*. Manuscripts should be uploaded electronically at

https://www.editorialmanager.com/jorganchem/default2.aspx

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Deadline: 15 January 2024

International Symposium on Bioorganometallic Chemistry 2023 (ISBOMC´23)

TOC Abstracts

Plenary, Special and Award Lectures

Keynote Lectures

Short Lectures

* invited lecture

Poster Presentations

ISBOMC 2023

Monday 18 Sept.	**Tuesday 19 Sept.**	**Wednesday 20 Sept.**	**Thursday 21 Sept.**
	Session 3 *Hartinger / Schmidt*	**Session 7** *Graf / Romero-Canelon*	**Session 10** *Chellan / Metzler-Nolte*
PL: plenary lecture (45min)	PL-1: Smith G. 09:00-09:45	PL-2: Gimeno M. C. 09:00-09:45	AL: Hartinger C. 09:00-09:45
SPL: special lecture (45min)	SL-9: Lord R. 09:50-10:10	SL-24: van Niekerk A. 09:50-10:10	SL-34: Golding T.M. 09:50-10:10
AL: award lecture (45min)	SL-10: dePaiva R. 10:10-10:30	SL-25: Schmidt C. 10:10-10:30	SL-35: Coverdale J. 10:10-10:30
KL: keynote lecture (30min)	Coffee Break 10:30-11:00	Coffee Break 10:30-11:00	Coffee Break 10:30-11:00
SL: short lectures (15 or 20min)	**Session 4** *Castonguay / Ward*	**Session 8** *Hess / Moriuchi*	**Session 11** *Karges / Rodriguez*
	SL-11: Marrone A. 11:00-11:20	SL-26: Plażuk D. 11:00-11:20	SL-36: Hadjikakou S. 11:00-11:20
	SL-12: Cariou K. 11:20-11:40	SL-27: Wang Y. 11:20-11:40	SL-37: Das S. 11:20-11:40
	SL-13: Kowalski K. 11:40-11:55	SL-28: Varbanov H. 11:40-11:55	SL-38: Francescato G. 11:40-15:55
Registration: 12:00-13:25	SL-14: Kulak N. 11:55-12:10	SL-29: Basu U. 11:55-12:10	SL-39: Wieczorek-Błauż A.11:55-12:10
Opening of ISBOMC 2023: 13:25-13:30	Lunch: 12:10-14:00	Lunch: 12:10-14:00	Lunch: 12:10-14:00
Session 1 *Bertrand / Gimeno*	**Session 5** *Casini / Frei*	**Session 9** *Meier-Menches / Rudolf*	**Session 12** *Gil-Moles / Kowalski*
KL-1: Casini A. 13:30-14:00	KL-2: Ang W. 14:00-14:30	KL-3: Salmain M. 14:00-14:30	KL-4: Hayashi T. 14:00-14:30
SL-1: Hess J. 14:00-14:20	SL-15: Chellan P. 14:30-14:50	SL-30: Bertrand B. 14:30-14:50	SL-40: Liu W. 14:30-14:50
SL-2: Rudolf B. 14:20-14:40	SL-16: Rodríguez L. 14:50-15:10	SL-31: Müller J. 14:50-15:10	SL-41: Gaschard-Stefanelli M. 14:50-15:10
SL-3: Frei A. 14:40-15:00	SL-17: Moriuchi T. 15:10-15:30	SL-32: Karges J. 15:10-15:30	SL-42: Paira P. 15:10-15:30
Coffee Break: 15:00-15:30	Coffee Break: 15:30-16:00	SL-33: Moreth D. 15:30-15:45	Farewell / Announcements: 15:30
Session 2 *Basu / Schatzschneider*	**Session 6** *Lord / Smith*		
SL-4: Graf D. 15:30-15:50	SL-18: Ronconi L. 16:00-16:20		
SL-5: Castonguay A. 15:50-16:10	SL-19: Le Lagadec R. 16:20-16:40		
SL-6: Meier-Menches S. M. 16:10-16:25	SL-20: Pizarro A. 16:40-17:00		
SL-7: Gil-Moles M. 16:25-16:40	SL-21: Banti C. 17:00-17:15		
SL-8: Pitto-Barry A. 16:40-16:55	SL-22: Thomas S. R. 17:15-17:30		
short break 16:55-17:15	SL-23: Muñoz-Osses M. 17:30-17:45		
SPL Alberto R.: 17:15-18:00	poster 17:45-		
Welcome R. / poster 18:00-		**Conference dinner: 19:00**	

Special Lecture

International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

Technetium and Rhenium in Bioorganometallics Over the Years

Roger Alberto[a]

a) Department of Chemistry, University of Zurich, Winterthurerstr. 190, CH-8057 Zurich, Switzerland

ariel@chem.uzh.ch

The application of organometallic compounds or complex fragments in the life sciences spreads over most of the d-elements, but is limited to group 7 when it comes to molecular imaging with radionuclides. Either the former have suitable radionuclides but little organometallic chemistry, e.g. Cu or Zr, or they have appropriate organometallic compounds but no suitable or easily accessible radionuclides, e.g. Ru or Au. For being (pre)clinically useful, molecular imaging requests quantitative preparations from water, conditions not really compatible with organometallics. Without having ever heard of bioorganometallic chemistry, a term already coined in 1985,[1] this author was rather interested in fundamentals than in applications. The preparation of the water-stable complex $[^{99}Tc(OH_2)_3(CO)_3]^+$ made him recognizing the emerging opportunities of bioorganometallics, leading ultimately to a plethora of fundamental and applied chemistry with Tc and Re, never believed to be feasible before.[2] Some highlights and lessons/perspectives will be presented.

The "invisible" chemistry of ^{99m}Tc inspired Re chemistry, which became a common element in bioorganometallics. Before the *fac*-$[^{99m}Tc(CO)_3]^+$ core was introduced, it was exactly the other way round; technetium chemistry followed the one rhenium.

A combination of fundamental research with the objective of finding new cores and/or complex structures for bioorganometallic chemistry is an indispensable necessity for diversifying the field, which is defined by a few core structures only since a long time. Striving for new incentives in group 7 chemistry, we left carbonyls and cyclopentadienyls and introduced $[Re(\eta^6\text{-arene})_2]^+$ sandwiches, classic complexes but little explored in organometallics. Beside the opportunities arising from the one pot preparation of the ^{99m}Tc homologues,[3] wonderful fundamental organometallic chemistry for Re and Tc emerged,[4] useful for bioorganometallic chemistry or not, which will be presented as an outlook for our field.

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3. Nadeem, Q., Meola, G., Braband, H., Bolliger, R., Blacque, O., Hernandez-Valdes, D., Alberto, R., To Sandwich Technetium: Highly Functionalized Bis-Arene Complexes $[^{99m}Tc(\eta^6\text{-arene})_2]^+$ Directly from Water and [(TcO4)-Tc-99m](-). *Angew. Chem. Int. Ed.* **2020,** *59*, 1197-1200.
4. Nadeem, Q., Battistin, F., Blacque, O., Alberto, R., Naphthalene Exchange in $[Re\eta^6\text{-napht})_2]^+$ with Pharmaceuticals Leads to Highly Functionalized Sandwich Complexes $[M(\eta^6\text{-pharm})_2]^+$ (M=Re/Tc-99m). *Chem. Eur. J.* **2021,** *28*, e202103566.

Plenary Lectures

Bioorganometallic Chemical Biology Tools To Study Malaria Parasites

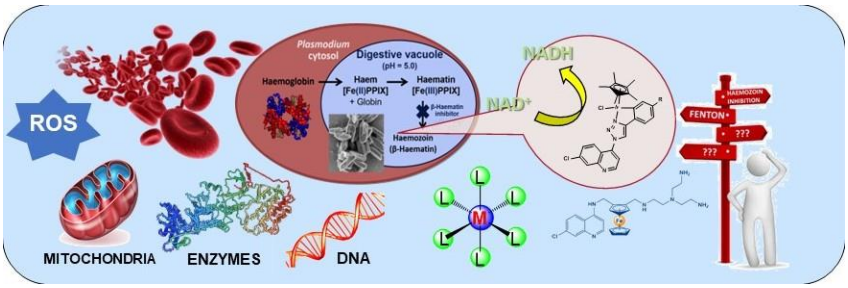
Gregory S. Smith [a]

a) Department of Chemistry, University of Cape Town, Cape Town, South Africa
Gregory.Smith@uct.ac.za

Malaria is a parasitic disease that has an impact on millions of people globally. The pathogenic protozoan *Plasmodium*, which invades the red blood cells of the human host, is the primary cause. Despite advancements in the fight against the disease, reports of rising drug resistance render the present generation of conventional chemotherapies inadequate. To combat resistance and find new compounds with excellent antiplasmodial capabilities, ongoing research is crucial.

Ferroquine, which incorporates ferrocene in the lateral side-chain of the conventional chemotherapeutic chloroquine, has shown to overcome the resistance experienced by the parent compound and thus exemplifies the promising effects displayed by metal complexes in the treatment of malaria, especially in combating rising resistance. This has spurred investigations into the design of new metal-containing systems, with improved potencies, to combat resistance.

This lecture will summarise some of our recent efforts in the design of bioorganometallic antiplasmodial complexes, some of which have demonstrated remarkable activity, notably against resistant forms of the *Plasmodium falciparum* parasite. Invariably, we have consistently demonstrated that the inclusion of sandwich (ferrocene) and half-sandwich organometallic complexes based on compounds containing platinum group metals can enhance the biological activity. Studies on microsomal metabolic stability and putative mechanisms of action will also be discussed.



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Metal Complexes in Cancer Therapy: Challenges and Opportunities

M. Concepción Gimeno

Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza, C/Pedro Cerbuna 12, 50009 Zaragoza, Spain

gimeno@unizar.es

Biorganometallic chemistry offers numerous opportunities for designing therapeutic agents with superior biological properties that are not exhibited by organic compounds alone. Although cisplatin has become a global standard in the use of metal-based drugs for treating various tumors, it has several drawbacks such as the presence of undesirable side effects and the development of platinum drug resistance. Gold compounds have emerged as a viable alternative due to their exceptional anticancer properties.

This presentation will focus on the design of several bioactive metallic or heterometallic complexes that have been developed by our group. We have employed several strategies to achieve better activity and selectivity. The first one is the use of several types of ligands which will modify the properties of the metal complexes and improved stability, solubility, and activity may be achieved. Secondly, the combination of two different metals that has the potential to yield complexes with synergistic properties. These final compounds may exhibit enhanced cytotoxic activities, different pharmacokinetic and pharmacodynamic properties, and different biological targets, which could make them multitarget agents, providing a potential solution to drug resistance. Furthermore, the presence of two distinct metals with different properties could lead to the development of theragnostic agents, a new type of chemotherapeutic drugs. The integration of diagnosis and therapy, or theragnosis, has been proposed as a possible way to facilitate the transformation of conventional medicine into precision or personalized medicine. Therefore, designing imaging agents that can be combined with drugs to make them visible, quantifiable, and traceable over time will enable the development and optimization of specific and more effective treatments.

ISBOMC Award

A Multifaceted Approach Towards Organometallic Anticancer Agent Development

Christian G. Hartinger

University of Auckland, School of Chemical Science, Auckland 1010, New Zealand
c.hartinger@auckland.ac.nz

The approaches taken to develop novel metal-based anticancer agents have considerably changed over the last 50 years since the discovery of the platinum drugs and focus now on compounds that interact with proteins overexpressed in tumor cells, show novel modes of DNA interactions or accumulate with higher selectivity in tumors, to name a few. The structural diversity of anticancer agents has steadily increased and organometallic compounds are widely investigated. Over the years, bioorganometallic chemistry has developed into the thriving field of research it is today and in particular the development of anticancer agents with bioactive co-ligands coordinated to the metal center has received a lot of attention.[1]

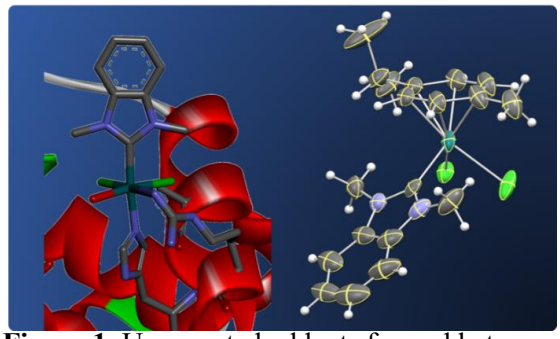

Figure 1. Unexpected adducts formed between anticancer organometallics and proteins.

I will discuss concepts we use in anticancer metallodrug design (Figure 1) and metallomics strategies to interrogate their modes of action. I will focus on the impact of ligand structures on the biological activity of their organometallic complexes,[2] which will be complemented by observations of unexpected reactions and surprising behavior in the presence of biomolecules.[3]

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Keynote Lectures

Insights into the interactions of organogold compounds with biomolecules enable new therapeutic approaches

Angela Casini

Chair of Medicinal and Bioinorganic Chemistry, Department of Chemistry, Technical University of Munich, Germany

angela.casini@tum.de

Several studies have proven that metal-based compounds can be used to develop new drugs, diagnostic agents, as well as chemical probes to study the molecular mechanisms of diseases. This lecture summarizes recent developments for different families of bioactive organometallic gold compounds and provides insights into their reactivity in biological environments. For example, anticancer Au(I) NHCs compounds with caffeine-derived ligands were shown to potently and selectively stabilize G-quadruplexes structures via non-covalent interactions (Fig. 1).[1] Moreover, organogold complexes have recently emerged as promising tools for bio-orthogonal transformations, endowed with excellent chemoselectivity, compatibility within aqueous reaction medium and fast kinetics of ligand exchange reactions. Recent findings from our group on Au(III)-catalyzed reductive elimination in aqueous media provide the proof-of-concept for the use of cyclometalated Au(III) C^N complexes to achieve efficient modification of proteins through C-atom transfer, enabling chemoproteomic studies (e.g. profiling of cysteine residues) and novel therapeutic approaches (gold-PROTACs).[2]

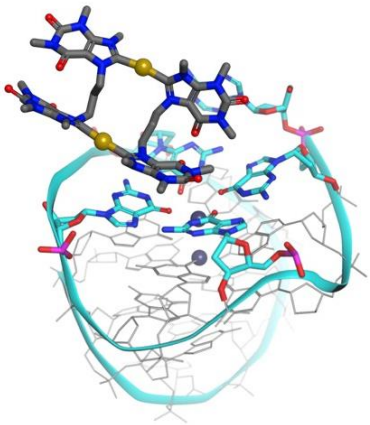

Figure 1 - Adduct of a cyclic dinuclear Au(I) *N*-heterocyclic carbene complex with G4 DNA.

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Engineering Ruthenium-Arene Schiff Base Complexes for Therapy

Wee Han Ang, Cheng Weng, Boon Shing Loh

Department of Chemistry, National University of Singapore, 4 Science Drive 2, Singapore 117544

ang.weehan@nus.edu.sg

Traditionally, drug discovery research has focused on the development of organic molecules as pharmacophores. Yet, their limited structural diversity makes it difficult for them to access other scaffolds that span the entirety of the biologically-relevant chemical space. Organotransition metal scaffolds are uniquely suited for the development of potential drug candidates as they can accommodate higher coordination numbers and access molecular geometries not possible with a purely organic framework. To exploit these advantages, we designed a water-promoted multi-component reaction for the combinatorial assembly of organoruthenium-arene complexes (C3A) for rapid assembly of Ru(II)-Arene Schiff-base (RAS) complexes for therapy.

We apply this C3A methodology towards identification of highly active anticancer compounds that act via an p53-independent pathway. Most clinically-approved anticancer drugs induce DNA damage and activation of transcription factor p53, leading to a downstream induction of apoptosis. Some cancers may be inherently resistant or may acquire resistance by modulating their expression of apoptotic factors in favour of cell survival. I will discuss a phenotypic screening strategy that identified p53-independent RAS compounds with high potency in apoptosis-resistant colorectal cancer cells [1].

We have also extended this strategy towards developing RAS complexes that act against pathogenic bacteria by using endogenous formate metabolites. These complexes mediate activation of exogenous substrates including azide-caged and nitro-caged sulfanilamide antibiotics in the presence of native formate as well as direct reduction of dioxygen into ROS. In both cases, they exerted targeted antibacterial effects against formate-abundant methicillin-resistant *S. aureus* [2].

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"Click chemistry" for intracellular localization and protein targets determination of a cytotoxic half-sandwich iridium(III) complex

Robin Ramos,[a] Sadek Amhaz,[a] Candice Botuha,[b] Anthi Karaiskou,[a] Joëlle Sobczak-Thépot,[a] and Michèle Salmain[b]

a) INSERM, Sorbonne Université, Centre de Recherche de Saint-Antoine, CRSA, F-75012 Paris, France, b) Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, F-75005 Paris, France

Michele.salmain@sorbonne-universite.fr

Bioorthogonal chemistry is now an essential tool in chemical biology, for instance to visualize (bio)molecules in the cellular context and even in whole animals.[1] In the context of metal-based anticancer agents development, we recently introduced a family of half-sandwich iridium(III) complexes with promising antiproliferative properties on cancer cell cultures, inducing regulated cell death by apoptosis. To get insight into the subcellular localization of our lead compound and profile its interactome at the protein-wide scale, we slightly modified its structure to introduce an azide chemical handle for in-cell fluorescence labeling and mass spectrometry chemoproteomics (figure).

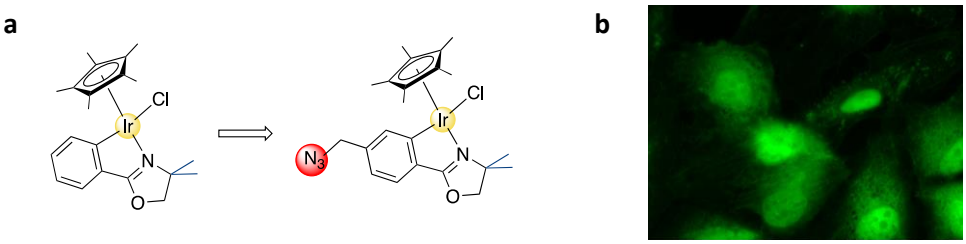

Figure. (a) "Clickable" iridium complex for in-cell fluorescent labeling; (b) Huh-7 cells treated with 1 µM azido complex for 1 h, then fixed and incubated with FITC-alkyne under CuAAC conditions

In-cell reaction with ethynyl-fluorescein was achieved, allowing the complex to be precisely localized (figure). Preferential accumulation of the iridium complex in the cytoskeleton network and nucleus was observed by colocalization studies with specific dyes. The same bioorthogonal probe was used to pull out target proteins from cell lysates. Their identification provided key information to understand the mechanisms underlying cytotoxicity of our lead iridium complex.

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Hemoproteins reconstituted with artificial cofactors that promote organometallic reactions

Takashi Hayashi

Department of Applied Chemistry, Osaka University, Suita 565-0871, Japan.
thayashi@chem.eng.osaka-u.ac.jp

Myoglobin, an oxygen storage hemoprotein, generally does not exhibit enzymatic activity. In contrast, apomyoglobin, obtained by removing heme from the heme pocket, seems to be an attractive reaction scaffold because artificially created metal complexes can be inserted into the cavity of the apoprotein. Our group has focused on replacing the native heme cofactor with several metalloporphyrinoids to generate artificial metalloenzymes. Recently, we have converted myoglobin into a peroxidase and hydroxylase.[1] Furthermore, several reconstituted myoglobins were found to catalyze abiotic reactions. In this presentation, the following reactions promoted by modified myoglobins will be presented:

Methionine synthase has a cobalamin cofactor and is known to provide methionine from homocysteine via Co(I) species and Co(III)–CH_3 key intermediates. Our group prepared myoglobin reconstituted with a tetradehydrocorrin cobalt complex as an enzymatic model. In the reconstituted protein, a tetracoordinated Co(I) species and Co(III)–CH_3 organometallic intermediate were smoothly formed and methyl group transfer to the imidazole moiety of His64 occurred gradually.[2]

F430 is a nickel cofactor responsible for CH_4 generation in methyl-coenzyme M reductase. Myoglobin with a tetradehydrocorrin nickel complex was found to be a model of the enzyme, showing the methanogenic activity. The nickel complex was smoothly reduced to Ni(I) species in the protein matrix, and the addition of methyl iodide resulted in the formation of CH_4 generation in the GC analysis.[3]

Cyclopropanation from olefins via metal-carbenoid species is an abiotic reaction. Our group has recently performed the cyclopropanation of styrene by myologibin reconstituted with iron porphycene as a catalyst. Particularly, iron porphycene was found to accelerate the formation of metal-carbenoid intermediate from ethyl diazoacetate.[4]

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Short Lectures

Rationalised discovery of new organometallic antimicrobials

Jeannine Hess,[a,b]

a) the Biological Inorganic Chemistry Laboratory, the Francis Crick Institute, 1 Midland Road, London, NW1 1AT, United Kingdom, b) Department of Chemistry, King's College London, Britannia House, 7 Trinity Street, London, SE1 1DB, United Kingdom
jeannine.hess@crick.ac.uk / jeannine.hess@kcl.ac.uk

Antimicrobial resistance (AMR) is one of the most significant public health challenges of our time, having caused more than one million deaths globally in 2019 alone.[1] To counteract the raising prevalence of drug-resistance bacteria, we need to move beyond conventional strategies to discover and develop radically new antibiotic agents.[2,3] My research group addresses this problem *via* the rational design of metal-based compounds. Inorganic and organometallic molecules have extensively been studied as anticancer agents but their study as potential antimicrobials has only recently gained traction.[4,5] We are particularly keen in utilising organometallic moieties as a structural 'frame' on which we elaborate and build on through iterative cycles of design and chemical synthesis guided by biophysical data or structural analysis. Metal-based compounds not only have an increased shape diversity, but they can also promote metal-specific mechanisms of action, which we aim to leverage to develop much required novel antibiotics.[6]

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Ruthenium(II) cyclopentadienyl complexes with maleimide and phosphine or phosphite ligands: Synthesis and biological studies.

Bogna Rudolf[a], Sujoy Das[a], Aneta Kosińska[a], Katarzyna Woźniak[b], Michał Juszczak[b], Saranya Vasudevan[c], Arkadiusz Chworos[c]

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

b) Department of Molecular Genetics, Faculty of Biology and Environmental Protection, University of Lodz, Pomorska 141/143, 90-236, Lodz, Poland.

c) Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Lodz, Poland

bogna.rudolf@chemia.uni.lodz.pl

In recent years, the possibility of cancer treatments based on ruthenium complexes has attracted considerable attention. The most studied are half-sandwich Ru-arene complexes that display hydrophilic and hydrophobic properties. Some of them have shown superior anticancer profiles, such as increased selectivity towards cancer cells and improved toxicity against normal cells compared to existing platinum-based anticancer drugs [1].

Recently, we have found that cyclopentadienyl ruthenium complex bearing maleimidato ligand $CpRu(CO)_2(\eta^1$-*N*-maleimidato) is highly cytotoxic and genotoxic, both for normal and cancer cells [2]. In this study, we designed and investigated the cytotoxic and genotoxic potential of ruthenium cyclopentadienyl complexes bearing maleimide and different phosphine or phosphite ligands. For biological studies, we used three types of cells - normal peripheral blood mononuclear (PBM) cells, leukemic HL-60 cells and doxorubicin-resistance HL-60 cells (HL-60/DR). The cytotoxicity studies and the plasmid relaxation assay showed that the cytotoxic effects of the ruthenium complexes are weakly related to the direct degradation of genomic DNA or ROS generation but may affect the DNA damage repair mechanisms leading to cell death. These findings corroborate with the molecular docking studies performed for selected complexes [3].

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Machine Learning to find Organometal Drugs for Bad Bugs

Angelo Frei,[a] Mirco Scaccaglia,[a,b] Markus Orsi[a], Boon Shing Loh,[c] Cheng Weng,[c] Wee Han Ang[c]

[a] *Department of Chemistry, Biochemistry & Pharmaceutical Sciences, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland*

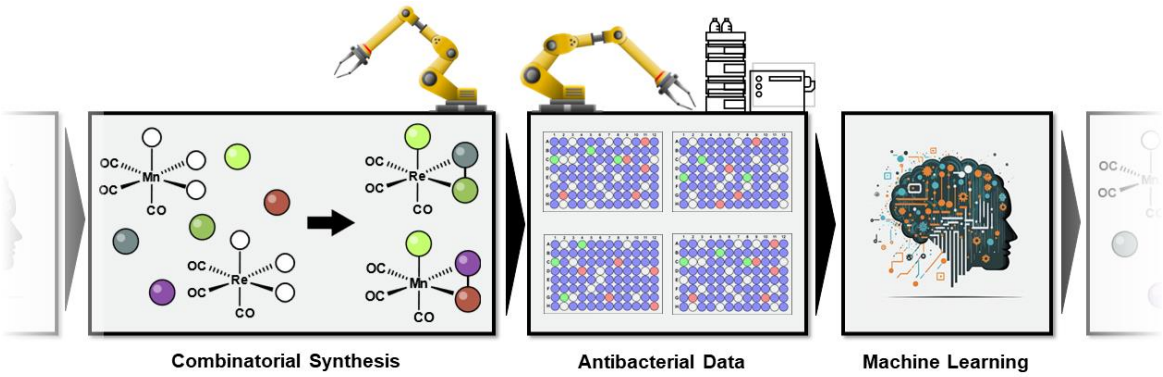
[b] *Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, 43124 Parma, Italy*

[c] *Department of Chemistry, National University of Singapore, 4 Science Drive 2, Singapore 117544, Singapore*

E-mail: angelo.frei@unibe.ch

With the rapid spread of Antimicrobial Resistance (AMR) which is causing >1 million preventable deaths already today, new sources for effective antibiotics are urgently needed. Metal complexes have shown promise in the treatment of infections caused by drug-resistant bacteria and fungi.[1,2] At the same time, we have but scratched the tip of the iceberg that is the transition metal chemical space. To make any significant progress in exploring transition metal complexes as antimicrobial agents, conventional batch-style chemistry is not enough.

To accelerate the discovery of antimicrobial metal complexes, we turned to automated combinatorial synthesis techniques. By careful choice of ligand chemistry and metal synthon, optimized reaction conditions can be found and applied to the synthesis of hundreds of metal complexes in parallel. The reactions are directly screened first for purity and then for antimicrobial activity, identifying potential active compounds. The data obtained by this approach is then utilized to train machine-learning models that guide subsequent synthesis iterations into promising areas of chemical space. We have utilized these models to predict and synthesize antimicrobial metal complexes from a virtual library of ~10^9 possible compounds, improving hit-rates significantly.



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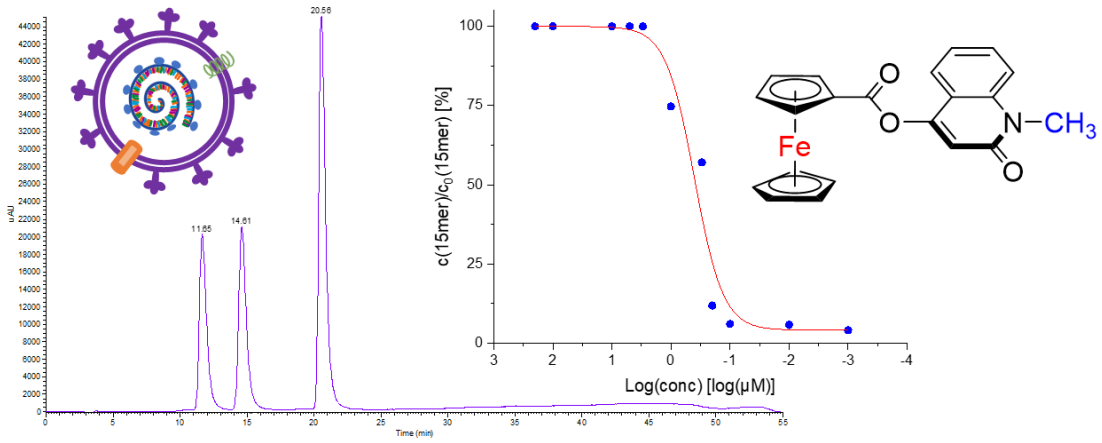
Development of a LCMS-based inhibition assay and the introduction of new quinolinone-derived organometallic inhibitors for the 3CL^{pro} in SARS-CoV-2

Dominic Graf,[a] Nikolas Farn,[a] Jonas Klopf,[a] Mahniya Hojjati,[a] and Ulrich Schatzschneider.[a]

a) Institut für Anorganische Chemie, Julius-Maximilians-Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany

dgraf@uottawa.ca

The 3-chymotrypsin-like protease with a cysteine in the active center is the highly conserved main protease in *Coronaviridae* and therefor a viable target for SARS-CoV-2. The inhibition of this enzyme leads directly to ceased replication.[1]



The newly developed LCMS-based inhibition assay has advantages over commonly used FRET-based inhibition assays, since the information and insight accumulated by the evaluation of uv/vis traces and mass spectra are valuable.[2] Additionally, the IC_{50} value found for ebselen compares to the literature values which underlines the validity of the method. A new organometallic inhibitor with an IC50 value of 2.32 ± 0.21 µM was established as well and compares to other organometallic inhibitors in recent literature.[3,4]

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Design of biologically active organoruthenium complexes

Annie Castonguay,[a] Dulal Musib,[a] Mohammad Mehdi Haghdoost,[a] Golara Golbaghi,[a] Robin Vidal,[a] Hoang-Van Tran,[a] Sam Rezak,[a] Marine Luc[a]

a) Institut national de la recherche scientifique (INRS) - Centre Armand-Frappier Santé Biotechnologie, Université du Québec, Laval, QC, H7V 1B7, Canada

annie.castonguay@inrs.ca

Our research program aims at creating innovative metal-based therapeutics that could potentially overcome problems associated with existing chemotherapies. This presentation will focus on different aspects of a promising class of anticancer, antimicrobial and antifungal metal-based compounds, notably Ru(II) organometallic complexes, and the influence of structural transformations on their biological properties. We are particularly interested in the design of ruthenium complexes that include biologically active ligands in their structure, leading to drug candidates that display a considerable activity via multiple modes of action, simultaneously. We also aim at developing novel strategies for the delivery of ruthenium complexes that include moieties with the ability to undergo reversible cycloaddition reactions with cell-penetrating/targeting agents. This talk will provide an overview of our most recent findings.

Target Identification and Mode of Action Deconvolution of the Organoruthenium Compound Plecstatin-1

Samuel M. Meier-Menches,[a,b,c] Christopher Gerner[a,b]

a) Department of Analytical Chemistry, University of Vienna, Waehringer Str. 38, 1090 Vienna, Austria.
b) Joint Metabolome Facility, University of Vienna and Medical University of Vienna, Waehringer Str. 38, 1090 Vienna, Austria
c) Institute of Inorganic Chemistry, University of Vienna, Waehringer Str. 42, 1090 Vienna, Austria.

samuel.meier-menches@univie.ac.at

Organometallic anticancer drug candidates can be designed as metallo-prodrugs that exhibit unique chemo-reactivities. Despite their interesting chemical properties, carrying such candidates even to advanced preclinical stages is challenging because of the difficulty of characterizing their pleotropic effects in cellular systems. Recently, mass spectrometry-based methods were established to account for the complexity of cellular effects of such candidate molecules, including target identification.[1]

This progress will be illustrated by plecstatin-1, an organoruthenium compound. Plecstatin-1 is a classical half-sandwich ruthenium(II) metallo-prodrug, which is activated by ligand exchange reactions. Chemoproteomic approaches were tailored to identify protein targets of the prodrug and the activated drug. In its activated state, plecstatin-1 featured an unexpected specificity for plectin, a scaffold protein and cytolinker, which was validated as one of the main targets. Additionally, cellular stress responses were comprehensively characterized, including a mitochondrial integrated stress response. Plecstatin-1 is a *first-in-class* modulator of plectin and induces a phenotype that resembles genetic plectin knock-out.[2] Thus, mass spectrometric methods are valuable discovery tools for deconvoluting modes of action of organometallic drug candidates originating from phenotypic drug discovery.

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Metallodrugs against SARS-CoV-2 target proteins

María Gil-Moles,[a, b,c] Ingo Ott[a]

a) Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, Beethovenstr. 55, 38106 Braunschweig, Germany. b) Departamento de Química, Universidad de La Rioja, Centro de Investigación de Síntesis Química (CISQ), Complejo Científico Tecnológico, 26004 Logroño, Spain. c) Departamento de Química Inorgánica, Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza, 50009 Zaragoza, Spain.
m.gilmoles@unizar.es / *m.gil-moles@tu-bs.de*

The antiviral effects of metal-based drugs have occasionally been reported, nevertheless, this area of application has not been studied as intensively compared to the development of metallodrugs against cancer among others.[1]

We have been analysing the potential ability of different metallodrugs to inhibit two different pathways of the viral cycle. For this purpose, we conducted a preliminary study with different gold complexes where promising results were obtained. Taking these results into account, we decided to extend the study to other metals. We screened over 100 structurally diverse compounds. The metallodrug profiling afforded strong inhibitors of the spike/ACE2 interaction and in particular of the PL^{pro} enzymatic activity.[2]

Based on these results we decided to further study the antiviral activity of Ag-NHC complexes. These derivatives were shown to be excellent PL^{pro} inhibitors but inactive against $3CL^{pro}$. Mechanistic studies on a selected complex confirmed zinc removal from a zinc binding domain of PL^{pro} as relevant factor of their activity. In addition, enzyme kinetic experiments revealed that the complex has a rare uncompetitive binding mode (Figure 1) where the inhibitor interacts with the enzyme-substrate complex. Some silver NHC complexes showed strong effects on viral replication in cells infected with SARS-CoV-2.

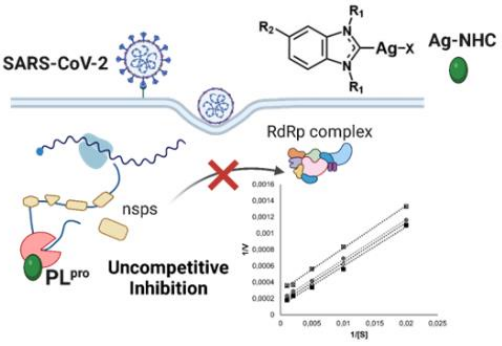

Figure 1: Mechanism of action of Ag-NHC complexes

Taken together, the results of these studies provide the basis for the design of new antiviral metallodrugs against SARS-CoV-2 in future studies. Furthermore, they point out that metallodrugs as antiviral agents have a great potential, which is still largely unexplored.

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Half-sandwich ruthenium complexes for anticancer applications

Anaïs Pitto-Barry,[a,b] Linh K. Nguyen,[a] Maria Azmanova,[b] Laia Rafols[b]

a) Institut Galien Paris-Saclay, CNRS UMR8612, Université Paris-Saclay, 17 avenue des sciences, 91460 Orsay, France, b) Faculty of Life Sciences, University of Bradford, Bradford BD7 1DP, UK

anais.pitto-barry@universite-paris-saclay.fr

Cancer is expected to kill up to 24 million people worldwide by 2030 and to cost the world more than 20 trillion euros by 2050 if no further investments in research and prevention are done.[1] Whilst tremendous progress has been observed in the development of chemotherapeutics capable of fighting cancers, drug resistance and toxicity are still major limitations. Metal complexes, owing to their more varied properties than organic drugs, are ideal candidates to obtain specific functions.[2]

We have recently developed a strong interest in bidentate dithiolato metal-sandwich complexes and investigated their applications in biology,[3] and in the fabrication of nanocrystals.[4] By modification of the bidentate ligand, we have been able to design new families of such compounds.[5] Here we will discuss our latest syntheses of organometallics, their biological properties, and their overall potential.[6]

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Exploring the antimicrobial activity of cobalt(II) picolinamide complexes

Rianne Lord,[a] Ilyas Alav,[b] Pedro W. de Resende,[a] Laura Ghandhi,[c] Stefan Bidula,[a] Hannah Partington,[b] Simon Gibbons,[a] Patrick C. McGowan,[c] Michelle M. C. Buckner[b]

a) Schools of Chemistry and Pharmacy, UEA, Norwich, NR4 7TJ, b) Institute of Microbiology and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT c) School of Chemistry, University of Leeds, Leeds, LS2 9JT

r.lord@uea.ac.uk

The development of new microbials with unique modes of action is crucial and urgent, as the overuse of current clinical agents has led to surges in bacterial and fungal resistance.[1] Cobalt plays a significant role in biological processes, from metabolism and formation of red blood cells, to the maintenance of normal brain and nerve function. Therefore, its inclusion into cells is well tolerated in comparison to other transition metals. Over the last decade, the design of cobalt complexes for their antibacterial and antifungal properties has significantly increased.[2] We recently reported Co(II)-picolinamide complexes which exhibited high growth inhibition against *C. albicans* (up to 86.8%) with no observed cytotoxicity in normal mammalian cells and limit antibacterial activity.[3] One compound (Figure 1A) displayed significant growth inhibition against *A. fumigatus* (86.7%, Figure 1B/C) and *C. albicans* (85.9%), highlighting a broad spectrum of antifungal activity, which is desirable for drug development. We also highligh these compounds to inhibit genetic transfer, and report the first Co(II) complexes to exhibit anti-plasmid activity in *E. coli*.[3]

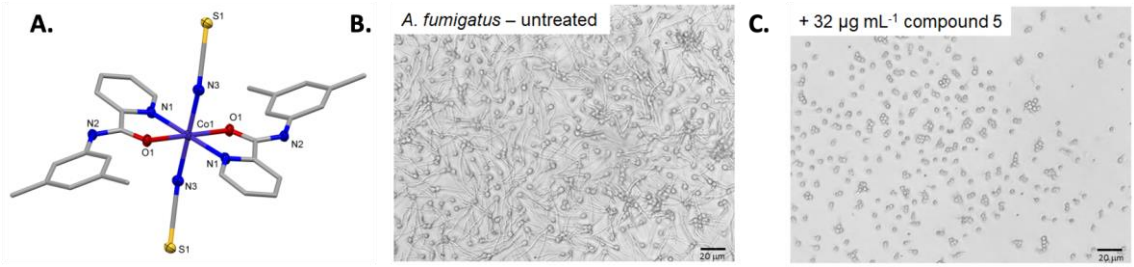

Figure 1 A. *Co(II) compound; Hyphal growth of A. fumigatus)* ***B.*** *in the absence and* ***C.*** *presence of an active Co(II) compound (32 µg/mL for 24 h).*

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Cyclometallated gold compounds for biocompatible chemical modification of proteins

Douglas H. Nakahata,[a] Alex Inague,[b] Ioannis Kanavos,[c] Luca Salassa,[a,d,e] Luisa Ronga,[c] Sayuri Miyamoto,[b] Raphael E. F. de Paiva[a*]

a) Donostia International Physics Center - DIPC, Paseo Manuel de Lardizabal, 4, 20018, Donostia, Spain; b) Department of Biochemistry, Institute of Chemistry, University of São Paulo, São Paulo, Brazil; c) Institute of Analytical and Physical Chemistry for the Environment and Materials (IPREM), CNRS, University of Pau, 64053 Pau, France; d) Polimero eta Material Aurreratuak: Fisika, Kimika eta Teknologia, Kimika Fakultatea, Euskal Herriko Unibertsitatea UPV/EHU, Paseo Manuel de Lardizabal 3, Donostia, 20018, Spain; e) Ikerbasque, Basque Foundation for Science, Bilbao, 48011, Spain

*raphael.depaiva@dipc.org , raphael.enoque@gmail.com

Chemical tools that promote protein modification have become staples in chemical biology. When exploring canonical amino acids (cAAs) as reactive handles, site-selective reactions require exquisite control over both chemo- and regioselectivity, all under ambient, aqueous conditions. When exploiting Cys residues as a native reactive handle, gold compounds have been shown to be endowed with excellent selectivity. The Au(I)/Au(III) redox cycle enables the reductive elimination of Au(III) compounds to mediate C-C, C-halogen and C-S bond formation.[1]They can also be tailored for aqueous compatibility, promoting chemical modifications under mild reaction conditions. Initial emphasis in the field was given to S-arylation and we have shown that [Au(bnpy)Cl_2] (bnpy = C-deprotonated 2-benzylpyridine) is capable of inhibiting viral zinc finger proteins via a brand new mechanism, a C-S coupling.[2]

Our group is currently focused on further exploring the unique reactivity of cyclometallated gold(III) compounds and expanding the reaction scope to new biological nucleophiles. The intrinsic affinity of gold towards selenium and its low abundance in proteins makes selenocysteine (Sec) a promising reactive handle for chemoselective bioconjugation and a relevant target for enzyme inhibition with a wide variety of redox-related implications. Only few examples of metal-mediated selenium arylation reactions exist in the literature.[3] In this contribution we will also share some of our most recent findings, based on NMR and HPLC-MS data, where we unambiguously demonstrate that a family of cyclometallated gold(III) compounds is capable of promoting C-Se coupling across biomolecules of increasing complexity. The implications of this mechanism in Se-related cell death have also been looked at.

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Density Functional Theory and Molecular Dynamics Approaches in the Studies of Bioorganometallic Chemistry Mechanisms: An Insightful Overview

Alessandro Marrone,[a] Richard H. Fish,[b] Iogann Tolbatov,[c] Roberto Paciotti,[a]

a) Dipartimento di Farmacia, Università "G d'Annunzio" di Chieti-Pescara, Italy, b) Lawrence Berkeley National Laboratory, University of California, Berkeley, CA, United States, c) Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Tarragona, Spain

amarrone@unich.it

Recently, the computational sciences have played a prominent role in the generation, interpretation, and comprehension of experimental data, and provided reliable predictions of the thermodynamics and kinetics of chemical processes, including bioorganometallic reactions.[1,2]

In this presentation, the application of density functional theory (DFT) techniques, either used singly or in combination with other methods, to the investigation of the structure and/or reactivity of bioorganometallic complexes will be described. Examples are illustrated to show the reliability of DFT approaches in dissecting the biological activity of organometallic drugs,[1] or the structure and/or reactivity of bioorganometallic complexes, e.g. η^6-coordination of the $[Cp^*Rh]^{2+}$ ion at Tyr side chain (Figure 1).[2]

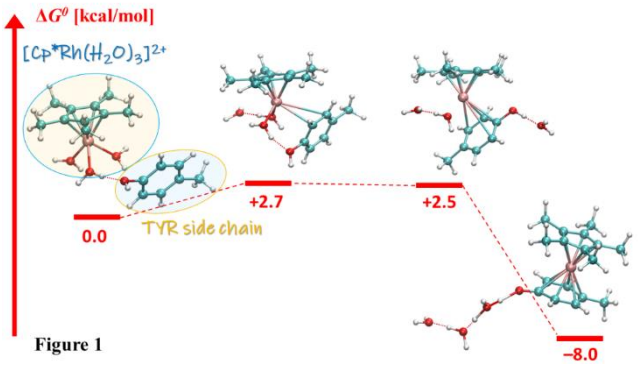

Figure 1

Alternatively, the combination of classical MD with DFT approaches is shown to enhance the comprehension of bioorganometallic system in which the conformational flexibility of the involved biomolecular targets plays a key role.[2,3]

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International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

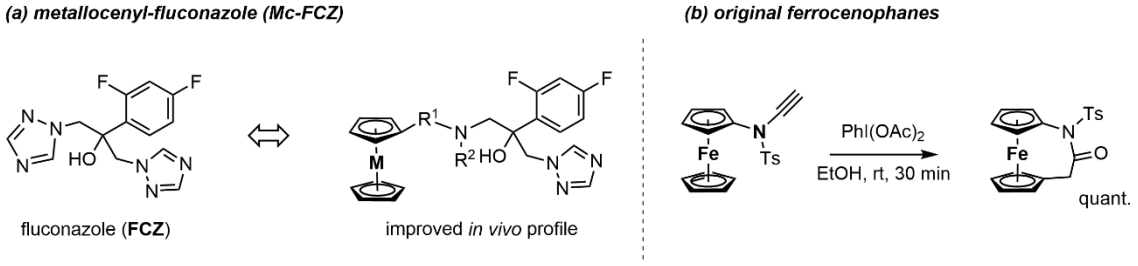
Amino-Metallocenyls Moieties for Therapeutic Applications

Kevin Cariou[a]

a) Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, Laboratory for Inorganic Chemical Biology, 75005 Paris, France
kevin.cariou@chimieparistech.psl.eu

Metal-based drugs constitute an ever-growing class of therapeutic agents, with a wide array of modes of actions,[1] that can allow overcoming therapeutic dead ends. A sub-category of these drugs consists of organometallic compounds, which are defined as metal complexes containing at least one metal-carbon bond. They have many applications in the fields of chemical biology and medicinal chemistry. A very successful example is the ferrocene-containing compound ferroquine, which is a close derivative of the antimalarial drug chloroquine and which is currently in clinical phase II trials as an antimalarial drug candidate.

In this context, we pursue two lines of research: 1. the incorporation of metallocenyl-moieties into drug-frameworks to improve their therapeutic profile and 2. the development of new methods to access original metallocenyl-containing synthons.



During this talk, we will first present our latest results on the development of promising metal-based antimycotic[2] compounds based on fluconazole (FCZ) analogues incorporating a metallocenyl moiety (Figure, left). [3] We will also describe a new synthetic methodology allowing access to unprecedented amino-ferrocenophanes from ynamides (Figure, right).[4]

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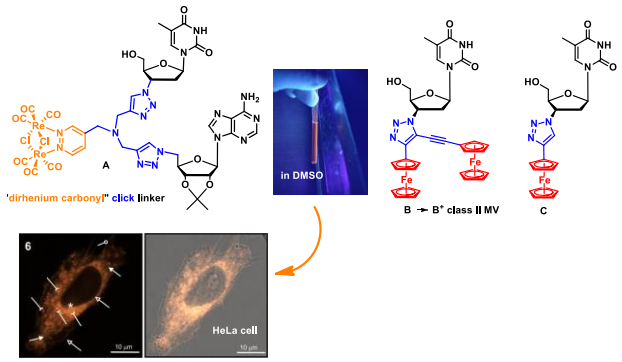
Organometallic “click” nucleosides: synthesis and biological activity

Konrad Kowalski[a]

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

konrad.kowalski@chemia.uni.lodz.pl

This presentation focuses on dinucleoside phosphate analogs with the [Re_2(μ-Cl)$_2$(CO)$_6$(μ-pyridazine)] 1,2,3-triazole (“click”) linker as a replacement for the natural phosphate group (see compound **A** as an example [1]) and on di- and mono-ferrocenyl 1,2,3-triazole nucleosides **B** and **C** [2]. Rhenium complexes exhibited orange phosphorescence in air-equilibrated DCM and DMSO at ambient temperature. Confocal microscopy revealed that these nucleoside analogs were localized mainly in the membranous structures of HeLa cancer cells and were distributed uniformly inside the cells of *S. aureus* and *E. coli*.



Nucleoside **B** showed better ability to generate reactive oxygen species than its mononuclear congener **C**. Nucleoside **B** also exhibited better anticancer activity against A549 and H1975 NSCLC cells than **C**. The better activity of **B** than that of **C** might be due to the fact that after oxidation, **B** is transformed into a weakly coupled class II mixed-valence cation $\mathbf{B}^+$.

Acknowledgments: KK thanks NCN (UMO2018/29/B/ST5/00055) and the Alexander von Humboldt Foundation for the financial support.

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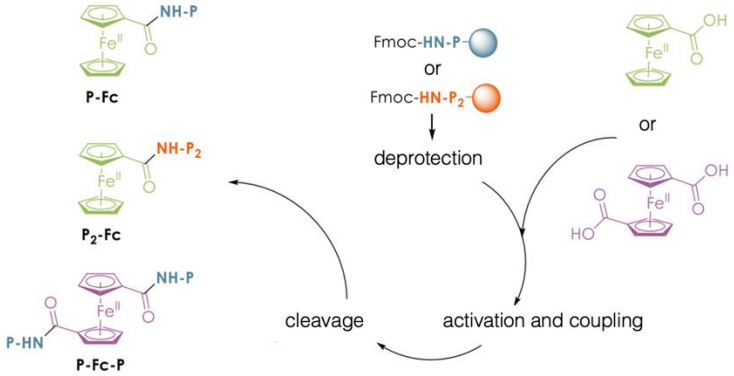
Cu(II) ATCUN-Ferrocene Hybrid Peptides for DNA Cleavage

Christian Wende,[a] Nora Kulak[a,b]

a) Institut für Chemie und Biochemie, Freie Universität Berlin, Fabeckstr. 34/36, 14195 Berlin, Germany b) Institut für Chemie, Otto-von-Guericke-Universität Magdeburg, Universitätsplatz 2, 39106 Magdeburg, Germany.
nora.kulak@ovgu.de

ATCUN (aminoterminal Cu(II) and Ni(II)-binding) metallopeptides have been designed and applied for different purposes comprising e.g. hydrogen evolution from water and antitumor drug treatment.[1] The redox activity of these complexes usually plays a decisive role for such activities. In the last few years, we have been working on tuning their redox activity. Whereas the Cu(II) complex of the most simple peptide motif Gly-Gly-His has been proven to be almost redox inert,[3] we were able to restore the redox activity by incorporating artificial β-amino acids and *N*-heteroaromatics, which led to increased production of reactive oxygen species (ROS) from O_2 for DNA degradation and cytotoxicity.[4] An alternative approach next to incorporation into the amino acid sequence is functionalization at the N-terminus. We have shown in the past, that appended fluorophores can be used for Cu(II) sensing.[5] In the present work, we studied the effect of ferrocene (Fc) functionalization: The synthesis (according to ref. [6]) and DNA cleavage activity of different Cu(II) ATCUN-Fc hybrid peptides will be presented.



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International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

Developing new organometallic complexes for antimicrobial applications

Prinessa Chellan,[a] Brandon L. Munnik,[a] Malcolm T. Ndlovu,[a] Katleho Setlaba[a] and Clare Harding[b]

a) Department of Chemistry and Polymer Science, Stellenbosch University, Stellenbosch, Western Cape, South Africa
b) Wellcome Centre for Integrative Parasitology, Institute of Infection, Immunity and inflammation, University of Glasgow, UK
pchellan@sun.ac.za

The investigation of novel metal complexes as therapeutics is a thriving area of research [1]. In particular, organometallic complexes have been intensely investigated for their inhibitory effects against different parasite and bacterial strains which has affirmed their prospective application as antimicrobials [2]. One popular approach to combat infectious illnesses such as malaria or tuberculosis, is the incorporation of a metal into currently used clinical drugs or known pharmacophores, thus modifying their biological activity [1]. In this presentation, I will discuss some of our recent results on the synthesis and application of ferrocenyl derivatives as inhibitors for malaria, toxoplasmosis and mycobacterium tuberculosis. Our most recent study focused on new ferrocenyl derivatives of the malaria drug, artesunate, sulfa drugs and the pharmacophore, benzimidazole (Figure 1).

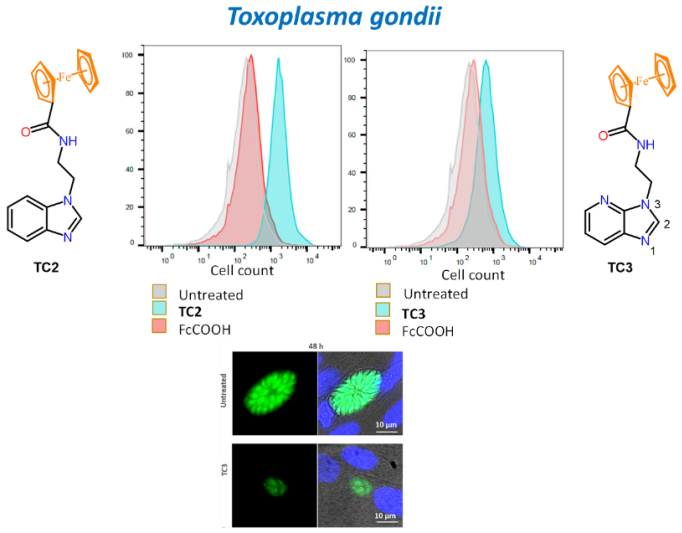

Figure 1. Detection of ROS formation by fluorescence activated cell sorting and immunofluorescence assay image for the growth inhibition of *T. gondii* in the presence of a ferrocenyl-benzimidazole complex.

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Gold(I) supramolecular systems as photosensitizers

Andrea Pinto,[a] Laura Rodríguez[a]

a) a) Departament de Química Inorgànica i Orgànica, Secció de Química Inorgànica, Universitat de Barcelona, Martí i Franquès 1-11, E-08028 Barcelona, Spain
laurarodriguezr@ub.edu

Population of the triplet state in chromophores is an important aspect that plays a key role in many numerous applications such as photodynamic therapy, bioimaging, photocatalysis, light-emitting diodes (OLEDs) and oxygen sensing among others. In particular, singlet oxygen production stays at the forefront of research due to its reactivity as a synthetic reagent, as an intermediate in oxygenation reactions of polymers or as a reactive oxygen species (ROS) for biological purposes. Molecules acting as photosensitizers must have a populated triplet excited state higher in energy but close to the lower excited state of the oxygen, $^1O_2$. Thus, molecules with populated triplet excited states are of great relevance in this field and this can be managed by the presence of heavy atoms. Metal complexes containing heavy atoms, such as gold(I) complexes, are scarcely explored in this field and deserve their investigation.[1]

On the other hand, supramolecular chemistry and thus, intermolecular contacts, are of great importance in these studies. This is particularly relevant in gold(I) complexes due to the possibility of establishing Au···Au contacts that may increase the intermolecular contacts and that also play a key role in the population of the triplet state and photophysical properties.[2]

In this work, we have explored the photophysical properties of a series of gold(I) complexes and we have managed to get the ideal conditions to modulate phosphorescence emission versus singlet oxygen production playing with aggregation and inclusion within different type of materials[3].

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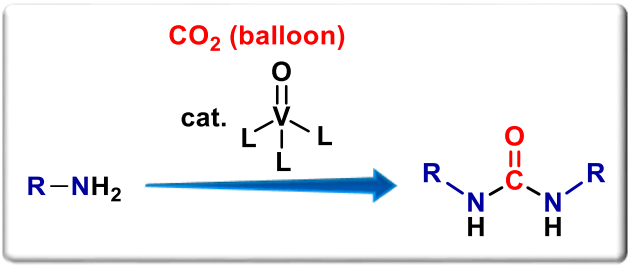
International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

Sustainable Catalytic Synthesis of Ureas by Oxovanadium(V)-Catalyzed Carbon Dioxide Activation under Ambient Pressure

Toshiyuki Moriuchi

Department of Chemistry, Graduate School of Science, Osaka Metropolitan University
3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan
moriuchi@omu.ac.jp

The transformation of carbon dioxide as a C1 building block into valuable compounds has attracted much attention for the future sustainable society. Ureas are among the most important carbonyl compounds that widely used in pesticides, herbicides, and raw materials for resins. Generally, catalytic synthesis of ureas using carbon dioxide requires high carbon dioxide pressure and high temperature. We have already performed one-step synthesis of imidovanadium(V) compounds from amines and oxovanadium(V) compounds.[1] Catalytic reaction of carbon dioxide with *in situ* generated imidometal compounds have not been achieved. From these points of view, we herein report a practical catalytic system for the synthesis of ureas from amines and carbon dioxide under ambient pressure by using a commercially available oxovanadium(V) compound.[2]



The reaction of 2-phenylethylamine with carbon dioxide (balloon) in the presence of $VO(O^iPr)_3$ as a catalyst, *N*,*N*-diisopropylethylamine as a base, and MS3A as a dehydrating reagent in DMA was found to afford the corresponding urea in 93% yield. Various primary amines were demonstrated to transform into the corresponding ureas by using this catalytic system.

The catalytic synthesis of ureas from disilylamines and carbon dioxide under ambient pressure will also be present.[3]

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Vitamin B_{12}-functionalized metallotheranostic agents for the targeted treatment and imaging of tumors

R. Mehder,[a] E. de la Torre-Rubio,[b] E. Royo Cantabrana,[b] L. Ronconi[a]*

a) University of Galway, School of Biological and Chemical Sciences, Galway (Ireland), b) University of Alcalá, Department of Organic and Inorganic Chemistry, Alcalá de Henares (Spain)

luca.ronconi@universityofgalway.ie

Vitamin B_{12} (cyanocobalamin) is an essential nutrient with very low bioavailability. Upon cell internalization, it undergoes conversion into its cofactors methylcobalamin (used to produce methionine) and adenosylcobalamin (a coenzyme involved in Krebs cycle).[1] Compared with normal ones, tumor cells show higher accumulation of vitamin B_{12} to support their abnormal proliferation,[2] and such increased demand for cyanocobalamin can be exploited for the tumor-specific delivery of therapeutic/diagnostic agents by functionalizing vitamin B_{12} with suitable metallodrugs and/or luminescent probes.[3]

In this context, we here report on the development of fluorescent vitamin B_{12}-metallodrug conjugates of the type [FLUO-B_{12}-{M}] in which cyanocobalamin is functionalized at the 5'-hydroxo group of the ribose unit with a fluorophore (FLUO: Rhodamine 6G), whereas the Co^{III}-cyano moiety is coordinated to a metal-based anticancer scaffold ({M}: Pt(II) substrate). The rationale behind the proposed designing approach is based on the evidence that vitamin B_{12} is converted into its cofactors (methylcobalamin or adenosylcobalamin) inside the cell through the reduction of Co^{III} to Co^{II} and the subsequent release of the cyano group. Therefore, by binding platinum(II)-containing bioactive substrates[4] to the cyanocobalamin Co^{III}-CN moiety, should the overall bioconjugate accumulate preferentially in the tumor cells, the cytotoxic species {CN-metallodrug} would be released directly into the diseased site where it can exert its anticancer activity without affecting healthy tissues. Additionally, the fluorophore attached at the 5'-ribose moiety would allow the transport and biodistribution to be followed and assessed by fluorescence spectroscopy.[5]

Acknowledgements

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Group 8 metallocycles as multitarget cytotoxic agents

Ronan Le Lagadec

Instituto de Química, Universidad Nacional Autónoma de México, Ciudad de México, Mexico

Email: ronan@unam.mx

Our research team has been evaluating the anticancer properties of organometallic complexes, with a special interest in cyclometalated derivatives. To assess the influence of the metal and physicochemical properties on the activity and mechanisms, series of structurally analogous iron, ruthenium, and osmium metallacycles have been prepared (Fig. 1). The impact of the complexes on potential biological targets has been evaluated and contrasting modes of action than for clinically approved platinum-based drugs and within the Fe, Ru and Os series were established [1]. For instance, the cytotoxicity is mostly independent of DNA damage, while the redox enzymes activity can be altered, and the endoplasmic reticulum stress pathway induced. Furthermore, ruthenium and osmium complexes showed distinct responses towards resistance mechanisms by ABCB1 and EGFR [2]. Another series of experiments showed that the activity of complexes bearing metalated π-expansive ligands can remarkably be increased through the formation of singlet oxygen upon irradiation by visible light [3]. Hence, our multitarget agents could be considered as new therapeutic alternatives, potentially able to bypass various resistance mechanisms developed by tumors.

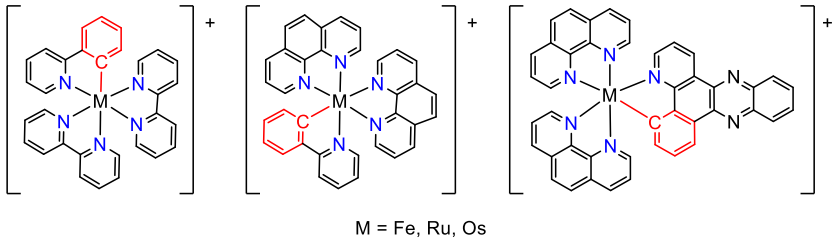

Figure 1. Examples of cationic metallacycles studied.

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International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

Potent Tethered Osmium(II) Half-Sandwich Anticancer Agents Bearing Phenylpyridine

S Infante-Tadeo,[a] V Rodríguez-Fanjul,[a] A Habtemariam,[a,b] A M Pizarro[a]

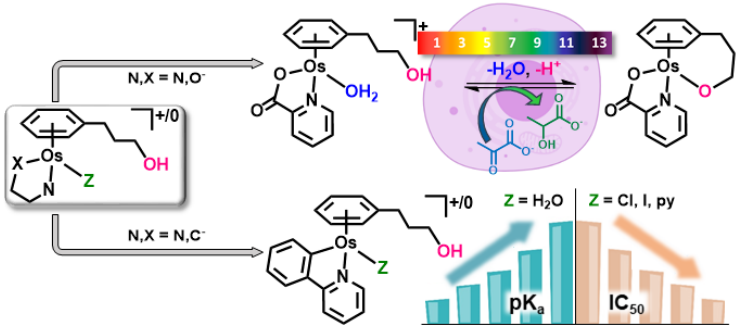
a) IMDEA Nanociencia and Unidad Asociada de Nanobiotecnología CNB-CSIC-IMDEA, Faraday 9, 28049 Madrid, Spain; b) Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, UK

ana.pizarro@imdea.org

Half-sandwich complexes of Ru(II), Os(II), and Ir(III) have recently received much attention due to their potency against cancer cells.[1] These complexes often bear a labile chlorido ligand, which upon substitution in water, renders the metal active towards biomolecule interaction. However, for osmium(II) half-sandwich complexes of formula $[Os(\eta^6\text{-arene})(XY\text{-bidentate})Z]^{n+}$, aquation of the Z monodentate ligand often inhibits Os-reactivity by affording inert Os–hydroxido dimeric species.[2]

We have overcome this activity-loss by introducing a hemilabile arene/alcohol ligand – whereby the pendant alcohol occupies the Z position–, which protects the metal centre against hydroxido-mediated inactivation by forming a tether ring.[3] We have carefully fine-tuned the design, including XY negatively charged chelating ligands (C,N- or N,O-) that lead to faster hydrolysis and enhanced anticancer activity. Additional proof that Os-reactivity is maintained in cells has been demonstrated by the Os-mediated transformation of pyruvate to lactate in breast cancer cell lines.[3]

We looked into the aqueous solution behaviour of highly potent Os-arenes, tethered and non-tethered, bearing phenylpyridine as XY-bidentate ligand. The Os–Cl bond is stable in pure DMSO yet readily hydrolyses in DMSO:aqueous solution leading to rapid formation of Os–DMSO adduct (following aquation). We could determine the pK_a in DMF:aqueous solutions, which is above 9.6 in all cases. These values are some of the most basic Os-arene aqua-adducts reported to date.[4] The data are discussed in the context of hydrolysis readiness, low acidity of Os-OH_2, and high cytotoxic potency of the Os-phenylpyridine-arene core.



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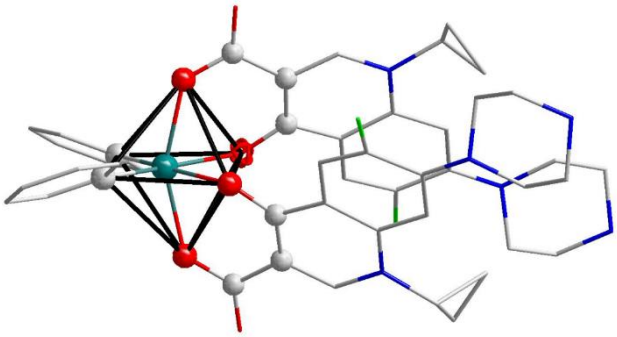
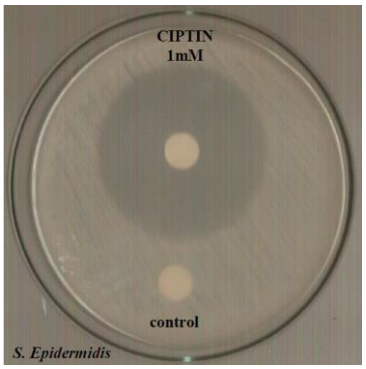
Ciprofloxacin conjugated to diphenyltin(IV): a novel formulation with enhanced antimicrobial activity

Christina N. Banti and Sotiris K. Hadjikakou.
University of Ioannina, Department of Chemistry, 45110, Ioannina Greece
cbanti@uoi.gr

The synthesis of the metallo-antibiotic of formula $Ph_2Sn(CIP)_2$ (CIPTIN) (HCIP = ciprofloxacin) is reported. The complex was characterized in the solid state by melting point, FT-IR, X-ray Powder Diffraction (XRPD) analysis, ^{119}Sn Mössbauer spectroscopy, X-ray Fluorescence (XRF) spectroscopy, and Thermogravimetry/Differential Thermal Analysis (TG-DTA) and in solution by UV-Vis, 1H NMR spectroscopic techniques and Electrospray Ionisation Mass Spectrometry (ESI-MS). The crystal structure of CIPTIN and its processor HCIP was also determined by X-ray crystallography.

The antibacterial activity of CIPTIN, HCIP·HCl, HCIP and DPTD was evaluated against the bacterial species *Pseudomonas aeruginosa (P. aeruginosa*), *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*) and *Staphylococcus epidermidis* (*S. epidermidis*), by the means of Minimum Inhibitory Concentration (MIC), Minimum Bactericidal Concentration (MBC) and Inhibition Zones (IZs). CIPTIN is classified into bactericidal agents. The developing IZs classify the microbes *P. aeruginosa*, *E. coli*, *S. aureus* and *S. epidermidis* to susceptible ones to CIPTIN. CIPTIN exhibits 2 to 9-fold lower MIC values than its IC_{50} against HaCaT, while its genotoxic effect determined by micronucleus assay is equivalent to the corresponding ones of HCIP·HCl or HCIP.





Acknowledgments
This program is co-financed by Greece and the European Union (European Social Fund- ESF) through the Operational Programme «Human Resources Development, Education and Lifelong Learning 2014-2020» in the context of the project "Sub-project 6 ("Biological Inorganic Chemistry (BIC)" (MIS 5162213)."

Water-soluble gold nanoparticles stabilized by N-heterocyclic carbenes for applications in catalysis and medicine.

Sophie R. Thomas,[a] Ana Luiza de Andrade-Querino,[a,b] Nikolaos Dimitratos,[c] Angela Casini[a]

a) Chair of Medicinal and Bioinorganic Chemistry, School of Natural Sciences, Technical University of Munich, Garching, Germany, b) Department of Chemistry, Federal University of Minas Gerais, Belo Horizonte, Brazil, c) Department of Industrial Chemistry "Toso Montanari", Universita' degli Studi di Bologna, Viale Risorgimento, Bologna, Italy.

sophie.thomas@tum.de

In recent years, N-heterocyclic carbenes (NHCs) have emerged as an alternative to thiol ligands for stabilization of gold nanoparticles (AuNPs) due to the formation of strong Au-C interactions and the facile derivatization of the NHC scaffold at the NP surface, which can be useful to implement the applications of AuNPs in biomedicine and catalysis.[1]

In this work, two water-soluble mono- or bidentate NHC stabilized AuNPs (NHC@AuNPs, **AuNP-1** and **AuNP-2, Figure 1**) were formed from their corresponding Au(I) NHC complexes *via* the 'bottom-up' approach.[2] The NPs were characterized by various spectroscopic and analytic methods. The NHC@AuNPs were then tested for their catalytic activity towards the reduction of nitrophenol substrates in the presence of sodium borohydride ($NaBH_4$) as a model reaction. The more stable NHC@AuNPs (**AuNP-2**) were also tested for their application in photothermal therapy (PTT) by measuring their photothermal efficiency and assessing their cytotoxicity in human cancer cells *in vitro*.[2]

More recent work involves functionalisation of these NHC@AuNPs with carboxylic acid groups (**AuNP-3, Figure 1**) for future bioconjugation to peptides for targeted PTT treatment or fluorophores for intracellular tracking.

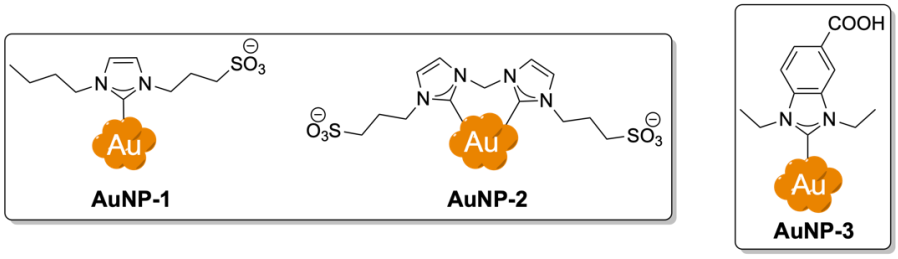


Figure 1 – Structures of the NHC@AuNPs used in this work.[2]

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Organometallic and organic chalcones as new dual COX-2/5-hLOX inhibitors.

Michelle Muñoz-Osses[1], Elizabeth Navarrete[1], Pilar Morales[1], Carolina Mascayano[1] and Nils Metzler-Nolte[2]

[1]Faculty of Chemistry and Biology, University of Santiago of Chile, Av. Libertador Bernardo O´Higgins 3363, Estación Central, Santiago, Chile.
[2] Faculty of Chemistry and Biochemistry, Ruhr University Bochum, Universitaetsstrasse 150, D-44780, Bochum, Germany
E-mail: michelle.munoz@usach.cl

In the search for new COX-2/5-hLOX inhibitors, a family of organometallic chalcones (**2a-c**) and their respective organic analogs (**1a-c**) were evaluated as potential dual inhibitors. The docking study between the ferrocenyl chalcones (**2a-c**), their organic analogs (**1a-c**), and the 5-hLOX and COX-2 proteins showed an attractive affinity for both inflammatory enzymes, with binding energy values between -4.0 and -5.2 kcal/mol for the organic chalcones **1a-c**, and between -5.8 and -6.8 kcal/mol for the ferrocenyl chalcones **2a-c**. In addition, the inhibitory activity of **1a** and **2a** against 5-hLOX was determined. The results showed a potent inhibition for **2a** with an IC_{50} value of 0.4 ± 0.08 mM, while its organic analog **1a** exhibited a 100-fold higher IC_{50} value. Furthermore, **2a** showed a binding energy of -6.07 kcal/mol at the catalytic site of 5-hLOX, where the ferrocenyl fragment was oriented towards the catalytic iron of the enzyme, suggesting a possible redox mechanism.

On the other hand, chalcones **1a-c** and **2a-c** showed interesting percentages of inhibition against COX-2, between 20 and 92%. These attractive results motivate us to continue evaluating the *in vitro* activity of these derivatives and thus correlate the theoretical and experimental data obtained.

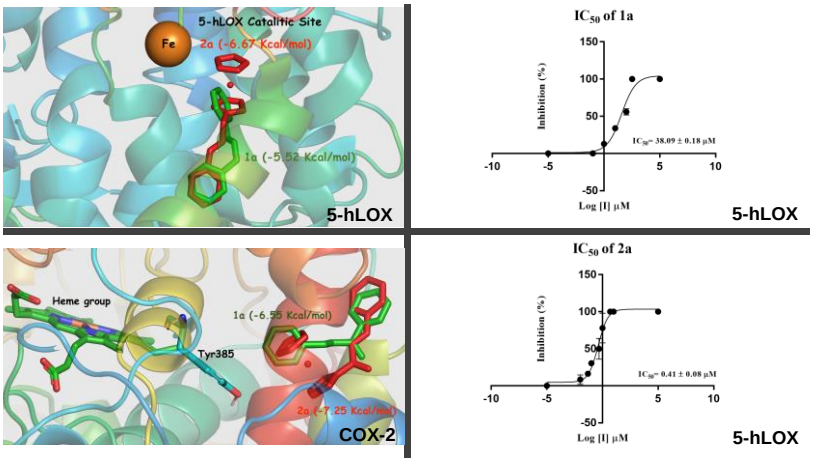

Figure 1. Docking studies between **1a**, **2a**, 5-hLOX and COX-2 respectively, and IC_{50} (mM) values of **1a** and **2a** against 5-hLOX.

Acknowledgments: M.M-O and C.M acknowledge to Fondecyt Iniciación Project No. 11230581 and Fondecyt Regular Project No.1200378.

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An unexpected encounter with cytotoxic cationic palladacycles.

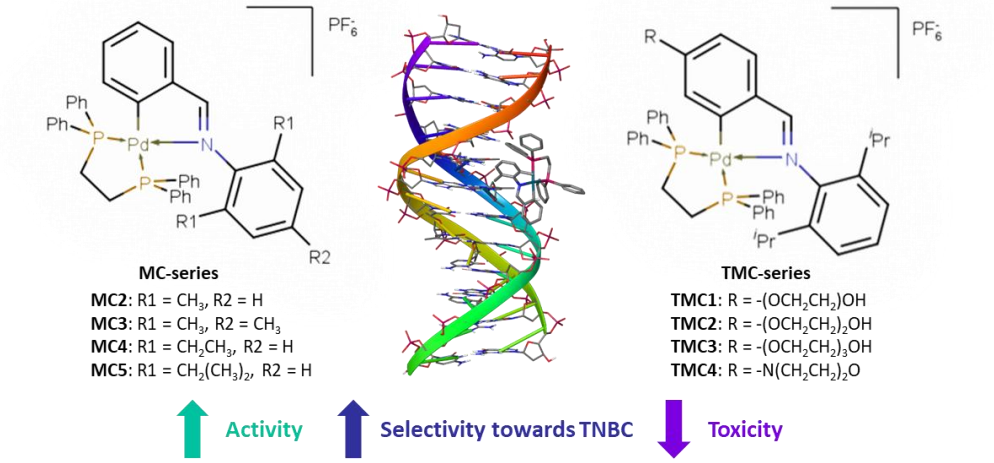
Annick van Niekerk,[a] Prinessa Chellan,[a] Selwyn F. Mapolie,[a]

a) Department of Chemistry and Polymer Science, Stellenbosch University, Stellenbosch, South Africa

16011988@sun.ac.za

In 2020 breast cancer surpassed lung cancer as the most diagnosed cancer worldwide, and accounts for 6.9% of cancer related deaths in developing countries.[1] For triple-negative breast carcinoma (TNBC), the widely used treatments are often not effective and patients typically receive a poor prognosis.[2] However, palladium-based complexes have shown excellent potential against TNBCs and has been a longstanding topic of interest in our research group.[3]

While our group has a rich history with neutral binuclear palladacycles.[4,5], an unexpected detour led us to investigate a number of cationic mononuclear palladacycles. We found that not only were these compounds more active than cisplatin against the same cell lines, they were also less toxic and a few of them were specifically selective towards the TNBC cell line, MDA-MB-231. The DNA-binding properties of the complexes were also investigated with various spectroscopic and computational methods and revealed a group of complexes with high potential for further development.



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Applications of Au^{III} cyclometalated derivatives as biologically active agents in bacteria and human cancer cells.

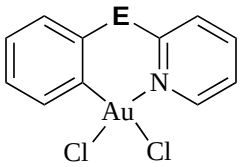
Claudia Schmidt,[a] Lukas Skos,[b] Mihyun Park,[a] Samuel Meier-Menches,[b] Angela Casini[a]

a) Department of Chemistry, Technical University of Munich, Lichtenbergstr. 4, 85748 Garching, Germany; b) Institute of Analytical Chemistry, University of Vienna, Währinger Str. 38, 1090 Vienna, Austria.

cla.schmidt@tum.de

In recent decades, organometallic transition metal compounds have emerged as efficient homogenous catalysts for in vitro and in vivo applications.[1] In chemical biology, metal-templated reactions can be exploited for bio-orthogonal transformations, including bond-forming processes (e.g., cross-coupling reactions), enabling site-selective protein modification at specific positions. In particular, Au^{III} C^N complexes emerged as an attractive catalyst for bioconjugation reactions in native proteins since they are endowed with improved properties with respect to established palladium-based probes under physiological conditions.[1] Derivatives of cyclometalated Au^{III} complexes with either antibacterial or anticancer properties can template the formation of covalent C^N-peptide adducts with model peptides and proteins via C–S cross-coupling at cysteine residues.[2]

Cysteines/selenocysteines are likely part of the active binding sides of several enzymes. Therefore, their ability to induce covalent modifications can lead to irreversible protein inhibition.[1-3] Several $[Au^{III}(C^EN)Cl_2]$ (C^EN = 2-benzoylpyridine) derivatives (see figure) have been investigated to showcase their potential for expanding the spectra of ligandable cysteines/selenocysteines in the bacterial[2,4] and human proteasome, and causing significant modulations in the protein expression of human cancer cells.



E = carboxy, carboxymethyl hydroxylamine

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Overcoming multidrug resistance in cancer by organometallic and antimitotic agents hybrids

Damian Plażuk,[a] Karolina Rózga,[a] Andrzej Błauż,[b] Błażej Rychlik[b]

a) University of Lodz, Faculty of Chemistry, Department of Organic Chemistry, ul. Tamka 12, 91-403 Lodz, Poland

b) b) University of Lodz, Faculty of Biology and Environmental Protection, Department of Oncobiology and Epigenetics, Cytometry Lab, ul. Pomorska 141/143, W24, 90-236 Lodz, Poland

damian.plazuk@chemia.uni.lodz.pl

Although chemotherapy is one of the oldest ways to combat neoplastic diseases, it still remains a widely used therapeutic approach for many types of malignancy, either alone or combined with other anticancer treatments. Antimitotic agents disturbing microtubule (MT) dynamics can be classified as MT stabilisers (e.g. taxanes) or destabilisers (e.g. Vinca alkaloids). However, using anticancer drugs can lead to tumour cell resistance to structurally different cytotoxic drugs (multidrug resistance - MDR), which may ultimately lead to treatment failure. Decreased tumour sensitivity to anticancer drugs may be correlated with overexpression of certain ATP-binding cassette superfamily (ABC) proteins, which play a crucial role in transporting xenobiotics and secondary metabolites out of the cells, protecting them from toxins. In tumours exhibiting multidrug resistance, three major ABC transporters, namely P-glycoprotein (ABCB1), breast cancer resistance protein (ABCG2), and multidrug resistance-associated protein (ABCC1), are overexpressed. These proteins actively excrete many anticancer drugs from the cell. It is believed that blocking or inhibiting activities of these proteins by small-molecule inhibitors can be used to sensitise MDR tumours toward commonly used anticancer drugs with no activity against MDR tumours. Therefore, it is crucial to search for novel compounds active toward MDR tumours or sensitise them to commonly used anticancer agents.[1]

We will present the synthesis and evaluation of the biological activity of new organometallic compounds able to overcome MDR in cancer cells.

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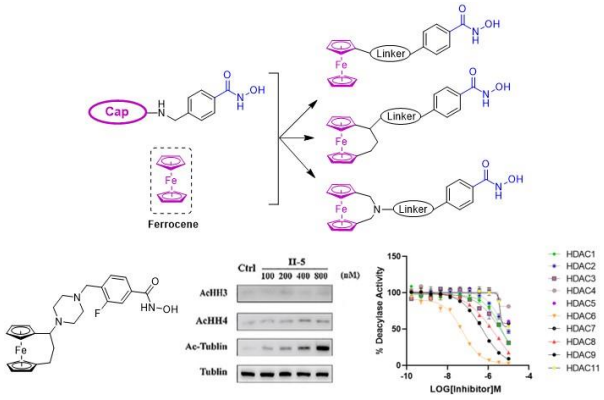
Versatility of Ferrocene Motif as Selective Histone Deacetylase 6 Inhibitors

Jiangkun Yan,[a] Kairui Yue,[a] Xuejing Fan,[a] Ximing Xu,[a] Jing Wang,[a] Xiaoyang Li,[a] and Yong Wang *[a]

a) Key Laboratory of Marine Drugs, Chinese Ministry of Education; School of Medicine and Pharmacy, Ocean University of China, Qingdao 26003, Shandong, P. R. China; Laboratory for Marine Drugs and Bioproducts, Pilot National Laboratory for Marine Science and Technology, Qingdao 266200, P. R. China

wangyong8866@ouc.edu.cn

Medicinal organometallic chemistry is one of the major areas that has garnered most interest, thanks to its potential to provide approaches in oncology to complement those of platinum drugs. In this context, our long term project aims to study the versatility of ferrocene for their innovative behavior against intractable cancers.[1,2] By employing a wide variety of rational designed linker groups, ferrocenes, [3]-ferrocenophanes and 2-aza-[3]-ferrocenophanes have been connected with benzohydroxamic acid, which led to a series of novel ferrocenyl hydroxamic acids. [3] Particularly, two of the ansa- series of ferrocene complexes display remarkable inhibition toward HDAC6. Further biological evaluation of **II-5** on cancer cells corroborates a moderate antiproliferative effect, which appears predominantly undergoing apoptosis verified by flow cytometry and western blot data. These results strengthen the unique role of ferrocene to develop selective protein inhibitors, and indicate that compound **II-5** may be a suitable lead for further evaluation and development for the treatment of HDAC6 relevant diseases



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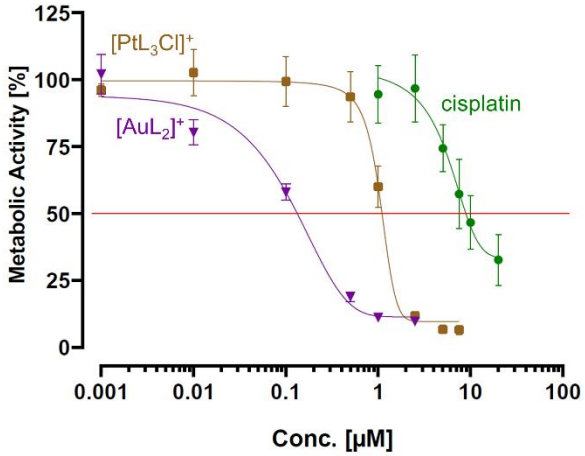
NHC metal complexes as anticancer drug candidates: Gold(I) vs. platinum(II)

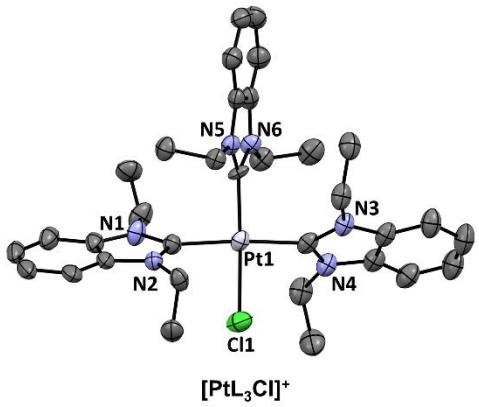
Hristo P. Varbanov,[a] Paul Kapitza,[a] Amelie Scherfler,[a] Klaus Wurst,[b] Ronald Gust[a]

a) Pharmazeutische Chemie, Universität Innsbruck, Innrain 80/82, A-6020 Innsbruck
b) Anorganische Chemie, Universität Innsbruck, Innrain 80/82, A-6020 Innsbruck
hristo.varbanov@uibk.ac.at

Organometallic compounds with *N*-heterocyclic carbene (NHC) ligands represent intriguing candidates as new chemotherapeutics to overcome some of the limitations of current clinically used platinum drugs. In particular, gold and platinum NHC complexes have demonstrated considerable activity against various chemo-resistant bacteria and cancer cells.

Herein, we present a comprehensive comparative study on (NHC)Pt(II)/Au(I) compounds of the *cis/trans*-$[PtL_2X_2]$, [AuLX], $[PtL_3X]^+$, and $[AuL_2]^+$ type, where L is a benzimidazolydene-derived NHC ligand and X = Cl or I. Their physicochemical and biological properties were investigated in detail. Cationic $[AuL_2]^+$ and $[PtL_3X]^+$ species displayed cytotoxicity in the nanomolar range against several cancer cell lines and overcame cisplatin resistance. To obtain further mechanistic insights into the antiproliferative activity of the complexes, their potential interactions with representative biomolecules were evaluated by RP-HPLC and ESI-MS. Notably, (NHC)Pt(II) compounds form 5'-GMP adducts under physiologically relevant conditions and interact with plasmid DNA, in contrast to their Au(I) analogs.





Finally, several strategies to enhance the water solubility and to modulate physicochemical properties of (NHC)Pt(II) complexes were exploited.

Synthesis, Mechanistic and Toxicity Studies on Alkynyl-Gold(I) Complexes for Anticancer Drug Discovery

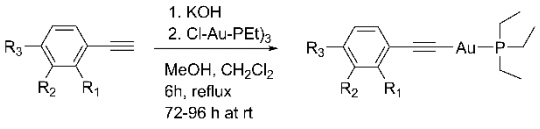
Uttara Basu,[a,b] Andre Prause,[b] Ingo Ott,[b]

a) BITS Pilani K K Birla Goa Campus, Goa 403726, India b) Technische Universität Braunschweig, 38106 Braunschweig, Germany

uttarab@goa.bits-pilani.ac.in

The search for metal-based anticancer compounds remains as we are yet to discover a "magic bullet" against cancers which continue to cause significant morbidity and mortality worldwide. Gold compounds have been used historically by mankind to treat bacterial infections, relieve joint pains, as antiviral agent etc. [1] Auranofin is recognized by the WHO for treatment of rheumatoid arthritis and is under several clinical trials for its anticancer efficacy with multiple mechanisms of action and alternate intracellular targets especially the thiol-containing enzyme thioredoxin reductase. [2]

We wanted to explore the antiproliferative properties of some alkynyl-Au(I) complexes having the triethyl phosphine-Au(I) backbone. We synthesized the 9 complexes in high yields using a one-pot method (unpublished results). Our studies have indicated that the complexes are cytotoxic in a panel of cancer cell lines with IC_{50} values in the low micromolar range. We also envisaged that thioredoxin reductase (TrxR), with its selenocysteine core is a potential target for our complexes. We selected complex **5** to study mechanistic aspects and toxicity in mice models. The TrxR inhibition activity was checked in isolated enzyme obtained from rat liver and in A549 cells which showed comparable activity as auranofin. Wound healing assay showed doubling of the time taken for the closure of half the wound compared to untreated MDA-MB-231 cells and disrupted the mitochondrial respiration in HT-29 and MDA-MB-231 cells. A toxicity study in a lung carcinoma mice model showed no signs of untoward toxicity in comparison to the vehicle treated cohorts with notable reduction in the tumour volume.



1 R_1=-H, R_2=-H, R_3=-H
2 R_1=-H, R_2=-H, R_3=-CH_3
3 R_1=-OCH_3, R_2=-H, R_3=-H
4 R_1=-H, R_2=-OCH_3, R_3=-H
5 R_1=-H, R_2=-H, R_3=-OCH_3
6 R_1=-H, R_2=-H, R_3=-Cl
7 R_1=-F, R_2=-H, R_3=-H
8 R_1=-H, R_2=-F, R_3=-H
9 R_1=-H, R_2=-H, R_3=-F

Figure 1. Structures of the Alkynyl-Au(I) complexes studied

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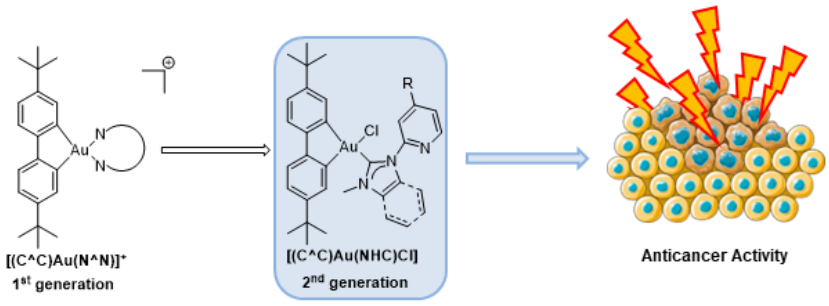
[(C^C)Au(NHC-R)X] complexes: Syntheses and biological studies

Edwyn Remadna,[a,b] Nicolas Stadler,[b] Jérémy Forté,[a] Serge Thorimbert,[a] Patricia Forgez,[b] Benoît Bertrand[a]

a) Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire (IPCM UMR 8232), 75005 Paris, France b) University Paris Cité , INSERM UMR-S 1124 T3S, Eq 5 Cellular Homeostasis, Cancer and Therapy, Campus Saint Germain, 75270 Paris, France

Benoit.bertrand@sorbonne-universite.fr

Although Au(III) complexes are easily reduced by biological reductants, Au(III) complexes with (C^N^C) ligands appeared highly stable even in the presence of glutathione.[1] However, out of the four available coordination sites, three are blocked with these ligands, leaving little possibilities of functionalization for optimization purposes. The objective here is to synthesize a new family of gold(III) complexes, replacing the ligand (C^N^C). After a first study of compounds with a biphenyl ligand (C^C) and a dinitrogen ligand (N^N) which appeared too labile for further drug development,[2] we focused on the synthesis of a new family of complexes composed of a biphenyl ligand (C^C), a chlorido ligands and pyridinyl-NHC based on imidazole and benzimidazole scaffolds. The antiproliferative activity, uptake, excretion reactivity with biomolecules *in vitro* has been investigated enabling the determination of a structure-activity relationship. The *in vivo* antitumoral efficacy has been studied on nude mice with triple-negative breast cancer.



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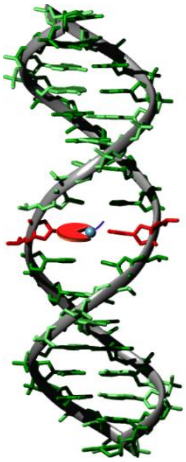
Site-specific metalation of DNA oligonucleotides with phosphorescent platinum(II) complexes

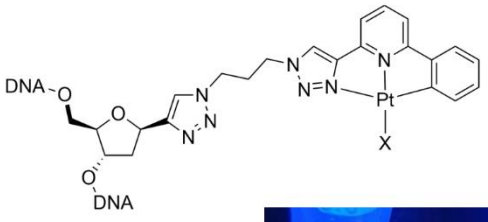
Felix Boisten,[a] Ivan Maisuls,[a,b] Tim Schäfer,[a] Cristian A. Strassert,[a,b,c] Jens Müller [a,c]

a) Westfälische Wilhelms-Universität (WWU) Münster, Institut für Anorganische und Analytische Chemie, Corrensstr. 28/30, 48149 Münster, Germany, b) WWU Münster, Center for Nanotechnology, c) WWU Münster, Center for Soft Nanoscience and Cells in Motion Interfaculty Centre

mueller@muellerlab.org

The ability to decorate nucleic acids site-specifically with transition metal ions allows interesting applications in nucleic acid nanotechnology, in sensors, and in responsive nucleic acid systems.[1] In this respect, many examples of metal-mediated base pairs have been published over the last decades.[2] We report here the first example of a site-specific incorporation of phosphorescent platinum complexes into DNA oligonucleotides.[3] By modifying the identity of the complex and the mode of attachment, a variety of duplexes was obtained with different photophysical properties. Fascinatingly, an oligonucleotide with two adjacent platinum complexes may serve as a sensor for molecular dioxygen, as its photoluminescence spectra change dramatically upon deoxygenation.





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Immunogenic Cell Death Inducing Platinum Complexes

Dengshuai Wei,[a] Nicolás Montesdeoca,[b] Yun Huang,[a] Bin Wang,[a] Lili Ma,[a] Haihua Xiao,[a] and Johannes Karges,[b*]

[a] Institute of Chemistry, Chinese Academy of Science, Beijing 100190, China.

[b] Faculty of Chemistry and Biochemistry, Ruhr-University Bochum, Universitätsstrasse 150, 44780 Bochum, Germany.

*Email: Johannes.Karges@ruhr-uni-bochum.de

The Pt(II) complexes cisplatin and its derivatives dominate the field of anticancer chemotherapeutic agents. Despite their clinical success, these compounds are associated with severe side effects (i.e., nerve and kidney damage, nausea, vomiting, bone marrow suppression) and tumor drug resistances. To overcome these drawbacks, increasing research efforts are devoted towards Pt(IV) complexes as prodrugs. These compounds are ideally inactive under physiological conditions but are reduced into their analogous Pt(II) therapeutically active compounds within the cancerous cells. In general, the reduction of the Pt(IV) center to Pt(II) is caused by electrochemical or photophysical triggers. To improve the therapeutic outcome, research efforts have been devoted to the synergistic combination of chemotherapy and immunotherapy. Clinical studies have shown an improved clinical long-time response upon co-administration of the chemotherapeutic agent carboplatin with the immune checkpoint inhibitors pembrolizumab or co-administration of the chemotherapeutic agent cisplatin with the immune checkpoint inhibitors nivolumab. Despite the enhanced therapeutic outcome, the application of drug mixtures may be limited as each component would reach the target after different circulation times, resulting in non-ideal drug doses. To circumvent this limitation, cytotoxic chemotherapeutic agents which are able to induce immunogenic cell death are sought. During immunogenic cell death, damage-associated molecular patterns are released that are able to generate a (long-term) immune response. Studies have shown that immunogenic cell death triggering agents could suppress tumor metastases and prevent tumor reoccurrence, the leading cause for cancer associated deaths. Herein, recent advances towards the development of immunogenic cell death inducing platinum complexes as novel therapeutic compounds against cancer are discussed.

Bioorthogonal complex functionalization with luminophores and carrier groups: A new application for the iClick reaction

Dominik Moreth,[a] Ulrich Schatzschneider [a]

a) Institut für Anorganische Chemie, Julius-Maximilians-Universität Würzburg, Am Hubland, 97074 Würzburg, Germany

dominik.moreth@uni-wuerzburg.de

The development of "click" reactions, including copper-catalyzed azide-alkyne cycloaddition (CuAAC), has been crucial in enabling the synthesis of small molecules and bio(macro)molecule conjugates. In contrast, inorganic click reaction ("iClick) has evolved a catalyst-free cycloaddition reaction that takes place in the inner coordination sphere of a metal-azido complex with a dipolarophilic C≡X compound (where X = C, N), leading to the formation of metal triazolato complexes.[1,2]

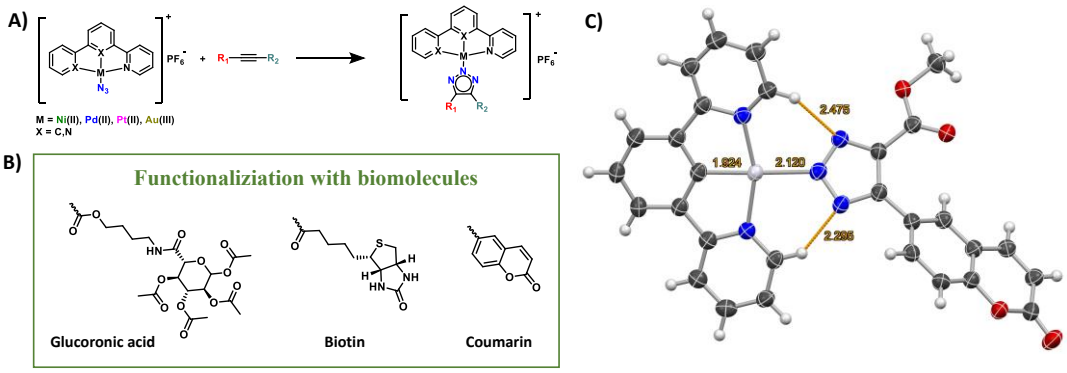

Figure 2: (A) iClick reaction monitored by ^{1}H NMR spectroscopy with different functionalized alkyne models (B) Biorelevant small molecules as carrier groups attached to metal complex via iClick reaction tuning their properties (C) Crystal structure of luminescent coumarin functionalized Pt(II) complex

The following contribution offers a comprehensive model study examining the reactivity of square planar metal azido complexes (M = Ni(II), Pd(II), Pt(II), Au(III)) with functionalized terminal and internal alkynes R-C≡C-R'. By analysing structural and electronic preferences of the reaction with kinetic data, we were able to highlight a general trend in reactivity. Additionally, we demonstrated the ability to modify these complexes through the attachment of alkynes to biorelevant small molecules such as coumarin, biotin, and sugars. Through this approach, we provide systematic insights into the behaviour of these metal complexes in the presence of modified alkynes and expand upon the potential for the functionalization of these complexes in Inorganic Chemical Biology.

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Multistage Antiplasmodial Activity and Mechanistic Insights of Ferrocenyl Aminoquinoline-Benzimidazole Molecular Hybrids

Taryn M. Golding[a], Larnelle F. Garnie[a], Kathryn J. Wicht[a], Janette Reader[b], Lyn-Marié Birkholtz[b], and Gregory S. Smith[a]

a) Department of Chemistry, University of Cape Town, Rondebosch, 7701, South Africa, b) Department of Biochemistry, Genetics and Microbiology, Institute for Sustainable Malaria Control, University of Pretoria, Hatfield, 0028, South Africa.

gldtar006@myuct.ac.za

Malaria, one of the most striking infectious diseases, is caused by several *Plasmodia* species. *Plasmodium falciparum* is the most virulent strain and responsible for the greatest number of malaria-related deaths globally. Despite the various treatment regimens available, the increasing threat of drug resistance has prompted investigations into alternative approaches toward antimalarial drug design.

To circumvent this rising resistance, the molecular hybridization of biologically important pharmacophores, such as the quinoline and benzimidazole scaffolds, has proven to be a fruitful avenue within antiplasmodial drug discovery.[1] Additionally, metal incorporation has been extensively explored, exemplified by the antimalarial drug candidate, Ferroquine (FQ).[2,3] FQ has demonstrated remarkable activity, notably against resistant forms of the *Plasmodium* parasite. Furthermore, there is an urgent need to develop antimalarials that can act across multiple stages of the parasites' life-cycle, such as the intraerythrocytic asexual and transmissible gametocyte stages. This will not only treat the infected patient but provide protection for the population by preventing further transmission.

This work will highlight the application of molecular hybridization and metal incorporation in the design of a series of bioorganometallic ferrocenyl aminoquinoline-benzimidazole molecular hybrids.[4] Therewith, their antiplasmodial activity against the *in vitro* asexual blood and sexual gametocyte stages, as well as putative mechanistic studies, such as β-haematin inhibition and cellular haem fractionation, will be discussed.

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In-cell catalysis: dose minimisation, cancer cell selectivity and overcoming drug resistance

J. P. C. Coverdale[a,b] Millie. E. Fry,[a] Chloe E. Pheasey,[a] P. J. Sadler,[b] and I. Romero-Canelon.[a,b]

a) School of Pharmacy, Institute of Clinical Sciences, University of Birmingham, Edgbaston, UK, b) Department of Chemistry, University of Warwick, Coventry, UK
j.p.coverdale@bham.ac.uk

Current estimates suggest that 1 in 2 people in the UK will be diagnosed with cancer in their lifetime.[1] While immunotherapies (e.g. CAR-T Therapy) have emerged as a promising treatment option for cancer, platinum agents (cisplatin, carboplatin, and oxaliplatin) continue to play a critical role and remain as essential drugs in the fight against cancer. Nonetheless, the emergence of platinum-associated drug resistance is of clinical concern and is stimulating the search for next-generation metallodrugs. Complexes based on Ru(II), Os(II) and Ir(III) have potential for novel catalytic mechanisms of action, especially disruption of the redox balance in cells[2-3] This strategy has been shown to increase selectivity for cancer cells over normal cells *in vitro*, and offers a unique approach to minimize drug dosage, while simultaneously overcoming platinum-associated resistance *via* a redox-targeting mechanism.

In this work, we describe the chemistry and pharmaceutical biology of Ir(III) TsDPEN catalysts. Structure-activity relationships have identified important correlations between arene size, ligand functionalization and hydrophobicity, and importantly, many Ir(III) catalysts exhibit lower *in vivo* toxicity compared to cisplatin.

The Ir(III) catalyst [Ir(Cp*)(TsDPEN)] is predominantly albumin-bound in the extracellular medium but remains active for *in-cell* transfer hydrogenation (TH) catalysis, using sodium formate as a source of hydride. Excitingly, the Ir(III) catalyst can overcome cellular resistance to cisplatin (A2780CIS, ovarian) and tamoxifen (MCF7-TAMR, breast) drugs, by an apparent mechanism of cell death involving catalytic redox stress.

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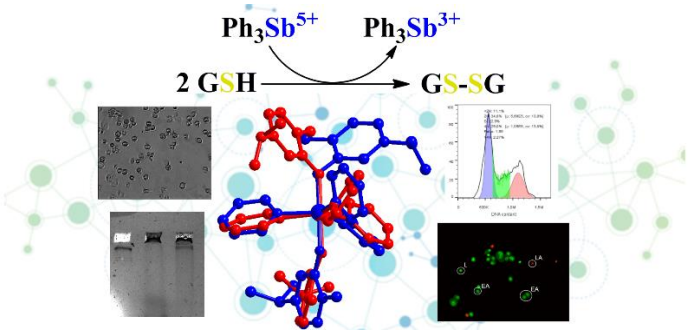
Natural products ingredients or Anti-metabolites conjugated with organometallic moieties; New efficient targeted chemotherapeutics

Christina N. Banti and Sotiris K. Hadjikakou.
University of Ioannina, Department of Chemistry, 45110, Ioannina Greece
shadjika@uoi.gr

The conjugation of organotin(IV) and organoantimony(III/V) moieties with natural products ingredients (NPI= carvacrol, acetic acid, salicylic acid, cholic acid) or anti-metabolites (AM= thio-barbituric acid, thio-pyrimidine) is reported. The new formulations (**orgMetNPI** and **orgMetAM**) were characterized in solid state by melting point, X-ray Fluorescence (XRF), Attenuated Total Reflection Furrier Transform Infra Red (ATR-FT-IR) spectroscopies, Thermogravimetric Differential Thermal Analysis (TG-DTA), Differential Scanning Calorimetry (DTG/DSC), while UV-Vis and NMR spectroscopies were used for the characterization in solution. The crystal structures of the **orgMetNPI** and **orgMetAM** have been refined by X-ray diffraction data crystallography.

The *in vitro* anti-proliferative activity of **orgMetNPI** and **orgMetAM** were evaluated against human breast adenocarcinoma cancer cell lines: MCF-7 (positive to hormones receptor (HR+)), MDA-MB-231 (negative to hormones receptor (HR-)). The *in vitro* toxicity was checked against normal human fetal lung fibroblast cells (MRC-5). The *in vitro* genotoxicity was tested with the micronucleus (MN) assay using fluorescence microscopy. Moreover, *Artemia salina* assay and *Allium cepa* assays were used for the *in vivo* toxicity. The MCF-7 cells morphology suggests apoptotic pathway, especially through the mitochondrion damage, which was confirmed by DNA fragmentation, Acridine Orange/Ethidium Bromide (AO/EB) Staining and permeabilization of the mitochondrial membrane tests. Their binding affinity toward the calf thymus CT-DNA was *ex vivo* investigated by Uv-Vis, Fluorescence spectroscopies and viscosity measurements.



Acknowledgments
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Piano-stool iron(II)/ruthenium(II) ionic complexes bearing pyridyl benzothiazole or α/β-naphthylamine ligands with anti-cancer and anti-oxidative properties

Sujoy Das,[1] Sławomir Wojtulewski[2], Krzysztof Krawczyk[3], Błażej Rychlik[3], Bogna Rudolf[1]

[1]Department of Organic Chemistry, Faculty of Chemistry, University of Lodz, 91-403 Lodz, Poland.
[2]Department of Structural Chemistry, Faculty of Chemistry, University of Bialystok, Ciołkowskiego 1K, 15-245 Bialystok, Poland
[3]Cytometry Lab, Department of Oncobiology and Epigenetics, Faculty of Biology and Environmental Protection, University of Lodz, Pomorska 141/143, 90-236 Lodz, Poland.
E-mail: sujoy.das@chemia.uni.lodz.pl.

Anti-cancer agents are drawing attention of the scientific community in recent time due to their wide range of biochemical applications in order to fight the disease at grassroot level.[1] Metal-organic complexes containing transition metals like Fe, Ru etc. are being massively investigated for their exquisite anti-mitotic properties.[2] The search for an appropriate ligand that effectively controls the stability and reactivity of metal complexes continues to play an essential role in organometallic chemistry.[3]

Herein, we reported three iron and three ruthenium cyclopentadienyl carbonyl ionic complexes bearing 2-(2′-pyridyl)benzothiazole, (2-pyridyl)methylene(α-naphthyl)amine and (2-pyridyl)methylene(β-naphthyl)amine ligands.[4] Diffraction of single crystals of these salts using XRD along with NMR, ESI-MS and FTIR analyses revealed their subsequent structures. The antiproliferative potential of the investigated complexes have been tested against three human cancer cell lines, i.e. A549 (pulmonary carcinoma), Hep G2 (hepatocellular carcinoma) and MCF7 (mammary adenocarcinoma) by neutral red uptake assay. Generally, the complexes were of at least an order of magnitude more active than corresponding ligands. Interestingly, as revealed by dihydrorhodamine 123 oxidation assay, the complexes tended to reduce reactive oxygen species production in exposed cells while pure ligands seemed to act as oxidation promoters.

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Synthesis of Metal Complexes Bearing Uracil Ligands

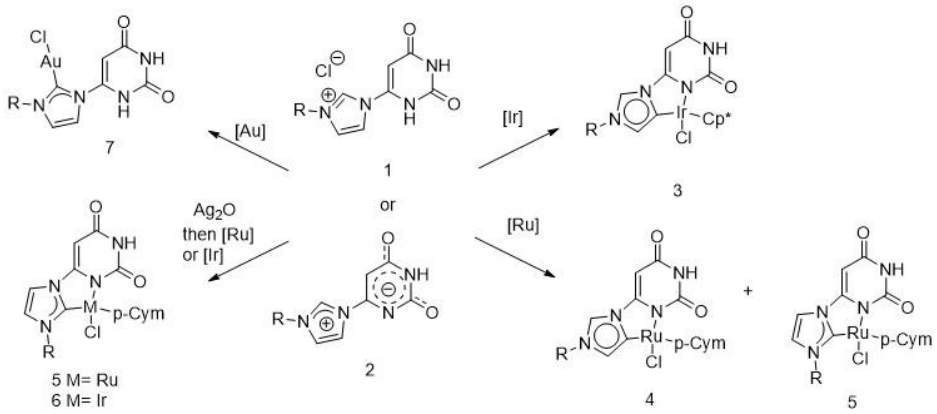
Giulia Francescato,[a] Ana Petronilho[a]

a) Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, 2780-157, Lisbon, Portugal

giulia@itqb.unl.pt

The development of ligands based on biologically-relevant compounds has raised interest over the last decade[1] . The main reason for this is the propensity of these ligands to provide access to more sustainable catalysts and/or more selective drugs, due either to a higher solubility in benign solvents (e.g. water) or a higher biocompatibility in physiological media and inside the cells.

Our group has been interested in the development of metal complexes bearing nucleobases as ligands and their application in medicinal chemistry and catalysis[2]. In this regard, we have examined the reactivity of uracil-based betaines. Schmidt et al. have shown that imidazolium salts functionalized with uracil can be converted into their corresponding betaines in the presence of a base [3]. Following on this, we synthesized uracil-imidazolium salts with different substituents at the imidazole ring. We thoroughly studied the reactivity of these ligand precursors toward metals with different geometries, both as imidazolium salts and as the corresponding betaines. The catalytic activity of these compounds towards the reduction of NAD+ to NADH was evaluated. These results will be discussed in this communication.



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Multi-modal antitumor activity of organometallic conjugates with paclitaxel

Anna Wieczorek-Błauż,[a,c] Andrzej Błauż,[b] Błażej Rychlik, [b] Christian Hartinger, [c] Damian Plażuk [a]

a) Department of Organic Chemistry, Faculty of Chemistry, University of Lodz, 12 Tamka St., 91-403 Lodz, Poland, b) Cytometry Lab, Faculty of Biology and Environmental Protection, University of Lodz, 141/143 Pomorska St., 90-236 Lodz, Poland, c) School of Chemical Sciences, University of Auckland, Auckland 1142, New Zealand

anna.wieczorek@chemia.uni.lodz.pl

Paclitaxel is one of the most important microtubule-poison, widely used in treating breast and ovarian carcinomas and Kaposi's sarcoma.[1] Nevertheless, paclitaxel application has been limited due to its biophysicochemical properties, enzymatic affinities, and ability to induce multidrug-resistance (MDR) phenotype.[2] The main MDR mechanisms associated with microtubule-targeting agents include abnormal expression of β-tubulin isotypes and the overexpression of ABC transporters where ABCB1 plays a key role in mediating the highest resistance paclitaxel.[3] Therefore, it is important to develop alternative strategies, to overcome paclitaxel limitations. The limitations of paclitaxel therapies can be overcome by attacking the disease system on multiple fronts. Multi-target therapeutics can be more efficacious and less vulnerable to adaptive resistance because the biological system is less able to compensate for the action of two or more drugs simultaneously.[4] Continuing our research on paclitaxel derivatives,[5] we will show metal – arene bioconjugates with paclitaxel as a multi-modal agent to overcome ABCB1 resistance in vincristine-resistant cancer cells.

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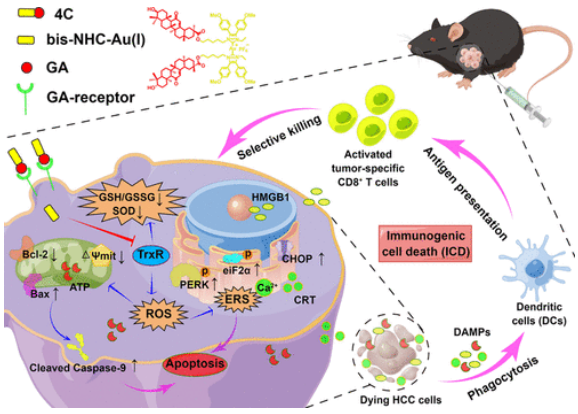
Metal *N*-Heterocyclic Carbene Complexes Derived from 4,5-Diarylimidazole as Potential Antitumor Agents

Wukun Liu

Nanjing University of Chinese Medicine, Nanjing, 210023, China.
liuwukun0000@njucm.edu.cn

Platinum complexes such as cisplatin and carboplatin are metal-based drugs, which are used in more than 50% of the treatment regimes for patients suffering from cancer. Despite their tremendous success, however, their use is extremely hampered by severe side effects such as nephrotoxicity and inefficient against platinum-resistant tumors during the therapy. In order to overcome these disadvantages, medicinal inorganic chemists have focused more and more on the use of transition metal complexes containing improved organic ligands.

Metal N-heterocyclic carbene (NHC) complexes have recently gained considerable attention because they perfectly fit prerequisites for efficient drug design and fast optimization. Promoted by the results of metal–NHC complexes with high antitumor activity, we started the examination of the antitumor activity of metal (e.g. Ag, Au, Pt and Rh)–NHC complexes with pharmacologically active 4,5-diarylimidazole ligands. In the presentation our contributions to metal NHC complexes derived from 4,5-diarylimidazole as potential antitumor agent will be summarized (see the figure for selected example). [1,2]



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Towards Deciphering the Cytotoxicity of Ferrocifens

Marie Gaschard-Stefanelli,[a,b] Michèle Salmain[a]

[a]IPCM, Sorbonne Université, 4 place Jussieu, 75005, Paris, France

[b]Start-up Feroscan, Paris, France

marie.gaschard_stefanelli@sorbonne-universite.fr

In 2020, 2.2 million new cases of breast cancers were estimated worldwide. The endocrine therapy consists in a dose of Tamoxifen (TAM), a selective estrogen receptor modulator. Even if it is widespread, TAM is inefficient on hormone-independent breast cancers.[1] To overcome this issue, Jaouen's group had the idea to include a ferrocenyl moiety to the TAM structure as it is considered to be a bioisotere of a phenyl group. This new family was named Ferrocifens and surprisingly showed a high cytotoxicity on both non-hormone and hormone-dependent breast cancer cell lines. Since then, efforts were carried out to find the mechanism of action (MoA) of this new family to offer new therapeutics to women suffering of breast cancer.[2-3] To decipher the MoA involved in the antiproliferative activity of ferrocifens, a chemical proteomic approach called Activity-Based Protein Profiling (or ABPP) can be employed to identify the protein targets (Figure 1). With this chemoproteomic strategy, two directions will be undertaken: protein targets fishing and identification and cellular imaging studies. For these purposes, an alkyne derivative of a highly toxic compound, patented by the start-up Feroscan, will be employed (Figure 1). With all the information collected, we hope to better understand the mechanism of action of these molecules, to select among the library of existing molecules those that are the most efficient and the most selective towards cancer cells. In conclusion, the results obtained can be the starting point of the adaptation of ferrocifens to offer more efficient and selective molecules targeting cancer cells.[4-5]

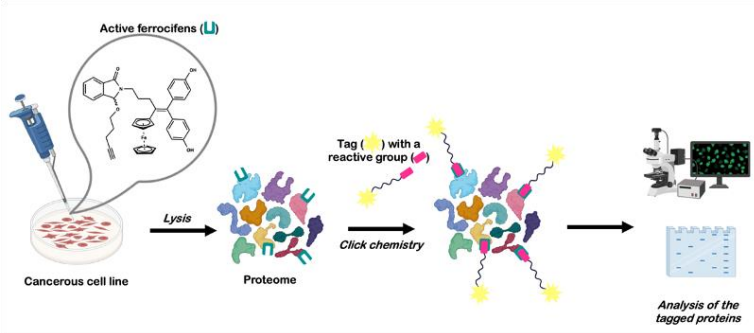

Figure 1. Workflow of the strategy to decipher the cytotoxicity of Ferrocifens

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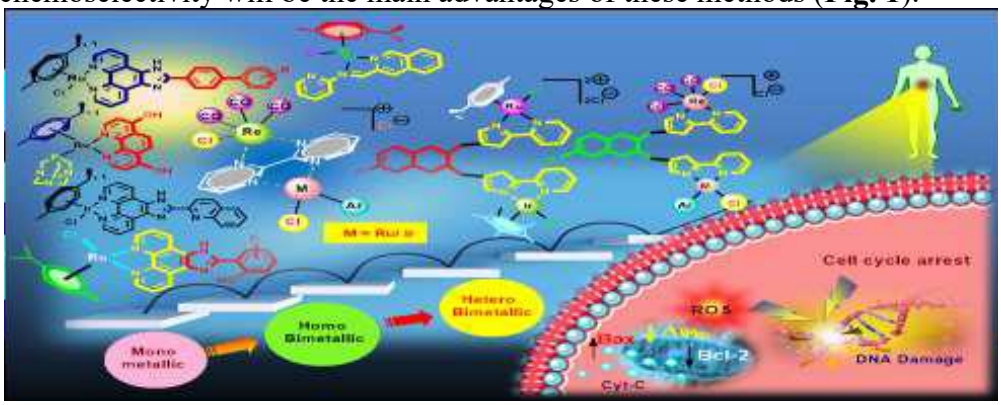
Organelle specific Ru(II)/Ir(III)/Re(I) based mono metallic and bimetallic complexes for cancer therapy

Priyankar Paira

Department of Chemistry, School of Advanced Sciences, VIT, Vellore-632014, Tamilnadu, India

priyankar.paira@vit.ac.in

Chemotherapy is the most prevalent traditional cancer therapy but it lacks tumor specificity and thus it renders normal cells at risk. Therefore, considerable attention should be given on the design and synthesis of new metal complexes by following approaches including (i) selectivity in cancer cell by non-covalent modes of DNA interaction (ii) mitochondria specificity (iii) development of various photo-toxic agents as these produce reactive oxygen species (ROS) at the photo-exposed cancer cells leaving the unexposed healthy cells minimally affected. (iv) "Theranostic", which includes simultaneous diagnostic and therapeutic functions in a single system improving the outcome of a disease state. With respect to therapeutic regimes, improved treatment effect is achieved by effective localization at the tumor specific sites of the therapeutic agents whereas from diagnostic aspect imaging agents along with therapeutic agents combined with biomarkers (tumor specific markers) are carried from one system to another enabling them to differentiate the tumor cells from normal cells. In continuation of our present work on anticancer organoruthenium, organoiridium and organorhenium complexes, we have introduced the convenient and effective synthetic approaches for designing the monometallic and bimetallic Ru(II)/Ir(III)/Re(I) complexes which can address all three approaches. The operational simplicity, good yield, ease of isolation of the products and high chemoselectivity will be the main advantages of these methods (**Fig. 1**).[1, 2]



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Poster Communication

Fluorescent recognition and visual detection of fructosyl-amino acids based on a Zn(II)-terpyridine complex with eosin-y in water

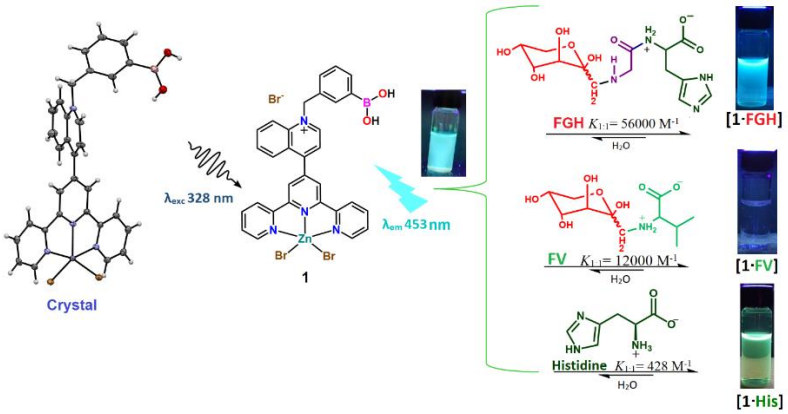
María K. Salomón-Flores [a], Iván J. Bazany-Rodríguez, [a] Alejandro Dorazco-González[a*]

a) Institute of Chemistry, National Autonomous University of Mexico (UNAM), Ciudad Universitaria, México, 04510, CDMX, México

karyq19@hotmail.com

Fructosyl L-valine (FV) and fructosyl L-glycil L-histidine (FGH) are chemical models of glycated hemoglobin (HbA_{1c}) because they correspond to the terminal sequence of the crystalline structure of this glycoprotein. HbA_{1c} is the main chemical indicator of diabetes mellitus.[1] Thus, selective sensing/recognition of FV/FGH is a central topic of modern supramolecular chemistry that impacts analytical and medicinal chemistry.

Herein, a new Zn(II)-terpyridine-boronic acid complex **1** was synthesized, structurally described by X-ray diffraction and studied in-depth as optical chemosensors for FV, FGH, L-histidine and D-fructose in water at physiological pH. Complex **1** has a tight affinity ($K_{1:1}$= 56000 M^{-1}), and selectivity towards FGH over FV, amino acids and monosaccharides at the micromolar level. Such FGH affinity by a metal-based receptor is still rare. On the basis of spectroscopic tools (^{1}H, ^{11}B NMR, UV-Vis and fluorescence titrations), MS-ESI experiments, and DFT calculations, the binding mode between complex **1** and FGH is via two-point recognition involving the simultaneous coordination of imidazole residue with the Zn(II) atom and reversible esterification of the boronic acid moiety with fructosyl fragment. Additionally, FGH can be visually detected in the micromolar concentration range using a supramolecular ensemble between **1** and the commercial dye eosin-Y.



Repurposing the Clinical Fe(III) Chelator Deferasirox as a Biocompatible Platform for the Development of new NIR-Probes and Photoacoustic Imaging Agents

Axel Steinbrueck, Nils Metzler-Nolte

Inorganic Chemistry I, Faculty of Chemistry and Biochemistry,
Ruhr University Bochum, Universitaetsstrasse 150, 44801 Bochum, Germany
axel.steinbrueck@rub.de

Cancer remains a leading cause of death in the developed world and the investigation into new and improved diagnostic options and treatment modalities is therefore urgently required. In fact, current clinical chemotherapy is plagued with frequent incidences of severe side effects as well as treatment resistance and future disease reoccurrence. Furthermore, newly developed chemotherapeutics frequently fail to produce satisfactory results in clinical trials. To address these challenges, we have recently focused our research efforts towards repurposing existing FDA-approved therapeutics, wherein we identified the clinical Fe(III) chelator deferasirox as a particularly promising scaffold that may serve as a versatile platform for the development of new theranostics, i.e., deferasirox derivatives have been shown to exhibit desirable therapeutic properties while remaining facile to monitor inside biological systems during treatment applications.[1] We have recently identified that Ru(III) complexes of deferasirox derivatives remain stable under physiological conditions and exhibit a strong absorption of near-infrared light inside the first optical window around 970 nm and thus serve as promising candidates in further explorations as potential probes in photoacoustic imaging and as photothermal therapy. Especially for theranostic development and due to the unique optical properties as an AIE fluorophore of this chelator, it is an appealing scaffold for further various strategical derivatizations with strong binding affinity to charge-dense metal cations, such as Ru(III). We will report structural and biological properties of the new generation of deferasirox derivatives in comparison to already existing detailed reports on the pharmacokinetic and pharmacodynamic properties of the clinically used parent chelator.[2]

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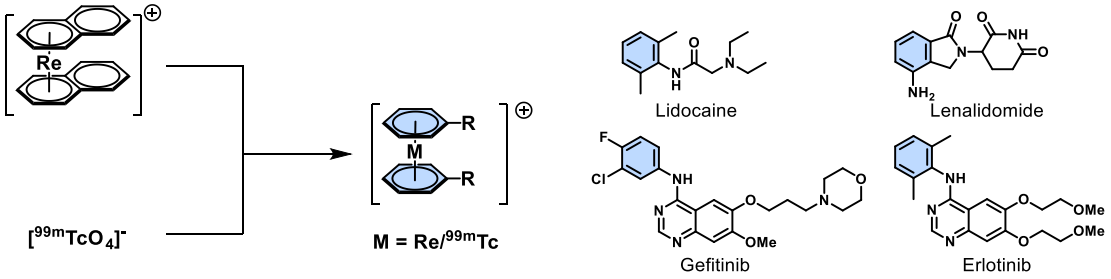
$[M(\eta^6\text{-arene})_2]^+$ (M=Re, ^{99m}Tc) Complexes of Pharmaceuticals

Joshua Csucker,[a] Federica Battistin,[a] Henrik Braband,[a] António Paulo,[b] Roger Alberto[a]

a) University of Zurich, Department of Chemistry, Winterthurerstrasse 190, 8057 Zürich, Switzerland

b) Departamento de Engenharia e Ciências Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Portugal

joshua.csucker@chem.uzh.ch



The strategy of conjugating pharmaceuticals with (radio)metals relies widely on strong chelators which are linked to pharmaceutical structures. The (radio)metal is coordinated in a last step to the chelator. We hypothesized that direct incorporation of the (radio)metal into pharmaceutical lead structures could be an equally attractive strategy.

We have developed the intricate chemistry of $[M(\eta^6\text{-arene})_2]^+$ (M = Re, ^{99m}Tc).[1] These are sandwich complexes featuring biological and chemical stabilities. Using this metal bis-arene chemistry, we aimed to directly coordinate arene motifs in commercial drugs to Re and ^{99m}Tc to investigate the effect of the metal-drug conjugates on the corresponding biological activities. Since ^{99m}Tc forms the backbone of single photon emission (SPECT) tomography, we were eager to probe the ^{99m}Tc as new SPECT tracers in this respect.

Our group has developed a library of $[M(\eta^6\text{-drug})_2]^+$ complexes with drugs like Lenalidomide, Benzocaine, Lidocaine, Gefitinib or Erlotinib a.o.[2-3] Biological evaluation of $[Re(\eta^6\text{-Erlotinib})_2]^+$ showed low micromolar LD_{50} values against epidermoid cancer line A431 *in vitro*. Biodistribution data of $[^{99m}Tc(\eta^6\text{-Erlotinib})_2]^+$ in mice showed rapid uptake and bio-circulation followed by renal excretion.

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The concept of PEGylation to enhance bioavailability of novel Rhenium(I) N-heterocyclic carbene complexes with promising antibacterial activity.

Janzen, Liudmila,[a] Schultz André [b], Bandow Julia [b], Metzler-Nolte, Nils [a]

a) Inorganic Chemistry I, Bioinorganic Chemistry, Faculty of Chemistry and Biochemistry, Ruhr University Bochum, Universitätsstr. 150, 44801 Bochum, Germany

b) Applied Microbiology, Fuculty of Biology and Microbiology, Ruhr University Bochum, Universitätsstr. 150, 44801 Bochum, Germany

Liudmila.Janzen@rub.de

A new class of organometallic antibiotics are rhenium(I) N-heterocyclic carbene (NHC) complexes with promising activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). To unravel the mode of action, one of the representatives of this class with the lead structure $Re^{I}(CO)_3$-NHC was investigated. After a series of biological experiments, a specific enzyme involved in translation processes was indicated as probable target in *Bacillus subtilis*. Furthermore, comparative proteomic profiling of already well characterized antibiotics with the same target supported the novelty of the mechanism of action of the complex.[1] However, the further development of the $Re^{I}(CO)_3$-NHC complexes as a novel antibiotic class is restricted by their relatively poor selectivity towards bacterial cells with respect to human cells. Subsequent studies have shown that the growing lipophilicity of different $Re^{I}(CO)_3$-NHC complexes is directly related to their increasing antibiotic and cytotoxic activity.[1] The growing lipophilic character also leads to diminished solubility in aqueous medium. Consequently, further biological tests are difficult to conduct. One of the approaches for improving water-solubility is the introduction of a polyethylene glycol (PEG) chain. Additionally, the synthetic linking of PEG chains (PEGylation) is already known to enhance the pharmacologic and pharmaceutical properties of several drugs.[2] The PEGylation of the rhenium complexes was facilitated via the well established alkyne-azide-click reaction.[3,4] The alkynyl was introduced on the benzimidazol-2-ylidene ligand of the $Re^{I}(CO)_3$-NHC complexes with different, equatorial bisimine ligands. After the “click” reaction, a series of PEGylated rhenium complexes were isolated and the antibacterial and cytotoxic activity of the complexes were determined using minimum inhibitory concentration value (MIC) and MTT assay, respectively.

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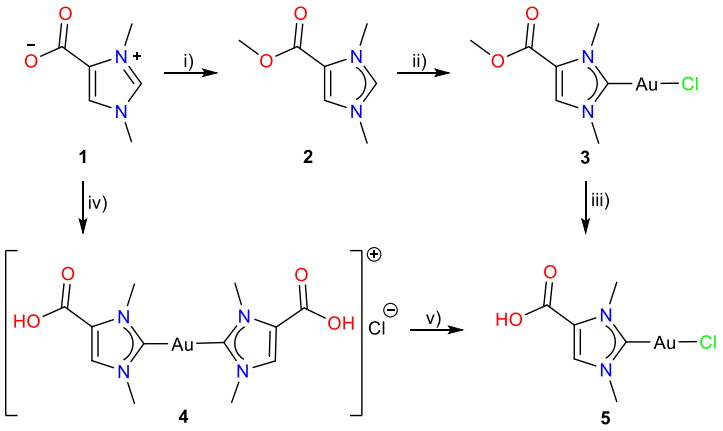
International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

N-Hetrocyclic Carbene–Gold(I) Complexes from the Marine Betaine as Anti-Infectives

S. Mahdavi[1], R. Büssing[2], B. Karge[3], M. Brönstrup[3], I. Ott[2], M. Tamm[1*]

[1] Institut für Anorganische und Analytische Chemie, TU-Braunschweig, Braunschweig (Germany)
[2] Institut für Medizinische und Pharmazeutische Chemie TU-Braunschweig, Braunschweig (Germany)
[3] Helmholtz-Zentrum für Infektionsforschung GmbH Abteilung Chemische Biologie, Inhoffenstraße 7, 38124 Braunschweig (Germany)
s.mahdavi@tu-bs.de

Gold has been used in medicine for thousands of years, along with extensive use in alchemy.[1] Recently, a special attention has been paid to the synthesise and characterization of gold(I)-N-heterocyclic carbene (NHC) complexes, primarily due to their potential applications in medicine, including antibacterial, anticancer, antiparasitic, and antimalarial properties.[2] Further, a carboxyl functionalized NHC, Norzooanemonin (**1**), has been isolated from the alcohol extract of Pseudopterogorgio Americana as betaine.[3] Gold complexes containing Norzooanemonin as a natural product may provide an innovative way into modern drug therapy. Herein, we introduce a novel strategy for preparing mono-NHC-Au(I) complex through the reaction of gold precursor and bis-NHC-Au(I) complex. In addition, a series of novel NHC-Au(I) complex is synthesized. The compound (**3**) inhibited Gram-positive bacteria such as MRSA and Enterococcus faecium more effectively than several Gram-negative bacteria but complexes (**4)** and (**5)** were almost inactive against both. In addition, complexes (**3)** and (**5)** were effective at inhibiting bacterial thioredoxin reductase activity with IC50 values of 0.293±0.163 and 0.786±0,118 [µM] respectively. The complexes were fully characterized by elemental analysis, ^{1}H and ^{13}C NMR, and X-ray diffraction.



Scheme 1. Key reagents and conditions. i) 1 equiv. MeOtf, DCM, 2 hours, rt. ii) 1 equiv. K_2CO_3, 0.5 equiv $(Me_2S)AuCl$, MeOH, 8 hours, rt iii) 1 equiv NaOH, HCl (2N), MeOH, rt. iv) a)1 equiv. K_2CO_3, 0.5 equiv $(Me_2S)AuCl$, MeOH, 8 hours, rt, b) HCl (2 N), pH=1-2, H_2O, rt. v) 1 equiv. $(Me_2S)AuCl$, MeOH, 8 hours, rt.

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International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

ARTIFICIAL RECEPTORS FOR THE FLUORESCENCE DETECTION OF NEUROTRANSMITTERS BASED ON AN ENSEMBLE OF CATIONIC Pd(II)-COMPLEXES WITH FLUORESCEIN

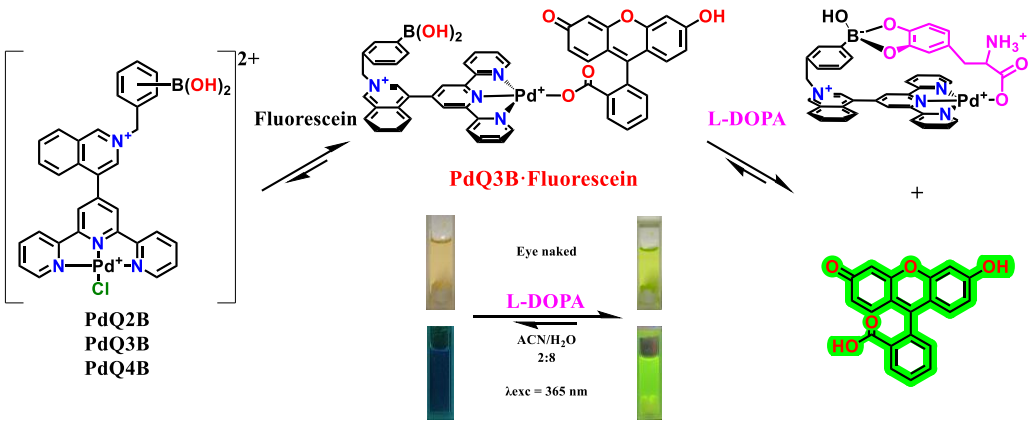
Alejandro O. Viviano-Posadas, Josue Valdes Garcia, Cristian Leonardo Pinzón Vanegas, Alejandro Dorazco González.

Inorganic Chemistry Department. Institute of Chemistry. UNAM.
osalvipo@me.com

Catecholamines-based neurotransmitters such as L-DOPA and dopamine play vital physiological roles in the brain and are chemical indicators of human diseases. Selective neurotransmitter sensing by fluorescent/chromogenic receptors is a central issue of modern supramolecular chemistry that impacts analytical and medicinal chemistry.

In this work, three novel isomers of cationic Pd(II)-terpyridine-boronic acid complexes were synthesized and studied in-depth as chemosensors for neurotransmitters in aqueous media. These Pd-based chemosensors contain a cationic *N*-isoquinolinium nucleus covalently linked to three different isomers of strongly acidified phenylboronic acids as catechol binding site (*ortho*, **PdQ2B**; *meta*, **PdQ3B** and *para*, **PdQ4B**). Additions at physiological pH of L-DOPA to Pd-chemosensors induce significant changes in the absorption spectrum with a peak of affinity towards L-DOPA (log K= 5.55) over dopamine, epinephrine, L-tyrosine and nucleosides in the micromolar concertation range. **PdQ3B** is two orders of magnitude more selective for L-DOPA than the other neurotransmitters. Such L-DOPA affinity for a metal-based chemosensor in aqueous media is still rare. This efficient response by L-DOPA was also observed in the presence of coexisting species in blood plasma and urine with a detection limit of 3.0 µM. On the basis of multiple spectroscopic tools (^{1}H, ^{11}B NMR, UV-Vis, and fluorescence), MS-ESI experiments and DFT calculations, the recognition molecular between **PdQ3B** and L-DOPA is driven by cooperative two-point binding involving reversible esterification of boronic acid moiety with the catechol fragment of L-DOPA together the coordination of carboxylate anion to Pd(II) atom with a strong electrostatic contribution.

L-DOPA can be selectively detected by an ensemble between **PdQ3B** and fluorescein with a visual change and turn-on response at the micromolar level.



International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

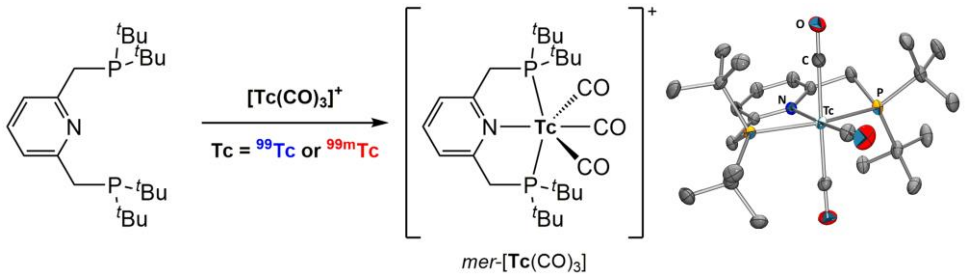
Changing the *fac* geometry of the $[^{99/99m}Tc(CO)_3]^+$-core to *mer* with a pincer-type ligand

Manuel Luca Besmer, Federica Battistin, Henrik Braband, and Roger Alberto

Department of Chemistry, University of Zurich, Winterthurerstrasse 190, 8057-Zürich, Switzerland

manuel.besmer@chem.uzh.ch

The synthesis of stable technetium and rhenium *fac*-tricarbonyl complexes retains continued interest in the development of radiopharmaceuticals for therapy (^{188}Re) and diagnostics (^{99m}Tc, γ decay).[1] The *fac*-$[^{99m}Tc(CO)_3(H_2O)_3]^+$-complex, readily produced from the commercially available kit, forms the basis for the radiolabeling of a plethora of (bioactive) molecules. Labeling strategies with the tricarbonyl core, involving mono-, bi- and tridentate ligands, have been assessed and studied due to the high stability of the *fac*-core. Only recently we started to investigate the ligand induced rearrangements of the *fac*-$[^{99}Tc(CO)_3]^+$ moiety to form *mer* tricarbonyl complexes of ^{99}Tc (β^- decay).



The reaction of *fac*-$[^{99}Tc(CO)_3Cl_3]^{2-}$ with a tridentate PNP pincer-type ligand yields the *mer*-$[^{99}Tc(^{Pyr}PNP^{tBu})(CO)_3]^+$ in the presence of $TlPF_6$ (Scheme). The SCXRD analysis confirmed the identity of the complex. Furthermore, we were able to transfer the ^{99}Tc chemistry, performed in THF, to the aqueous ^{99m}Tc chemistry and radiolabel the air-sensitive PNP molecule starting from *fac*-$[^{99m}Tc(CO)_3(H_2O)_3]^+$. The reaction was carried out under oxygen-exclusion in H_2O/EtOH (1:1) delivering *mer*-$[^{99m}Tc(^{Pyr}PNP^{tBu})(CO)_3]^+$ as a single product. The observed reactivity allows for the investigation of the *fac-mer* rearrangement in aqueous media with ^{99m}Tc while potentially enlarging the scope of the technetium tricarbonyl core to label further target molecules.

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Peaks and valleys in search for a perfect silver antibiotic: a case of halide NHC complexes

Igor V. Esarev[a], Bianka Karge[b], Petra Lipmann[a], Mark Brönstrup[b], Ingo Ott[a]

a) Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, Beethovenstr. 55, 38106 Braunschweig; b) Department of Chemical Biology, Helmholtz Centre for Infection Research, Inhoffenstr. 7, 38124 Braunschweig, Germany

i.esarev@tu-bs.de

Silver and its compounds have a long and remarkable history. Currently, silver nitrate and silver sulphadiazine are widely used for burn wound desinfection. The mechanism of antibacterial activity of silver is strongly related to the inhibition of RNA, DNA, thioredoxin reductase (TrxR) and glutathione reductase (GR) [1]. However, in form of free ions, silver can be highly toxic to mammalian cells [2]. The proper balance between antimicrobial and toxic effects can be achieved via binding of the metal with N-heterocyclic carbenes (NHC). However, the influence of halide co-ligands and test conditions on the antibacterial effect of silver complexes is often not taken into account.

Herein, we present a thorough physicochemical and antibacterial study of 16 silver(I) halido-NHC complexes. We show that iodides have better antibacterial activity (MIC=4.1-21.2 µM) than chloride and bromide analogs (MIC = 13.5-116 µM). Iodide complexes showed no toxicity on mammalian cells (IC_{50}>100 µM) in comparison to other halide compounds (IC_{50}=24-67 µM). To demonstrate the strong influence of type of culture medium on the performance of silver containing compounds, we performed UV-Vis binding studies and further antibacterial tests in selected culture media.

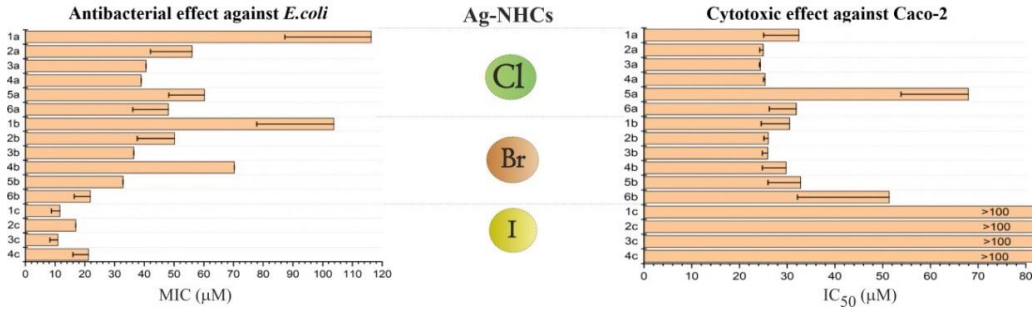

Figure 1. Schematic summary of in-vitro antibacterial and cytotoxicity studies

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Ruthenium-arene anticancer compounds – exploring pta alternatives

Jakob Kljun,[a] Mihaela Rebernik,[a] Lucía M. Balsa,[b] Jerneja Kladnik,[a] Uroš Rapuš,[a] Tomaž Trobec,[c] Kristina Sepčić,[d] Robert Frangež,[c] Ignacio E. León[b] and Iztok Turel[a]

a) Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia, b) CEQUINOR (UNLP, CCT-CONICET La Plata, Asociado a CIC), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Blvd. 120 N°1465, La Plata 1900, Argentina, c) Institute of Preclinical Sciences, Veterinary Faculty, University of Ljubljana, Gerbičeva 60, SI-1000 Ljubljana, Slovenia, d) Department of Biology, Biotechnical Faculty, University of Ljubljana, Jamnikarjeva 101, SI-1000 Ljubljana, Slovenia

uros.rapus@fkkt.uni-lj.si

Ruthenium based anticancer drugs have been studied for several decades. One of the well-known representatives is dichlororuthenium(II) (*p*-cymene) (1,3,5-triaza-7-phosphaadamantane) complex (RAPTA-C).[1] Various analogues have been prepared using different ligands with *O*,*O*-; *N*,*N*-; *N*,*O*- and *S*,*O*- donor atoms.[2] In prof. Turel's research group we have prepared various pyrithione analogues (*S*,*O*- type ligands) and their ruthenium complexes in both chlorido and pta variants. In addition, we evaluated the structure activity relationship of the prepared compounds.[3,4] To better understand the role of the monodentate ligand, complexes introducing some alternatives of pta ligand were synthesised to evaluate their biological activity and further explore the structure activity relationship. Thus, we synthesised ruthenium(II) (*p*-cymene) (pyrithione) complexes with hexafluorophosphate anion together with a neutral P or As donor ligand. All complexes were characterised by ^{1}H and ^{31}P NMR spectroscopy, mass spectrometry, IR spectroscopy and CHN elemental analysis. We were able to obtain single crystals of some compounds, and their structures were determined by X-ray diffraction. We have also used the prepared compounds for biological studies (enzyme inhibition; cytotoxicity).[5]

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Cyclometalated osmium(II) complexes with antiproliferative activity in cancer cells disrupt calcium homeostasis

Alba Hernández,[a] Lena Markova,[b] M. Dolores Santana,[a] Jitka Pracharova,[b] Hana Kostrhunova,[b] Vojtech Novohradský,[b] Viktor Brabec,[b] José Ruiz,[a] Jana Kasparkova[b]

a) Department of Inorganic Chemistry, University of Murcia, 30100, Murcia, Spain b) Czech Academy of Sciences, Institute of Biophysics, CZ-61200 Brno, Czech Republic.
alba.hernandezg@um.es

Osmium complexes have been less explored for cancer treatment than those based on platinum or ruthenium. Given the clinical success of the ruthenium complexes, research efforts have been directed towards investigating the therapeutic properties of osmium complexes.[1] Herein, we present new cyclometalated Os(II) complexes of the type $[Os(C^N)(N^N)_2]OTf$ where N^N is bipyridine or dipyrido[3,2-d:2,3'-f]quinoxaline and C^N is based on 2-arylbenzimidazole (Figure 1). The antiproliferative activity of the new osmium(II) compounds has been performed in cancer and noncancerous cell lines under dark conditions. The mode of action revealed that osmium complexes activate the endoplasmic reticulum stress pathway in cancer cells and disrupt calcium homeostasis.

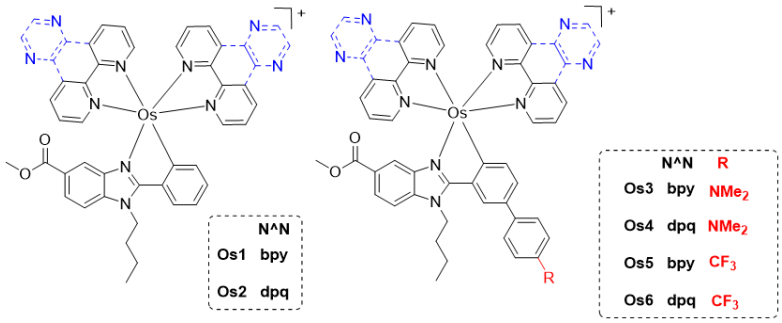

Figure 1.

Acknowledgements

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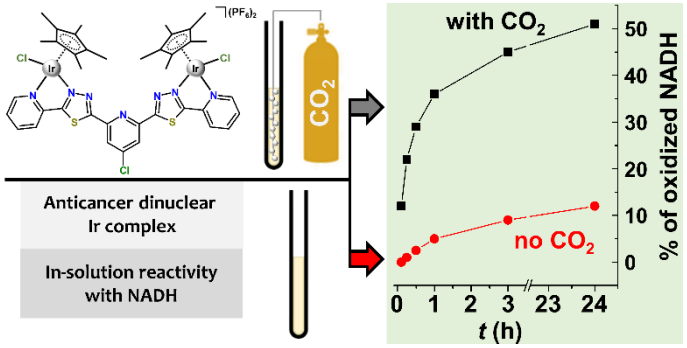
CO_2-responsive NADH oxidation by half-sandwich Ir(III) complexes - a curiosity or a problem for cancer cells?

Pavel Štarha

Department of Inorganic Chemistry, Faculty of Science, Palacký University Olomouc, 17. listopadu 12, 771 46 Olomouc, Czech Republic
pavel.starha@upol.cz

Half-sandwich complexes of Ru, Rh, Os and Ir have attracted the attention of medicinal chemists because they often exhibit high antiproliferative activity with a mechanism of action (MoA) different from Pt-based drugs.[1] One way to improve their activity and pharmacological prospects is to develop multinuclear compounds representing innovative chemotypes that again interfere differently with MoA-related processes.[2]

The dinuclear half-sandwich Ir(III) complex **1** (see figure) exhibited high antiproliferative activity *in vitro*, related to a different MoA than that of cisplatin. ROS-related processes were studied at both chemical and biological levels (e.g., in-cell ROS-dependent Nrf2 activation or cell-free NADH oxidation). We found for the first time that the extent of NADH-to-NAD^+ oxidation could be enhanced by CO_2 treatment. Since high intracellular CO_2 concentrations are characteristic of highly metabolic cells, such as cancer cells, this observation can be accepted as a pathway to a new class of anticancer metallodrugs, which effectively exploit the hypercapnic microenvironment (e.g. in cancer tissues).



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Click ferrocenyl-erlotinib conjugates active against erlotinib-resistant non-small cell lung cancer cells *in vitro*

Przemysław Biegański,[a] Joanna Kopecka,[b] Konrad Kowalski,[a]

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

b) Department of Oncology, University of Torino, via Santena 5/bis, 10126 Turin, Italy

e-mail: przemyslaw.bieganski@edu.uni.lodz.pl

Erlotinib (TarcevaTM) **(1)** (Fig.1) is an anticancer drug whose mechanism of action relates to the inhibition of epidermal growth factor receptor (EGFR).

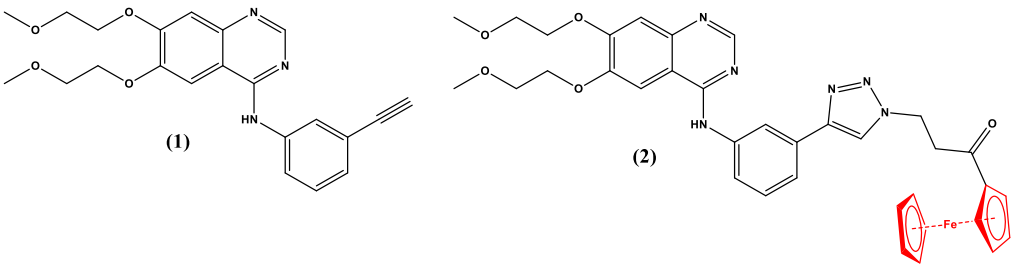

Fig 1. Structure of erlotinib (**1**) and most active ferrocenyl 1,2,3-triazolyl conjugate (**2**)

Specific mutations in EGFR cause lung cancer cells resistant to erlotinib **(1)**. Thus new drugs to overcome resistance are required.

The aim of my work was to obtain of ferrocenyl (Fc) derivatives of erlotinib and examine their anticancer activity against erlotinib-susceptible (A549 and H1395) and erlotinib-resistant (H1650 and H1975) lung cancer cells in vitro.[1] Five Fc-erlotinib conjugates were obtained with CuAAC and RuAAC reactions.

Anticancer activity assays showed that compounds with the $-C(O)CH_2CH_2-$ group are more active than erlotinib (1) against H1650 and H1975 cells. The most active was compound **(2)** (IC_{50} =12μM vs erlotinib IC_{50} = 40μM against H1650). It was also showed, that mechanism of action involve ROS generation, mitochondrial transmembrane potential imbalance and apoptosis.[1]

P.B. thanks the National Science Center in Cracow, Poland (grant PRELUDIUM 20 UMO-2021/41/N/ST4/00059) for financial support.

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Synthesis, anticancer activity and immunogenicity of gold complexes

Jana Seefeldt, Nils Metzler-Nolte [a]

a) Chair of Inorganic Chemistry I, Ruhr-University Bochum, Universitaetsstrasse 150, 44801 Bochum, Germany.

Jana.Seefeldt@ruhr-uni-bochum.de

Although there are different treatment strategies for cancer, the complexity and diversity of cancer is part of the reason why it is still one of the deadliest diseases in the world. Of particular concern remains the possibility of cancer recurrence, which can result from incomplete removal of the cancerous tissue. Resistances often emerge and the risk of developing metastases is also higher which in turn increases the mortality risk.[1] A relatively new approach is the use of metal complexes that, due to their specific interaction with cancer cells, can simultaneously activate the immune system and eliminate the cells. By involving the adaptive immune system a long-term effect against the specific cancer cells is achieved.[2] To date, a few anticancer complexes have shown that they are able to trigger the so-called immunological cell death (ICD), but all the mechanisms involved are not yet completely unraveled.[3] Within this project, several gold(I) and gold(III) complexes were synthesized, all bearing NHC ligands and showing structural similarities to known ICD inducers. The complexes were chemically characterized and studied with respect to their properties as anti-cancer drugs. IC_{50} values, the ability to cause reactive oxygen species in cells, and to elicit ICD characteristic damage-associated molecular patterns (DAMP) were investigated. In particular, the ability of the complexes to translocate Calreticulin to the cell membrane and to promote the release of ATP and HMGB-1 was studied. The results will be discussed in terms of their structural changes in comparison with the literature-known compounds.

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Thiourea and Thiazolidine–Thiourea Ligands for Metal Coordination (Au and Ag) and Preliminary Cytotoxic Studies

Guillermo Canudo-Barreras,[a] Daniel Salvador-Gil,[a] Eduardo Romanos,[a,b] Raquel P. Herrera,[a]* M. Concepción Gimeno[a]*

a) Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-UZ, C/Pedro Cerbuna 12, 50009 Zaragoza, Spain. b) Dpto. de Imagen y Fenotipado, Instituto Aragonés de Ciencias de la Salud, Centro de Investigación Biomédica de Aragón (CIBA), Avda. San Juan Bosco, 13, planta D, E-50009 Zaragoza, Spain

raquelph@unizar.es

Gold(I) and silver(I) complexes are known for their antitumor activities[1] and seem to avoid collateral effects in cancer treatment.[2] Although some thioureas may exhibit interesting biological properties, the ligands used in this research showed no significant cytotoxic activities. Interestingly, all metal complexes showed better anticancer activities for Jurkat, A549 and HeLa cell lines (leukemic T-cell lymphoblast, lung, and cervix cancer, respectively).[3]

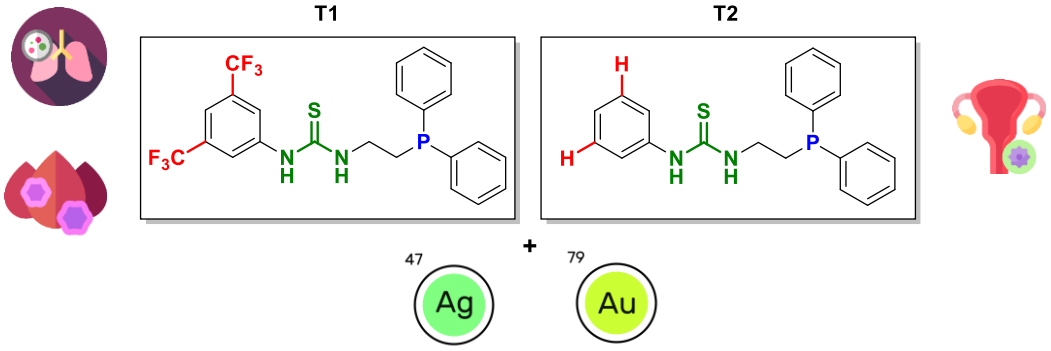

Figure 1. Synthesis of gold and silver-complexes with promising anticancer properties.

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Comparing the activities of silver(I) and gold(I) NHC complexes in cisplatin-resistant ovarian cancer cell lines

Julia H. Bormio Nunes,[a,b] Bernhard K. Keppler,[a] Petra Heffeter,[b] Christian R. Kowol[a]

a) Institute of Inorganic Chemistry, Faculty of Chemistry, University of Vienna, 1090, Vienna, Austria, b) Center for Cancer Research, Medical University of Vienna, 1090, Vienna, Austria.

e-mail: julia.helena.bormio.nunes@univie.ac.at

Ovarian cancer (OC) recurrence after platinum chemotherapy is very common due to resistance development, leading to a low survival rate of the patients [1,2]. Consequently, the search for new compounds for treating resistant OC is of high interest. While silver(I) compounds are usually employed as antibacterial drugs,[3] some publications have also shown anticancer potential.[4] Gold(I) compounds have been extensively evaluated for this purpose, with auranofin being the model complex and being tested in several clinical phase I and II trials.[5] N-heterocyclic carbenes (NHCs) are interesting ligands for comparing the activities of silver(I) and gold(I) compounds, since these complexes would present the same coordination mode and structure, and the ligands are also able to form strong bonds to these metal ions. In this work, two mono- and one bis- silver(I) complex with NHC ligands were synthesized. For each silver(I) compound also the respective gold(I) analog was prepared and fully characterized. For cytotoxicity determination all complexes were evaluated in A2780 and A2780/cis (cisplatin-resistant) ovarian cancer cells using the viability assay after 72 h of treatment. Interestingly, all silver(I) complexes were not affected by the drug-resistance of A2780/cis cells. Moreover, the mono-silver complexes were ~10-fold more active than the respective mono-gold analogs. However, the bis-gold complex revealed similar activity compared to the silver compounds for A2780 cells and A2780/cis displayed collateral sensitivity (higher activity in the resistant cells vs. the parental one). Further studies are envisaged to better understand the mechanism-of-action of these compounds, the role of the metal ion in the activity as well as the ability to overcome resistance.

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Chelate *N,O*- copper(II) complexes with Schiff base ligands: Synthesis, characterization and biological activity evaluation

María Esther Moreno Narváez,[1] David Morales Morales[1]

[1]Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior s/n, Ciudad Universitaria, C.P 04510, México, CDMX.

E-mail: memns@comunidad.unam.mx

The development of new metal complexes with different molecular architectures for the treatment of several diseases continues to be a growing research field worldwide. Proving that metals increase drug efficacy, however severe side effects associated to these metallodrugs and their lack of selectivity have limited their use. To overcome this, the choice of the ligand is crucial to regulate metal uptake and modify interactions in biological systems which can enhance their activity and simultaneously reduce side effects and drug resistance. In addition, fluorination of pharmaceutical agents, for instance, by the introduction of strong electron-withdrawing trifluoromethyl groups into organic molecules can significantly alter their properties, such as lipophilicity, metabolic stability, and bioavailability. On the other hand, Schiff bases are among the most studied ligands in coordination and organometallic chemistry due to their simple and facile synthesis, tunable framework, and commercial availability of a wide variety of potential starting materials. These species exhibit different pharmacological activities, including antibacterial, antifungal, antimalarial and anticancer. Besides, they form stable complexes with most transition metals making them of special interest in bioinorganic chemistry as biological active compounds and for the study on interactions with DNA. Furthermore, research on Schiff base copper(II) complexes has attracted a lot interest in recent years as an alternative to Pt(II) complexes for its biocompatibility and the many roles copper exhibits in biological systems. In fact, one of its main potentialities is that copper can behave as an antiproliferative agent generating reactive oxygen species (ROS) inside cells that are reported to damage DNA, offering discrimination between healthy and cancer cells. Yet, not many copper(II) complexes with *N,O*-Schiff based ligands have been evaluated for these purposes. Thus, in this work we synthetized a series of chelate *N,O*-copper(II) complexes for their biological evaluation in different human cancer cell lines.

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International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

Stability Experiments on Gold(I)(NHC) Complexes with Thiocarboxylate Ligands by HPLC-MS

Anna Wilsmann,[a] Ingo Ott [a]

Technische Universität Braunschweig | Institute of Medicinal and Pharmaceutical Chemistry | Beethovenstr. 55, 38106 Braunschweig

anna.wilsmann@tu-braunschweig.de

Within the last decade various types of organometallic compounds gained attention as promising anticancer drugs in medicinal chemistry. Among them are gold(I) *N*-heterocyclic carbene (NHC) complexes with a high potential concerning antiproliferative effects.[1]

Although enhanced stability is crucial regarding the design of metal-NHC based compounds, only a few analytical stability studies have been performed. However, these studies are of major importance not only to understand the behaviour in solution, but also to obtain new information on structure-activity-relationships and metabolic reactions.

Recent results indicated similar σ-donor abilities of thiocarboxylate ligands and NHC ligands, which had already shown high stability in form of gold(I) biscarbene complexes.[1,2] Thus, we synthesised gold(I)(NHC) complexes with thiocarboxylate ligands (NHC)Au(SCOR) to perform detailed analytical studies by HPLC-MS to investigate their chemical stability.

A RP-based chromatographic method was used to separate and examine possible degradation products of (NHC)Au(SCOR) complexes (Figure 1).[3] Each compound was incubated at 37°C in dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or aqueous solution.

The initial stability tests indicated variable stabilities based on the media used. The most recent results of this ongoing project will be presented on the poster.

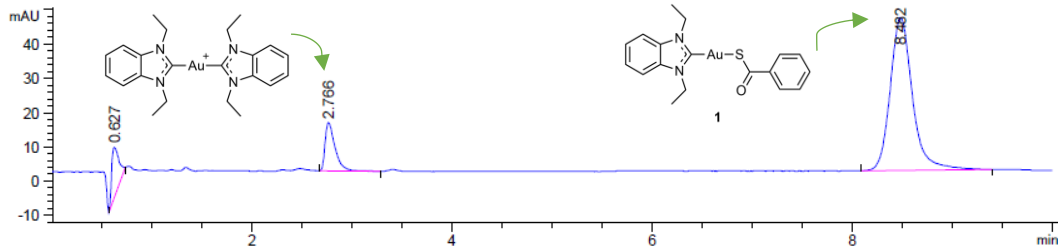

Figure 1. Chromatogram of a selected complex **1** in H_2O after 48h.

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Stability of [1,3-diethyl-4,5-diphenyl-2*H*-imidazol-2-ylidene]gold(I/III) complexes against components of cell culture medium and their influence on drug-resistant cancer cell lines

Paul Kapitza,[a] Amelie Scherfler,[a] Ronald Gust [a]

a) Pharmazeutische Chemie, Universität Innsbruck, Innrain 80/82, A-6020 Innsbruck
paul.kapitza@uibk.ac.at

During the past years, gold-containing drug candidates with *N*-heterocyclic carbenes (NHC) as ligands received high attention. Antiproliferative effects of such (NHC)gold(I/III) complexes are well documented. This particularly applies to halido(NHC)gold(I) complexes. While the influence of halido leaving groups at platinum(II) complexes on the reactivity in water and thus also on the cytotoxicity has been intensively studied, comparable investigations with (NHC)gold(I/III) complexes are rather rare.

Halido(NHC)gold(I) (halido = chlorido **1**, bromido **2**, iodido **3**), $(NHC)_2$gold(I) **4**, and dihalido$(NHC)_2$gold(III) (halido = chlorido **5**, bromido **6**, iodido **7**) were synthesized and reacted with each single component of cell culture medium. As a result, substitution reactions of halido(NHC)gold(I) complexes **1-3** with chloride or glutathione (GSH) occurred, but not with other amino acids present in the medium. In case of **2** even a quantitative transformation to **1** was observed, while **3** additionally underwent ligand scrambling to **4**. Dihalido$(NHC)_2$gold(III) complexes **5-7** are prodrugs and were reduced to **4** in the presence of GSH. On the example of **3** the degradation products in complete RPMI 1640/FCS medium were quantified. Complexes **2** (33.7%), **3** (2.6%) and **4** (7.1%) were free available, but the main fraction of **3** (56.6%) was protein-bound. These data clearly demonstrated that only **1** and **4** were stable under *in vitro* conditions all other complexes are "prodrugs" (**2**→**1**, **5-7**→**8**) or subject of partial transformation (**3**→**1** and **4**), which must be considered during the interpretation of biological results.

The complexes were further tested on the metabolic activity in wildtype and drug-resistant cancer cell lines. Complex **4** was the most active one with IC_{50} values in the low nanomolar range. The nearly identical activity of **1** and **2** in all cell lines resulted from the fast transformation of **2** to **1**, while the high antimetabolic activity of **3** was the consequence of a partial ligand scrambling to **4**. Complexes **5-7** possessed high cytotoxicity and reduced the viability of, e.g., A2780cis cells in the low nanomolar range (IC_{50} = 0.03-0.08 µM). The circumvention of Cisplatin-resistance in ovarian carcinoma cells is therefore feasible with these complexes. Remarkably, the complexes also show a promising potential to eradicate therapy-resistant cancer stem cells (CSCs).

Establishment of an affinity enrichment assay for the proteomic investigation of the human selenoproteome

Lukas Skos,[a,b] Claudia Schmidt,[c] Sophie Thomas,[c] Christopher Gerner,[a,d] Angela Casini [c] and Samuel Meier-Menches [a,d,e]

a) Department of Analytical Chemistry, University of Vienna, Waehringer Strasse 38, 1090 Vienna, Austria b) Vienna Doctoral School in Chemistry, University of Vienna, Waehringer Strasse 42, 1090 Vienna, Austria c) Chair of Medicinal and Bioinorganic Chemistry, School of Natural Sciences, Department of Chemistry, Technical University of Munich, Lichtenbergstr. 4, 85748 Garching, Germany d) Joint Metabolome Facility, University of Vienna and Medical Univeristy of Vienna, Waehringer Strasse 38, 1090 Vienna, Austria e) Department of Inorganic Chemistry, University of Vienna, Waehringer Strasse 42, 1090 Vienna, Austria

lukas.skos@univie.ac.at

Selenium is an essential element for the human organism and it is also part of selenocysteine, the twenty-first proteinogenic amino acid. The class of selenoproteins are involved in various biological processes such as redox protection, thyroid hormone production and protein folding. In a previous work, we found that an organometallic gold(III) C^N-cyclometalated complex displayed selective reactivity towards selenocysteine.[1] Here, we present a functional gold(III) C^N-cyclometalated probe, which can be immobilized on solid support to enable chemoproteomic affinity enrichment of selenoproteins from complex matrices such as whole cell lysates of cancer cells. The probe showed indeed a selectivity for thioredoxin reductase 1, a selenoprotein and known target of anticancer gold complexes. The organometallic gold(III) compound was further modified synthetically with different functionalities and was examined in different contexts, including cell viability assays, protein profiling and fluorescence microscopy. The fluorescence imaging revealed an accumulation of the compound in the nuclei of cancer cells. The proteomic results indicated disruption of the redox balance and the dysregulation of selenoproteins in cancer cells supporting the affinity enrichment analysis. Targeting the selenoproteome by gold(III) cyclometalated complexes might prove useful as an anticancer strategy.

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A link to the future!
Linkers to increase potency of Ru(II) piano-stool complexes

Rebecca A. Bedford, James P. C. Coverdale, Isolda Romero-Canelon.

School of Pharmacy, University of Birmingham, Birmingham B15 2TT, UK

rab710@student.bham.ac.uk

With cancer now affecting 1 in 2 of the population, new treatments eligible for all patients need to be developed[1]. Ru(II) piano-stool complexes offer an alternative to Pt(II) complexes by exploiting different mechanisms of action (MOA), avoiding mechanisms involved in resistance[2,3]. Ru(II) complexes are also often non-toxic in *in vitro* and *in vivo* models, in contrast to Pt(II) complexes which lack target specificity[4]. In Endothelial ovarian cancer (EOC), Pt(II) complexes are used but often unsuccessfully long term with high recurrence and continually increasing death rates[1]. This coupled with the lack of treatment advancements for EOC, treatment improvement is required.

In this work, twelve Ru(II) complexes were synthesised and fully characterised, differing in their monodentate ligand (Cl or I) and bidentate ligand (imine-phenyl or imine-CH_2-phenyl). All twelve complexes were stable in PBS and a variety of biologically relevant matrices for 24 h. *In vitro* antiproliferative activity screening using six human cancer cell lines revealed that complexes bearing a 'linker' (Im-CH_2-Py) ligand were significancy more potent (up to 5.4×) than their 'non-linked' (Im-Py) counterparts. As such, the most potent complexes, [Ru(η^6-*p*-Cym)(Im-Py)I]PF_6 (**RAB23**) and [Ru(η^6-*p*-Cym)(Im-CH_2-Py)I]PF_6 (**RAB38**) were selected for further investigation in A2780 EOC cells.

Insertion of the CH_2 linker not only increased potency but altered the mechanism of action. **RAB23** exhibited sub-G_1 cell cycle arrest, while **RAB38** caused G_1 arrest. **RAB23** lead to an increased population of late apoptotic cells compared to equipotent treatment of cells with **RAB38**. Unlike many structurally similar Ru(II) piano-stool complexes, neither complex appeared to induce ROS generation or mitochondrial membrane depolarization. Upon further investigation, nuclear morphology was significantly distorted by both complexes yet **RAB23** and **RAB38** do not appear to interact with ctDNA (UV-Visible spectroscopy), yet comet assays revealed ssDNA damage caused by **RAB38** but not **RAB23**. Interestingly, δ-H2A.X fluorescence (dsDNA damage) was increased by **RAB23**.

The structural modification appears to facilitate steric changes in the bidentate ligand, changing DNA damage from dsDNA to ssDNA breaks, increasing number of breaks, and resulting in greater potency. This highlights the potential improvement of similar highly potent complexes with the addition of a flexible linker such as FY26[5].

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Repurposing metallo-antimalarials for cancer

Aran E. Boakye-Smith,[a] Tameryn Stringer,[a,*]

a) School of Chemistry, University of East Anglia, Norwich, United Kingdom, NR47TJ
tameryn.stringer@uea.ac.uk

Quinolines have been used extensively for many years to treat malaria. Chloroquine, the most successful of the quinoline antimalarial treatments, has been rendered less effective due to the development of drug-resistant strains of the parasite. A large amount of research has been dedicated towards finding suitable alternatives, specifically with the development of metal-based quinolines, however not many of these have been as effective as ferroquine in treating chloroquine-resistant infections. Chloroquine and ferroquine have also been investigated for other diseases such as cancer and SARS-CoV-2. Chloroquine has been shown to sensitize cancer cells to radiation and other treatments, which may lead to a change in current cancer therapeutic strategies.[1] This also paves the way forward to repurpose metal-based antimalarials[2,3] as anticancer agents. Pharmacophore-containing metal complexes are popular anticancer candidates, especially if biologically active metals, like ruthenium, are incorporated as part of a complex, leading to an increase in activity. Another effect of the metal incorporation is a change in the shape and binding of the pharmacophore to biomolecules (DNA and proteins). The mechanisms of many metal-based compounds are still not yet fully understood, but this study aims to shed light on the mechanism of action of quinoline-based piano-stool complexes containing ruthenium towards cancer cells.

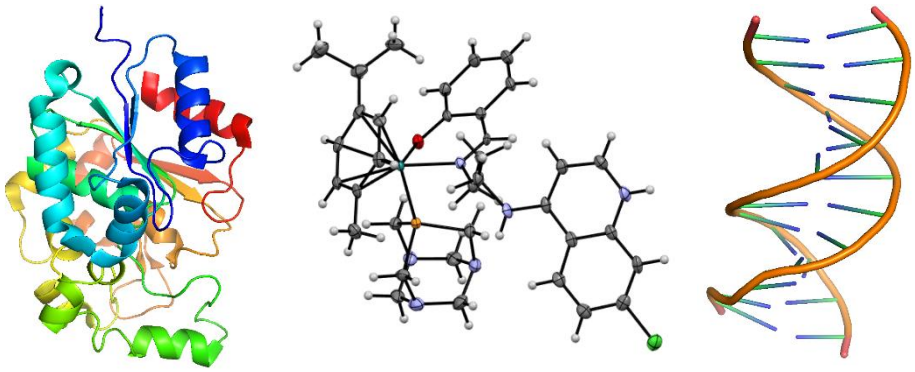

Figure 1. Piano-stool ruthenium quinoline complex and potential biological targets[4,5]

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Activation by Bicarbonation?
HPLC Analytics on Anticancer Ruthenium NHC Complexes

Pia Schneeberg[a], Ingo Ott[a]

a) Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, Beethovenstraße 55, 38106 Braunschweig, Germany.
pia.schneeberg@tu-braunschweig.de

For several decades, ruthenium complexes have been one of the most promising candidates in the development of antitumor metal complexes to succeed the well-established therapeutic cisplatin.[1] To date, numerous compounds have already been biologically tested.[2] Nevertheless, many questions about targets and active forms often remain unanswered.[3] To address these issues analytically, an HPLC method for (p-cymene)(NHC)Ru(II)X complexes (X = Cl_2, oxalate, salicylate) was developed. Stability in solvents and biologically relevant aqueous media as well as binding to various biomolecules, such as amino acids, were investigated. It was shown that the X-ligand has a significant influence on the hydrolysis of the compounds and on the rate and extent of binding to biomolecules. However, it is particularly noteworthy that all the compounds investigated bind to bicarbonate. Even in cell culture medium (DMEM), the only product formed for all compounds is the binding product with bicarbonate but at different rates (see **Fig. 1**). The compounds with faster binding to bicarbonate were also the ones showing higher cytotoxicity. These results allow the hypothesis that the resulting bicarbonate complex may be the active form for all of these compounds.

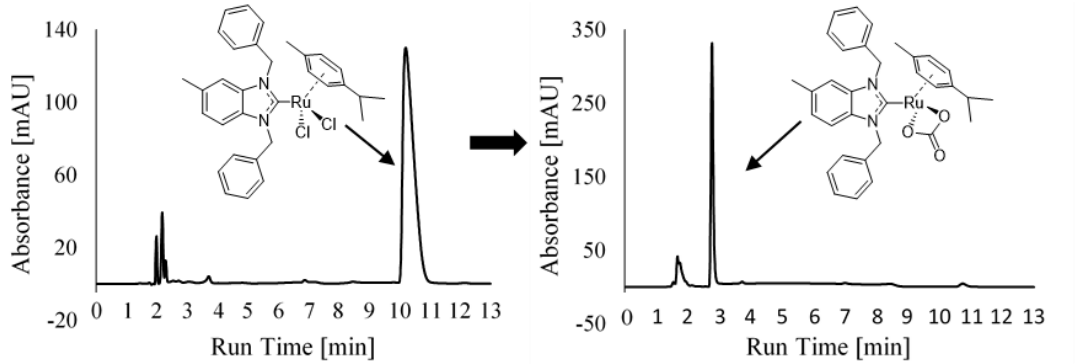

Fig. 1: (p-cymene)(NHC)Ru(II)Cl_2 600 µM in DMSO (left) and in DMEM (right) immediately after dissolution.

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Trimetallic ruthenium(II) 2-arylbenzimidazole complexes for chemotherapy and photodynamic therapy

Athi Welsh,[a] Refilwe Matshitse,[b] Tebello Nyokong,[b] Saif F. Khan,[c] Sharon Prince,[c] and Gregory S. Smith[a]

a) University of Cape Town, Faculty of Science, Department of Chemistry, Private Bag, Rondebosch, 7701, South Africa
b) Institute for Nanotechnology Innovation, Rhodes University, Makhanda, 6140, South Africa
c) Department of Human Biology, University of Cape Town, Faculty of Health Science, Observatory, 7925, South Africa

email: WLSATH001@myuct.ac.za

Platinum-based metallodrugs remain the mainstay chemotherapeutic agents for the treatment of various cancers. However, their scope of application is marred by the evolution of resistance and the detrimental side effects associated with the use of these platinum metallodrugs. These challenges have resulted in a paradigm shift in the development of novel metal-based chemotherapeutics to alternate platinum-group metals, with ruthenium complexes being at the forefront. However, these studies are mainly limited to monometallic ruthenium complexes, with polymetallic complexes seldom being investigated despite the several promising characteristics of polymetallic chemotherapeutic agents.

This presentation will highlight the rational design and development of a series of polymetallic ruthenium(II) complexes based on the benzimidazole pharmacophoric scaffold. The effects that varying the aryl substituents and alteration of the trimeric core may exert on the photochemical and overall biological activity of the complexes are investigated. Furthermore, the application of a set of ruthenium(II) complexes synthesized in this study were also investigated as photodynamic therapy (PDT) agents and were noted to show enhanced short and long-term cytotoxicity upon photoirradiation. This further highlights the versatility of the ruthenium(II) complexes in different treatment modalities for cancer, as we have shown how nuanced structural alterations may influence the overall biological activity and applications of these complexes in the treatment of cancer. Overall, the complexes developed in this study show appreciable activity in breast cancer, cervical cancer and rhabdomyosarcoma cell lines, which is either comparable or enhanced relative to clinically used cisplatin.

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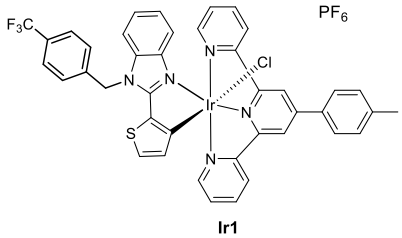
Ir(III) complexes with antimetastatic and antiproliferative activity against triple-negative breast cancer (TNBC) cells

Alicia Marco,[a] Vojtech Novohradsky,[b] Lenka Markova,[b] Natalia Cutillas,[a] José Ruiz,[a] Viktor Brabec.[b]

a) Departamento de Química Inorgánica, Universidad de Murcia e Instituto de Investigaciones Biomédicas de Murcia (IMIB-Arrixaca), E-30100 Murcia, Spain.
b) Czech Academy of Sciences, Institute of Biophysics, Kralovopolska 135, CZ-61265 Brno, Czech Republic.
alicia.marco@um.es

Triple-negative breast cancer (TNBC) is one of the most aggressive due to his potential ability to metastasize. Pt-based drugs or doxorubicin often fail in their treatment, so that the development of new antiproliferative and antimetastatic drugs is very important. In this sense, Ir(III)-based complexes offer the possibility of acting with different mechanisms of action to the reference drugs in clinical use.[1]

Herein, we describe the development of new Ir(III) complexes of the type $[Ir(N^N^N)(C^N)Cl]PF_6$, where N^N^N is 4'-(p-tolil)-2,2':6',2''-terpyridine and C^N is a benzimidazole based ligand. The biological studies show that the most active complex **Ir1** (Figure 1) is more efficient and selective than doxorubicin against 2D models and 3D multicellular models of TNBC cells. Furthermore, the studies indicate that complex 1 not only exhibits anti-invasive activity but also show the ability to supress its dissemination.



Ir1

Figure 1. Structure of the new terpyridine iridium complex **Ir1**.

Acknowledgements

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In-Cell Catalysis: Non-Toxic, Potent Iridium(III) Anticancer Complexes Can Overcome Platinum Resistance

Millie. E. Fry[a], I. Romero-Canelon,[a,b] and J. P. C. Coverdale[a,b]

a) School of Pharmacy, Institute of Clinical Sciences, University of Birmingham, Edgbaston, UK, b) Department of Chemistry, University of Warwick, Coventry, UK

mef963@student.bham.ac.uk

Ovarian cancer is the sixth most common cancer in the UK, where 11 women die of the disease every day [1]. Platinum drugs (cisplatin or carboplatin) are routinely administered with paclitaxel in first line treatments [1], and while these DNA targeting agents remain widely used in ovarian cancer chemotherapy regimes, their dose-limiting toxicity, poor selectivity for cancer cells, and high incidence of platinum-associated resistance (both intrinsic and aquired) highlights an urgent need for new chemotherapeutics which are less toxic and can overcome drug resistance.

Next generation metallodrugs have the potential to overcome these challenges by achieiving *in-cell* catalysis; a novel strategy which can achieve dose minimisation while exploiting an alternative mechanism of action to overcome drug resistance [2]. Using Ir(III) half-sandwich complex **1** [Ir(Cp*)(TsDPEN)], we have shown that this complex exhibits promising anticancer activity towards platinum-resistant cell lines, while offering over 10× less *in vivo* toxicity (LC_{50}) than cisplatin in a zebrafish embryo model [3]. The potency of **1** is enhanced by co-administration of sodium formate as a source of hydride to initiate *in-cell* catalysis, and the generation of reactive oxygen species (ROS) was conserved both *in vitro* and *in vivo*. Unlike cisplatin, no evidence of DNA damage was observed in a comet assay, highlighting how this unique catalytic mechanism of action can overcome cisplatin drug resistance.

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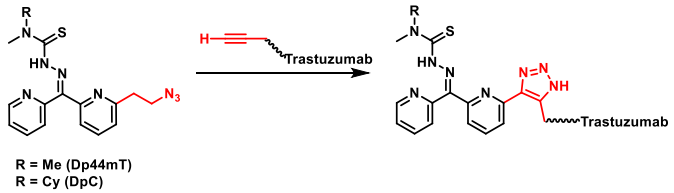
Novel thiosemicarbazone-antibody drug conjugates as candidates for HER2-positive breast cancer therapy

Nandan Sheernaly, Axel Steinbrück, Nils Metzler-Nolte

Anorganische Chemie I – Bioanorganische Chemie, Ruhr-Universität Bochum, 44780 Bochum, Germany

nandan.sheernaly@rub.de

Metal chelators have been gaining interest as adjuvant therapeutics for treating cancer. Despite recent advances, novel approaches are urgently required to address issues pertinent to selectivity and efficacy.[1] In this regard, chelators belonging to the di-pyridyl-thiosemicarbazone (DpTs) class have shown great promise. Currently, DpC and Dp44mT are the two lead candidates in this class of agents, off which DpC has entered phase I clinical trials.[2] DpTs exert anti-cancer activity by coordinating with iron or copper ions in the cancer cell, which leads to the formation of reactive oxygen species and, eventually, apoptosis. The chelation is necessary to express the metastasis suppressor N-myc downstream regulated gene-1 (NDRG1).[2] Recent studies have found that the upregulation of NRDG1 affects the expression of epidermal growth factor 2 (HER2), whose overexpression is associated with malignancy in 20-30% of all breast cancers.[2,3]



Trastuzumab, a monoclonal antibody targeting the HER2 receptor, has tremendously succeeded in breast cancer therapy. Over the years, the selectivity of antibodies and the potency of cytotoxic drugs have incentivized researchers to synthesize therapeutic agents called antibody-drug conjugates (ADCs), which has helped overcome certain limitations of chemotherapy while improving the therapeutic index.[4] Moreover, the advent of ADCs has helped address trastuzumab resistance and related side effects.[4] In our studies, we have successfully equipped the representative DpTs with an azido linker, and we envision conjugating them to trastuzumab via click reaction. We will also investigate the metal-binding properties of the conjugates and the effects of chelation on the IC_{50} values. We believe these conjugates possess tremendous potential, particularly since the drug and the antibody have similar cellular target sites.

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Salene complexes – Is increased lipophilicity key to enhanced cellular uptake?

Astrid D. Bernkop-Schnürch[a], Hubert Descher[a], Armida Clauser[a,b], Ronald Gust[a], Brigitte Kircher[b,c]

[a] Department of Pharmaceutical Chemistry, Institute of Pharmacy, University of Innsbruck, Innrain 80-82, [b] Immunobiology and Stem Cell Laboratory, Department of Internal Medicine V, Medical University of Innsbruck, Anichstraße 35, [c] Tyrolean Cancer Research Institute, Innrain 66, A - 6020 Innsbruck

astrid.bernkop-schnuerch@uibk.ac.at

Iron complexes with bis(salicyliden)ethylenediamine (salene) scaffolds (highlighted in red in Fig. 1) have already shown encouraging results despite poor cellular uptake.[1] Therefore, the aim of the study was to increase the lipophilic character by introducing the lipophilicity improving ligands fluorine, chlorine and bromine (highlighted in yellow in Fig. 1) and consequently to enhance their cellular uptake.

After chemical characterization, these complexes were tested for their anti-metabolic activity in MDA-MB-231 cells. Cell-death studies were performed by using inhibitors for ferroptosis and necroptosis. Furthermore, their redox potential was evaluated by cyclovoltammetry. Cellular uptake was investigated by atom absorption spectroscopy (AAS).

IC_{50} of inhibiting mitochondrial activity ranged from 0.25 µM to 1.1 µM. An active Fe^{2+}/Fe^{3+} redox pair for all complexes was identified, representing a prerequisite for ferroptosis.[2] However, both ferroptosis and necroptosis were detected as mechanism of cell death. The higher the log P of these complexes, the more enhanced was their cellular uptake.

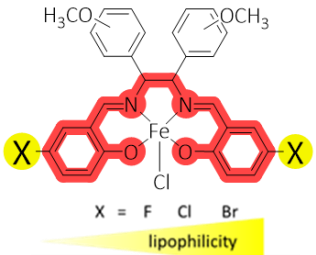

Fig. 1: Structure of iron(III)salene complexes

In summary, the potential of salene complexes can be improved by their halogenation increasing lipophilicity and consequently cellular uptake.

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International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

Protein rebridging by metallocarbonyl bromo- and dibromomaleimides

Karolina Koprowska,[a, b] Anna Wrona-Piotrowicz,[a] Aneta Kosińska,[a] Michèle Salmain[c], Bogna Rudolf[a]

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

b) Bio-Med-Chem Doctoral School of University of Lodz and Institutes of Polish Academy of Science, ul Banacha 12/16, 90-237 Lodz, Poland

c) Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, 75005 Paris, France

karolina.koprowska@edu.uni.lodz.pl

Advances in protein modifications by chemical means have led to the development of many protein bioconjugation methodologies useful in imaging and treatment of many diseases such as malaria, cancer, HIV, etc.[1] Among the methods of modification and labeling of peptides, a special attention should be paid to the "artificial stapling" (rebridging) of peptide chains by small molecules (like those containing a maleimide moiety) that leads to "replace" various types of bonds in proteins.[2]

It is well-known that bromomaleimides react with cysteine residues to form thiomaleimides. Recently, we have synthesized bromo- and dibromo metallocarbonyl maleimides and reacted them with cysteine and tripeptide glutathione[3]. Herein, we report the rebridging of subunits in IgG-type antibodies by metallocarbonyl bromo- and dibromomalemides, following the cleavage of interchain disulfide bridges by TCEP (fig).

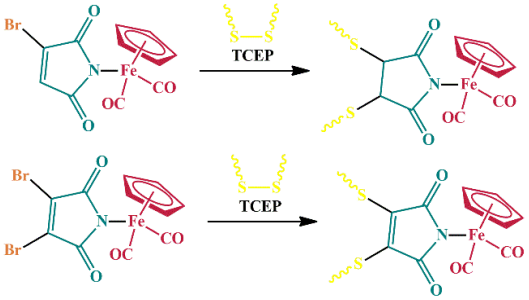

Fig. 1 Protein modification with metallocarbonyl bromo- and dibromo maleimides

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Chemical and biological studies of novel Re(I) complexes against cancer cells and *Caenorhabditis elegans*

Pezhman Ashoo,[a] Alicia Marco,[a] Samanta Hernández-García,[b] Pedro Martínez-Rodríguez,[b] Natalia Cutillas,[a] Fernando Gandía-Herrero,[b] Jose Ruiz,[a]

a) Departamento de Química Inorgánica, Universidad de Murcia, and Institute for Bio-Health Research of Murcia (IMIB-Arrixaca), E-30071 Murcia, Spain.
b) Departamento de Bioquímica y Biología Molecular A, Unidad Docente de Biología, Facultad de Veterinaria, Universidad de Murcia, E-30071 Murcia, Spain.
pezhman.ashoo@um.es

In the development of metal-based anticancer chemotherapeutic compounds, the ligand plays a pivotal role in enhancing the biological activity including entering the cells as well as interaction with major organelles such as nucleus and mitochondria.[1] Herein, we have designed, synthesized and characterized a series of organometallics Re(I) complexes containing 4-dimethylaminopyridine (DMAP) as the main ligand. The in vitro studies demonstrated high cytotoxicity against different types of cancer cells with apoptosis being produced as a mode of cell death. Model animal Caenorhabditis elegans was used to estimate the effects of the selected Re(I) compound in vivo.

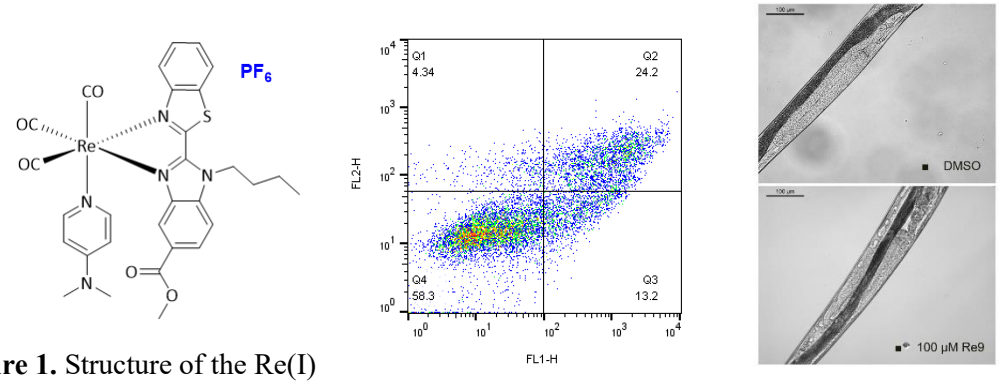

Figure 1. Structure of the Re(I) compound inducing apoptosis and reducing gonad tumor growth in *C. elegnas*.

Acknowledgements: This work was supported by funds from the Spanish Ministerio de Ciencia e Innovación-Agencia Estatal de Investigación (MCI/AEI/10.13039/501100011033) and FEDER funds (projects PID2020-117508RB I00, PID2021-122850NB-I00).

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A new rhodium(I) bioorganometallic complex and its biological evaluation against resistant leukemia cells

Janina Schmidt,[a] Aram Prokop,[b] Ingo Ott,[a]

a) Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, Beethovenstr. 55, 38106 Braunschweig, Germany
b) Helios Kliniken Schwerin, Universitätsklinikum der privaten Universität Medical School Hamburg (MSH), Wismarsche Straße 393 – 397, 19055 Schwerin, Germany
j.schmidt2@tu-braunschweig.de

Cisplatin is the most widely used drugs for cancer therapy. However, it has enormous side effects. For this reason and motivated by the tremendous effects of this drugs regarding their anticancer effects, the development and research on new anticancer drugs is urgently needed.[1] In recent years, novel *N*-heterocyclic carbene- metal complexes of the type [(COD)(NHC)RhCl] (COD = 1,5-cyclooctadiene, NHC = *N*-heterocyclic carbene) with Rh(I) as the metal center were synthesized and evaluated as new potential cytostatics with IC_{50} values in the low micromolar range.[2] Rh(I) is isoelectronic to Pt(II) and forms the same square planar complex structure as Pt(II).[3] NHCs are able to stabilize transition metal complexes, which are capable to affect the mitochondria- mediated cell death.[4] Cytostatics in cancer therapy often contain fluorine because of its properties, like its influence on lipophilicity or electrostatic interactions.[5] The combination of these three effects is promising for drug development.

An organometallic rhodium(I)-NHC complex (**Fig.1**) was prepared and evaluated for cytotoxic effects against selected leukemia cell lines, which are based on a Nalm-6- (B cell precursor leukemia), and a BJAB- cell line (Burkitt lymphoma) with different resistances against conventional cytostatics. The complex showed IC_{50}- values in the low micromolar range and also demonstrates promising results regarding proliferation inhibition and selectivity between healthy and cancer cell lines.

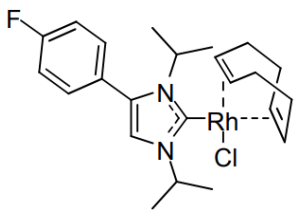

Figure 3: Structure of the investigated Rh(I)-complex.

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New Phototoxic Lanthanide(III) Complexes for Photodynamic Therapy in the Therapeutic Window

Daniel Obitz,[a] Karmel S. Gkika,[b] Marvin Heller,[a] Tia E. Keyes[b] and Nils Metzler-Nolte,[a]

a) Inorganic Chemistry I – Bioinorganic Chemistry, Ruhr-University Bochum, Universitaetsstrasse 150, Bochum 44780, Germany, b) School of Chemical Sciences and National Centre for Sensor Research, Dublin City University, Dublin 9, Ireland
Daniel.Obitz@rub.de

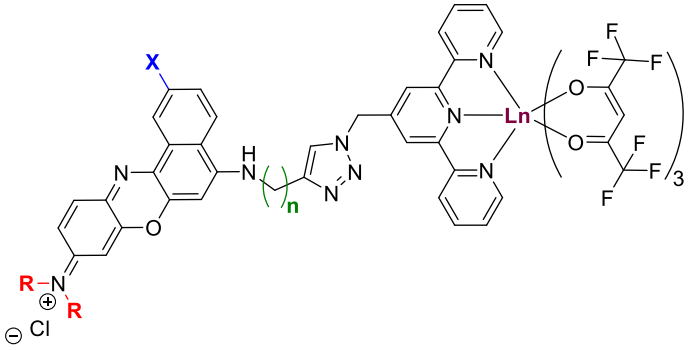

Figure 1: New lanthanide(III) photosensitiser complexes (with Ln = Dy, Ho, Er, Tm, Lu; R = Me, Et; X = H, OH and n = 1 or 2).

A series of lanthanide(III) complexes with dysprosium, holmium, erbium, thulium, and lutetium metal centres connected via a terpyridine unit to a phenoxazine based light harvesting antenna with strong absorption in the therapeutic window (600 nm – 1000 nm) was synthesised and tested as possible photosensitiser (PS) in photodynamic therapy (PDT). The Ho, Er, and Tm complexes exhibited significant phototoxic activity on cancer cells upon irradiation in the therapeutic window. In intracellular and in-solution studies ROS production was identified as the compound's phototoxic mode of action. In cell viability assays, an up to 10-fold lowered IC_{50} (thulium complex) value was obtained upon irradiation compared to the dark control for the synthesised complexes.[1] The complexes uptake in cancer cells and their cellular localisation was monitored by confocal microscopy and will be reported on the poster. For the -OH functionalised series (Ho, Er, Lu) localisation in the lysosomes and the endoplasmic reticulum was found.

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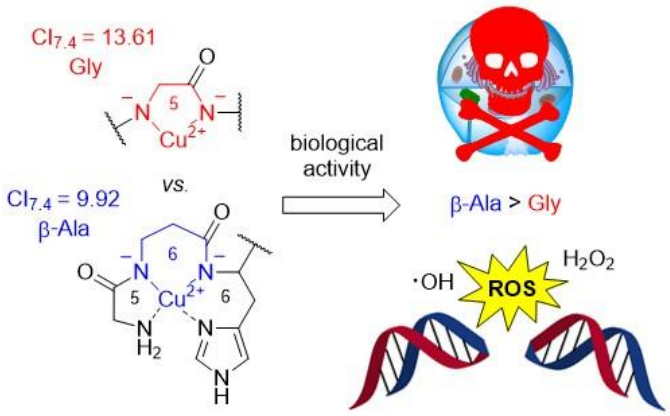
Incorporation of β-Alanine in Cu(II) ATCUN Peptide Complexes Increases ROS Levels, DNA Cleavage and Antiproliferative Activity

Julian Heinrich,[a, b] Christian G. Hartinger,[c] Wojciech Bal,[d] Nora Kulak,[a, b, e]

a) Institute of Chemistry and Biochemistry, Freie Universität Berlin Fabeckstr. 34/36, 14195 Berlin, Germany b) Institute of Chemistry, Otto-von-Guericke-Universität Magdeburg, Universitätsplatz 2, 39106 Magdeburg, Germany c) School of Chemical Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand d) Institute of Biochemistry and Biophysics, Polish Academy of Science, Pawińskiego 5a, 02-106 Warsaw, Poland e) Institute of Chemistry, University Potsdam, Karl-Liebknecht- Straße 24-25, 14476 Potsdam, Germany

julian.heinrich@ovgu.de

DNA can be oxidatively cleaved by Cu(II) complexes of the ATCUN peptide (amino terminal Cu(II)- and Ni(II)-binding motif) through reactive oxygen species (ROS) production. The simplest peptide mimicking the ATCUN motif is the tripeptide glycine-glycine-histidine, the Cu(II) complex of which exhibits antitumor activity.[1] Here, ATCUN-based peptides were synthesized by exchanging glycine for β-alanine at position 2 of the sequence. These metallopeptides were characterized at pH 7.4 via potentiometric titrations. High cytotoxic activity of the investigated metallopeptides correlates with their oxidative DNA cleavage activity and high cellular uptake into cancer cells.[2]



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International Symposium on Bioorganometallic Chemistry 2023 (Braunschweig)

A Glimpse on Effective Synthetic Strategy for Developing Mitochondria Specific Highly Efficient Ru(II)/Ir(III)/Re(I)-based Mixed Metallic Complexes for Cancer Therapy

Nilmadhab Roy,[a] Priyankar Paira*

a) Department of Chemistry, School of Advanced Sciences (SAS), Vellore Institute of Technology (VIT), Tamilnadu, Vellore-632014, India, 8110020748, 7719342439

E-mail:nmr.chem1@gmail.com

Cancer is the most incurable pernicious disease till date after the cardiovascular disease throughout the world with immeasurable rate of mortality. However, effective cancer therapy is still castles in the sky to the researchers being unable to develop appropriate anticancer drugs. In quest of an appropriate strategy to annihilate cancer, we have aspired to design a set of mixed metallic complexes having the cancer cell imaging and damaging capability with higher degree of cytoselectivity. These mixed metallic complexes are appreciably fluorescent with high quantum yield displaying the capability of diagnosing the cancer cells and have shown remarkable cytotoxicity against a series of cancer cell lines (HeLa, Caco-2, MDA-MB468, MCF-7, HT-29) accompanied with excellent binding efficacy with biomolecules (HSA, DNA) being resistant to glutathione(GSH) rendering the healthy cells unaffected. In line with this, complexes are highly capable of targeting the organelles (nucleus, mitochondria) and can destroy the cancer cells causing mitochondrial dysfunction through reduction of mitochondrial membrane potential (MMP) as well as triggering the emergence of ROS in association with DNA damage (**Figure 1**).[1] Optimistically, it can be presaged that all the characteristics of these complexes will be beneficial for exploring the brilliant cancer therapeutic agents in imminent future.

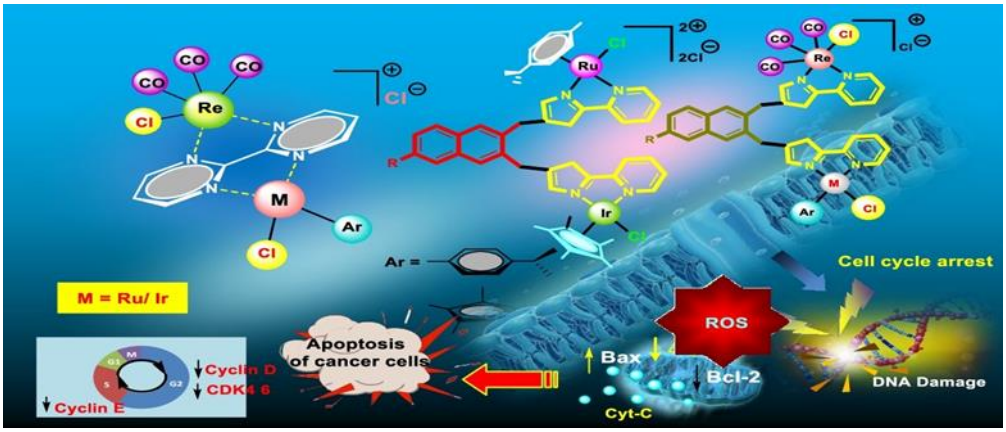

Figure 1. A Mechanistic Approach of the Synthesized Complexes in Destruction of Cancer Cells

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Gold(I) *N*-heterocyclic carbene complexes: effects of different functional groups on antiproliferative properties

Sebastian Türck, Ingo Ott

Technische Universität Braunschweig | Institute of Medicinal and Pharmaceutical Chemistry | Beethovenstr. 55, 38106 Braunschweig

s.tuerck@tu-braunschweig.de

The gold complex Auranofin has been therapeutically used for many decades. In addition to the treatment of rheumatoid arthritis, cytotoxic effects have also been reported.[1] Following this example, our research group has recently investigated the antiproliferative potential of gold(I)-*N*-heterocyclic carbene complexes, which are superior compared to Auranofin.[2,3] In this context, the interaction of gold compounds with selenocystein-containing biomolecules such as thioredoxin reductase (TrxR) is being investigated as a key function for the cell growth inhibitory activity,[3] and is therefore of great interest to further optimize these structures and investigate their effect on cancer cells.

On this basis, various derivatives of 4-methyl-1*H*-imidazole have been synthesized (Figure **1**) and evaluated for their biological activity. These initial studies show that smaller *N*-substituted side chains exhibit similar antiproliferative effects but differ fundamentally in the maximum tolerated concentration over 24h.

Recent results with refined structures on antiproliferativity, cytotoxicity and enzyme inhibition will be presented.

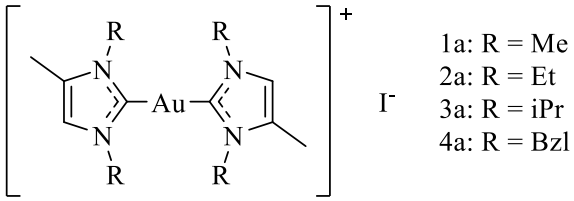

Figure **4**: structures of investigated gold(I) complexes.

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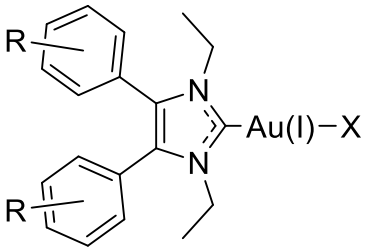
Correlation of protein binding, enzyme inhibition as well as cellular uptake and cytotoxicity of substituted halido(NHC)gold(I) complexes in A2780 ovarian cancer cells

Amelie Scherfler,[a] Paul Kapitza,[a] Ronald Gust [a]

a) Pharmazeutische Chemie, Universität Innsbruck, Innrain 80/82, A-6020 Innsbruck
amelie.scherfler@uibk.ac.at



X = Cl, Br, I, NHC
R = 3-OCH_3, 4-OCH_3, 4-F

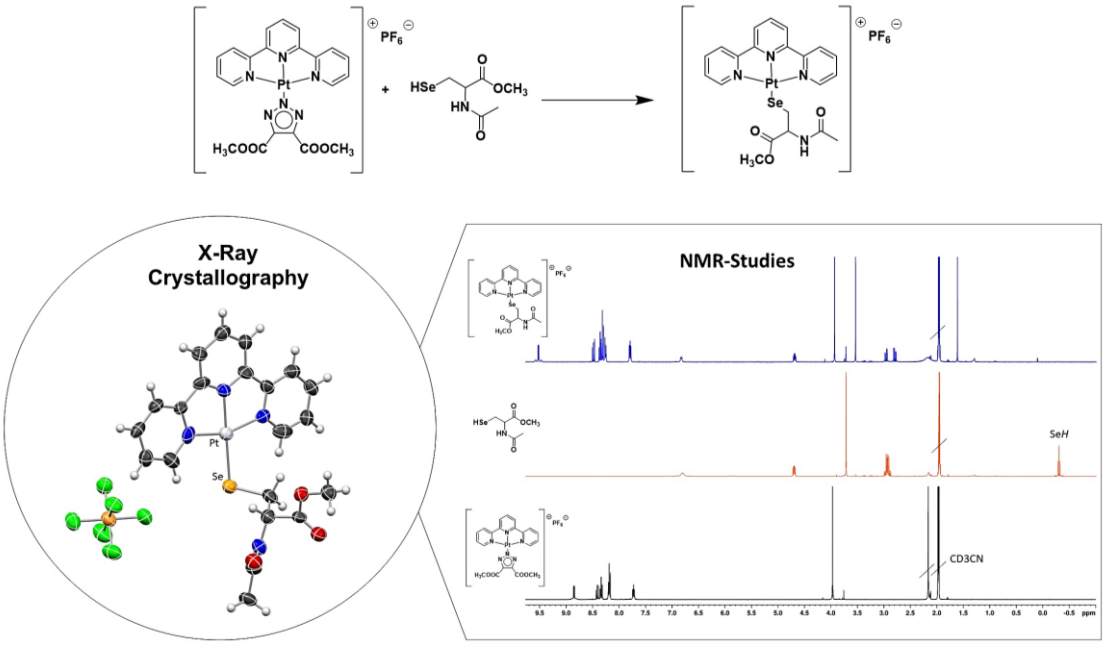
Since Auranofin was approved in 1985 for the treatment of rheumatoid arthritis, gold(I)-containing drugs have been developed as chemotherapeutics. Auranofin interacts with the reduction/oxidation system within the cell, causing cytotoxic effects in malignant and non-malignant cells. In order to increase the selectivity for tumor cells, the *N*-heterocyclic carbene (NHC) complexes of the halido[1,3-diethyl-4,5-diphenyl-2*H*-imidazol-2-ylidene]gold(I)- (halido: Cl (**1**), Br (**2**), I (**3**)) and the [1,3-diethyl-4,5-diphenyl-2*H*-imidazol-2-ylidene]$_2$gold(I)-type (**4**) have been developed. This study aimed to optimize the biological activity by substitution of the phenyl rings with either a 4-fluoro (**a**), a 3-methoxy (**b**) or a 4-methoxy (**c**) group. The resulting halido(NHC)Au(I) (halido = Cl: **1a-c**, Br: **2a-c**, I: **3a-c**) and $[(NHC)_2Au(I)]^+$ (**4a-c**) complexes were tested for cytotoxicity on the ovarian cancer cell line A2780wt and its corresponding Cisplatin-resistant subclone A2780cis as well as on the non-malignant SV-80 lung fibroblast cell line. The complexes **1a-4a** were selected for extended investigations on the uptake in A2780wt/cis cells and protein binding, since fluorine substituents have already been shown to increase hydrophobicity and cell penetration of metal complexes. The highest gold uptake into the cells (500 ng gold/mg protein) caused the $[(NHC)_2Au(I)]^+$ complex **4a**. Interestingly, the intracellular gold concentration slightly decreased with time. This might be the consequence of a higher amount of free complexes (45%) in the cell culture medium. The halido(NHC)Au(I) complexes **1a-3a** completely bound (100%) to serum albumin. First results on the interaction with the redox system of the cell, based on a shift of the GSH level after incubation with the complexes, and enzyme-based assays with the most prominent (NHC)gold(I) targets (glutathione peroxidase and thioredoxin reductase) will be presented. The findings of this study clearly suggest that the used NHC ligands make the halido(NHC)Au(I) and $[(NHC)_2Au(I)]^+$ complexes to promising potential antitumor agents, as they mediate high cytotoxic potential and a high accumulation in tumor cells.

Spectroscopic studies with selenocysteine as a model system - Pd(II) and Pt(II) triazolatocomplexes as potential inhibitors for thioredoxin reductase (TrxR)

Victoria V. L. Müller,[a] Ulrich Schatzschneider [a]

[a] Institut für Anorganische Chemie, Julius-Maximilians-Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany
victoria.mueller@uni-wuerzburg.de

Thioredoxin reductase (TrxR) is one of the few selenium-containing enzymes in the human body. It is overexpressed in a number of cancers and a promising target for drug development. The TrxR active side contains a cysteine and a selenocysteine residue which might be targeted by soft metal centers of the late transition metals [1].



Therefore, [MX(terpy)]PF_6 complexes with M = Pd(II) or Pt(II), terpy = 2,2':6',2"-terpyridine and X = triazolate were synthesised by iClick reaction and their reactivity towards nucleophilic biomolecules was studied [2]. ^{1}H NMR studies of these complexes with *N*- and *C*-protected amino acids (*N*-acetyl-L-cysteine methyl ester, *N*-acetyl-L-selenocysteine methyl ester, *N*-acetyl-histidine methyl ester) and 9-ethylguanine as protein and DNA model compounds were performed to establish potential modes of action. For both metal complexes, a selectivity towards sulfur- and selenium-containing residues was observed, and these adducts were further studied by NMR, ESI MS, and single-crystal X-ray diffraction.

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Oral Anticancer Heterobimetallic PtIV−AuI Complexes Show High In Vivo Activity and Low Toxicity

Tomer Babu[1], Hiba Ghareeb[2], Uttara Basu[3], Hemma Schueffl[4], Sarah Theiner[5], Petra Heffeter[4]*, Gunda Koellensperger[5]*, Norman Metanis[2]*, Valentina Gandin[6]*, Ingo Ott[3]*, Claudia Schmidt[1]*, and Dan Gibson[1]*

1 Institute for Drug Research, School of Pharmacy, The Hebrew University, 91120 Jerusalem, Israel; 2 Institute of Chemistry, The Center for Nanoscience and Nanotechnology, Casali Center for Applied Chemistry, The Hebrew University of Jerusalem, Jerusalem 9190401, Israel. 3 Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, 38106 Braunschweig, Germany; 4 Center for Cancer Research and Comprehensive Cancer Center, Medical University of Vienna, Austria;

5 Institute of Analytical Chemistry, Faculty of Chemistry, University of Vienna, Waehringer Strasse 38, 1090, Vienna, Austria; 6 Dipartimento di Scienze del Farmaco, Universita di Padova, 35131 Padova, Italy;

E-mail: Dang@ekmd.huji.ac.il

Recent statistics showed that a third of all diagnosed cancer patients receive chemotherapy.[1] Platinum(II) drugs are the clinically most frequently used anticancer drugs worldwide, with almost 50% of all chemotherapy patients receiving some type of platinum regimen.[2] As with most chemotherapeutics, severe adverse side effects and resistance limit the platinum doses that can be administered intravenously.[2-3]

We are addressing platinum(II) drawbacks by using multi-action Pt(IV) complexes as prodrugs. They are stable outside the cell, can be administered orally but once in the cell, they are activated by reduction, releasing the active Pt(II) drug and two bioactive axial ligands.[3-4]

Gold(I) complexes with N-heterocyclic carbenes (NHCs) ligands emerged as interesting anticancer agents as the NHC ligands stabilize the gold center and allow for a wide range of structural modifications and modulations at their backbone and wingtip positions.[5] Combining a DNA-damaging Pt moiety and a protein inhibiting and modulating Au(I)-NHC scaffold can provide synergistic properties with the potential to increase the anti-neoplastic activity, reduce side effects and overcome cisplatin-resistance.

We combined, for the first time, in a single prodrug the Pt(IV) precursors of FDA approved anticancer drugs (cisplatin, or oxaliplatin) with antiproliferative gold(I)-NHC scaffolds bearing variations in the backbone position that were conjugated to the Pt(IV) via an ethylenediamine-derivatized mercaptobenzoic (EDA-MBA) spacer.

We will report on the in vitro and in vivo activity as well as in vivo side effects compared to their individual components or their co-administration.

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Metal-glycoconjugates activity against ovarian cancer: investigations on cellular behaviour

Callum Daunter,[a] Ioannis Titilas,[b] Luca Ronconi [b] and Isolda Romero-Canelon [a]

a) School of Pharmacy, University of Birmingham, Birmingham, UK,

b) School of Biological and Chemical Sciences, University of Galway, Galway, Ireland

cxd946@student.bham.ac.uk

With over 4100 deaths a year in the UK alone from ovarian cancer, existing treatments for the disease are currently unsatisfactory. A high number of patients can expect recurrent disease with half of these facing mortality [1]. Currently, first line treatment regimes consist of combination therapy of platinum drugs combined with paclitaxel, however once the disease recurs, generally these treatments become ineffective. Platinum resistance occurs in most cases, and cross resistance to other therapies is likely due to shared mechanisms of action [2]. Attempts at targeted therapies have also fallen short with similar issues and the lack of improvement of overall survival.

We are therefore investigating metal-glycoconjugates as viable alternatives to platinum drugs in the clinic, particularly aimed at ovarian cancers. These compounds would allow for targeting the altered glucose metabolism of cancer cells which has become an attractive strategy. It has been reported that ovarian cancers highly overexpress glucose transporters, in particular GLUT1, potentially to facilitate increased glucose uptake. Therefore, there is a rationale to conjugate anticancer drugs to glucose to aid their delivery. Gold(I/III) and platinum(II) dithiocarbamato complexes have been shown to be effective in a range of ovarian cancer cell lines with micromolar potency. The present contribution is framed within the efforts to establish the fate of such compounds and their behavior at cellular level.

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Synthesis and Characterization of Gold(I) NHC PROTACs as Potential Degraders of Thioredoxin Reductase

Nils Wagner [a,b],Ingo Ott [a,b]

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

b) Center of Pharmaceutical Engineering, Technische Universität Braunschweig, Franz-Liszt-Straße 35a, 38106 Braunschweig, Germany

nils.wagner@tu-braunschweig.de

PROTACs (PROteolysis TArgeting Chimeras) are currently being considered as a powerful new tool in cancer therapy and against infectious diseases. These bifunctional molecules consist of two domains, connected by a linker. One domain binds to an E3 ligase that activates the proteasome of a cell. The other domain binds to a protein of interest. Formation of a ternary complex leads to ubiquitination and thus degradation of the protein of interest. This mechanism may lead to longer-lasting effects than classical enzyme inhibition.[1],[2]

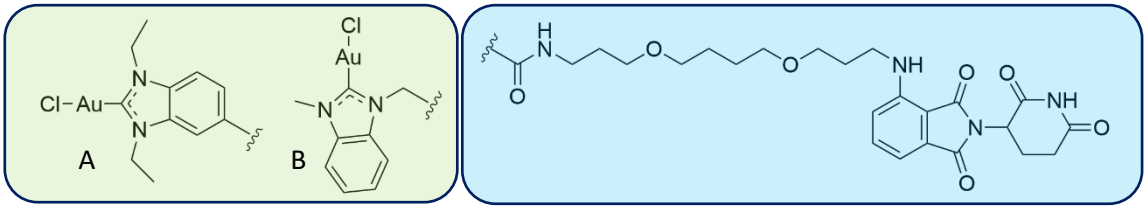

Figure 1. PROTACs (left: TrxR-ligands, right: CRBN-ligand linker conjugate)

To combine this promising approach with our acquired expertise with gold(I) NHC-based TrxR inhibitors, two CRBN-directed PROTACs were successfully synthesized using a pomalidomide-derivative as the E3 ligase binding moiety[3] and two benzimidazole-based gold(I) NHC complexes as TrxR binding warheads.[4],[5] Cell growth inhibitory effects of the new compounds were evaluated in A549 lung carcinoma cells and compared with the parent compounds. To investigate degradation effects on TrxR, western blot analyses will be performed. Latest results will be presented on the poster.

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Uridine and deoxyuridine complexes based on platinum: synthesis and antiproliferative activity

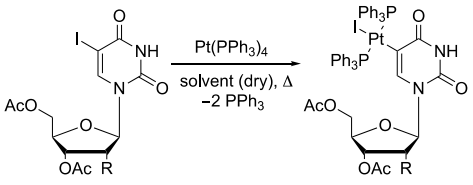
Giulia Orsini,[a] Ines Leitão,[a] Fernanda Murtinheira, [b] Federico Herrera,[b] Ana Petronilho [a]

a) ITQB NOVA Av. da República, 2780-157 Oeiras, Lisboa, Portugal, b) Faculdade de Ciências da Universidade de Lisboa Campo Grande, 1749-016 Lisboa, Portugal

giulia.orsini@itqb.unl.pt

Nucleosides are involved in the physiology of the cell and crucial in processes such as DNA and RNA synthesis, metabolic regulation, and cell signalling.[1] Modified nucleosides, being similar to their natural analogues, have long been employed as antitumor and antifungal agents. They act by mimicking endogenous nucleosides, resulting in DNA and RNA damage.[2] In cancer treatment, nucleoside analogues are often used in combination therapies, namely with platinum-based drugs.

Inspired by this, we aimed at combining a nucleoside with platinum (II) to form a single compound, able to promote anticancer activity by two complementary modes of action. Our aim is to reduce potential side effects and address the different pharmacokinetics for each of the drugs, that can often be problematic.[3] For this purpose, we developed a methodology for the metallation of uridine and deoxy-uridine through oxidative addition to Pt (0). Preliminary antiproliferative assays were performed and the activity compared to that of unmetallated nucleosides. These results will be discussed in this communication.



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Biological Activity of $Pt_2(COD)_2TTFtt$

Yasmin Borutzki,[a,b,c] Lauren E. McNamara,[d] John S. Anderson, [d] Samuel M. Meier-Menches [a,b,e]

a) Department of Inorganic Chemistry, University of Vienna, Waehringer Strasse 42, 1090 Vienna, Austria, b) Department of Analytical Chemistry, University of Vienna, Waehringer Strasse 38, 1090 Vienna, Austria, c) Vienna Doctoral School in Chemistry (DoSChem), University of Vienna, Waehringer Str. 42, 1090 Vienna, Austria, d) Department of Chemistry, The University of Chicago, Chicago, Illinois 60637, United States, e) Joint Metabolome Facility, University of Vienna, Waehringer Str. 38, 1090 Vienna, Austria.

yasmin.borutzki@univie.ac.at

Over the last 10 years, there has been a surge of interest in theranostic agents that allow treatment of a disease in parallel with monitoring capabilites.[1] Combining therapy and imaging potentially provides an immediate statement about the effectiveness of the treatment. However, there are still substantial challenges related to this technology, like the simultaneous optimization of dose-dependent therapy and imaging. To address these issues, some of us have recently discovered a new near-infrared (NIR) emitting organometallic platinum tetrathiafulvalenetetrathiolate ($Pt_2(COD)_2TTFtt$) complex. This compound features an efficient emission in the second NIR window, whose full biological transparency enables deep tissue imaging at comparatively low concentration.[2] Furthermore, the platinum moiety mimics the established cytotoxic drugs that are approved for various therapies. [3]

Here, we are investigating the biological activity of $Pt_2(COD)_2TTFtt$ in different scenarios of light exposure, including cell viability tests, reactivity towards proteins and biological nucleophiles, as well as proteomic response profiling in platinum-sensitive ovarian cancer cells. We are particularly interested in the light-dependent reactivity of $Pt_2(COD)_2TTFtt$ to deconvolute species-specific drug effects in cancer cells.

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Novel Activation Mechanisms for Rhodium(III) Cyclopentadienyl Complexes

Edward C. Lant,[1] Samya Banerjee,[1,8],[1] Juliusz A. Wolny, [1]Bryan Marzullo,[1] Jingsha Xu,[1] Marc Walker,[4] Christopher A. Wootton,[5] Guy J. Clarkson,[1] Volker Schünemann,[1] Peter B. O'Connor[1], and Peter J. Sadler[1*]

[1]Department of Chemistry, [2]Division of Biomedical Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL, UK.[3]Department of Physics, Technische Universität Kaiserslautern, Kaiserslautern, Germany. [4]Department of Physics, University of Warwick, Coventry CV4 7AL, UK. [5]Bruker Daltonik GmbH, Bremen, Germany, [8] Department of Chemistry, Indian Institute of Technology (BHU), Varanasi, UP-221005, India

The Cp x C-H protons in certain organometallic RhIII half-sandwich anticancer complexes [(η5-Cp x)Rh(N,N')Cl]+, where Cp x = Cp*, phenyl or biphenyl-Me4Cp, and N,N' = bipyridine, dimethyl bipyridine, or phenanthroline, can undergo rapid sequential deuteration of the 15 Cp* methyl protons in aqueous media at ambient temperature (1,2,4). DFT calculations suggest a mechanism involving abstraction of a Cp* proton by the Rh-hydroxido complex, followed by sequential H/D exchange, with the Cp* rings behaving like dynamic molecular 'twisters' (Fig.1). Calculations show the crucial role of pπ orbitals of N,N'-chelated ligands in stabilizing deprotonated Cp x ligands, and the accessibility of RhI-fulvene intermediates (4). We readily trapped and characterized RhI-fulvene intermediates by Diels-Alder [4+2] cyclo-addition reactions with the natural biological dienes isoprene and conjugated (9Z,11E)-linoleic acid in aqueous media, including cell culture medium (Fig.1). These findings will introduce new concepts into the design of organometallic Cp* anticancer complexes with novel mechanisms of action (3,4)

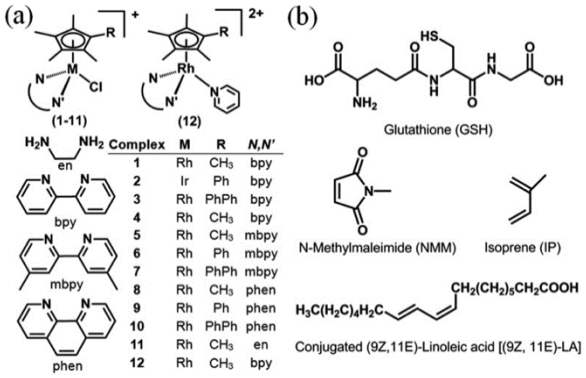

Figure 1

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