ISBOMC 25

International Symposium on Bioorganometallic Chemistry 2025

Abstract Book

Société Chimique de France - French Chemical Society

Program at glance

Tuesday 26th August	Wednesday 27th August	Thursday 28th August	Friday 29th August
	Session 3 *Chair: Angela Casini*	**Session 7** *Chair: Richard Fish*	**Session 11** *Chair: Gilles Gasser*
	PL1: 09:00-09:45 **Loi Do**	PL2: 09:00-09:45 **Maria Contel**	AL: 9:30-10 :15 **ISBOMC Award Winner**
PL: Plenary Lecture (40+5 min)	SL8: 09:45-10:00 Benoit Bertrand	SL23: 09:45-10:00 Christophe Biot	SL36: 10:15-10:30 Angelo Frei
AL: Award Lecture (40+5 min)	SL9: 10:00-10:15 Ghannish Soogary	SL24: 10:00-10:15 Pezhman Ashoo	SL37: 10:30-10:45 Dinorah Gambino
	SL10: 10:15-10:30 Chung-Hang Leung	SL25: 10:15-10:30 Nicola Brasch	SL38: 10:45-11 :00 Fabio Zobi
KL: Keynote Lecture (20+5 min)	**Coffee Break** 10:30-11:00	**Coffee Break** 10:30-11:00	**Coffee Break** 11:00-11:30
IL: Invited Lectures (17 + 3 min)	**Session 4** *Chair: Greg Smith*	**Session 8** *Chair: Ana Pizarro*	**Session 12** *Chair: Loi Do*
SL: Short Lectures (12 +3 min)	IL4: 11:00-11:20 **James Coverdale**	IL8: 11:00-11:20 **Malay Patra**	IL13: 11:30-11:50 **Thomas Scattolin**
	SL11: 11:20-11:35 Melaine Wang	SL26: 11:20-11:35 Yong Wang	SL39: 11:50-12 :05 Konrad Kowalski
	SL12: 11:35-11:50 Felix Böhm	SL27: 11:35-11:50 Priyankar Paira	SL40: 12:05-12:20 Zhigang Wang
Registration: 12:00-13:30	IL5: 11:50-12:10 **Éva Anna Enyedy**	IL9: 11:50-12:10 **Camilla Abbehausen**	KL4: 12:20-12:45 **Ana M. Pizarro**
Opening of ISBOMC 2025: 13:30-13:40 **Kevin Cariou & Gilles Gasser**	**Lunch** 12:10-14:00	**Lunch** 12:10-14:00	**Farewell / Annoncements** 12:45-13:00
Session 1 *Chair : Ingo Ott*	**Session 5** *Chair: Maria Contel*	**Session 9** *Chair: Ken Lo*	
KL1: 13:40-14:05 **Kenneth Lo**	KL2: 14:00-14:25 **Hannah Shafaat**	KL3: 14:00-14:25 **Justin Wilson**	
SL1: 14:05-14:20 Maria C. Gimeno	SL13: 14:25-14:40 Timothy Curran	SL28: 14:25-14:40 Chris Adams	
SL2: 14:20-14:35 Ronan Le Lagadec	SL14: 14:40-14:55 Marcel Annereau	SL29: 14:40-14:55 Oliver Scholtyssek	
IL1: 14:35-14:55 **Bogna Rudolf**	SL15 14:55-15:10 David Husbands	SL30: 14:55-15:10 Saverio Santi	
SL:-3 14:55-15:10 Greg Smith	SL16: 15:10-15:25 Carlos G. Navarro	SL31: 15:10-15:25 Wanhe Wang	
IL2:- 15:10-15:30 **José Ruiz**	SL17: 15:25-15:40 Annie Castonguay	SL32: 15:25-15:40 Tânia Morais	
Coffee Break 15:30-16:00	IL6 : 15h40-16h00 **Amanda Jarvis**	IL10: 15h40-16h00 **Felix Zelder**	
Session 2 *Chair : Annie Castonguay*	**Coffee Break** 16 :00-16:30	**Coffee Break** 16 :00-16:30	
IL3: 16:00-16:20 **Anaïs Pitto-Barry**	**Session 6** *Chair: Justin Wilson*	**Session 10** *Chair: Hannah Shafaat*	
SL4: 16:20-16:35 Chen Chen	IL7: 16:30-16:50 **Takashi Matsuo**	IL11: 16:30-16:50 **Alessandro Marrone**	
SL5: 16:35-16:50 G. Moreno-Alcántar	SL18: 16:50-17:05 M. Muñoz-Osses	SL33: 16:50-17:05 Maria GiLMoles	
SL6: 16:50-17:05 Angela Casini	SL19: 17:05-17:20 Sara Benetti	SL34: 17:05-17:20 Giulia Saggiotti	
SL7: 17:05-17:20 Georgia Lisney	SL20: 17:20-17:35 Igor Esarev	SL35: 17:20-17:35 Michael McGlinchey	
17:20-17:35 In memoriam **Toshikazu Hirao**	SL21: 17:35-17:50 Rianne Lord	IL12: 17:35-17:55 **Toshiyuki Moriuchi**	
	SL22: 17:50-18:05 Damian Plazuc	**Free time**	
Poster Slam: 17:40-18h00	**Poster Session + Drinks** 18:05-21:00	**Conference Dinner** 20:00-23:00	
Welcome Reception 18:00-21:00			

Loi DO

University of Houston
United States

BIOGRAPHY

Loi Do obtained a B.S. in Chemistry/Biochemistry at the University of California, San Diego where he conducted undergraduate research with Prof. Seth M. Cohen on supramolecular chemistry. He completed a Ph.D. under the tutelage of Prof. Stephen J. Lippard, working on synthetic diiron protein modeling chemistry, and then conducted postdoctoral training with Prof. John E. Bercaw at the California Institute of Technology, where he investigated the mechanism of selective ethylene trimerization by homogeneous chromium complexes. Loi joined the faculty in the Department of Chemistry at the University of Houston in September 2013 and was promoted to Associate Professor with tenure in 2019 and Professor in 2024.

PL1
Abiotic Catalysis for Life: A Report on Our 10+ Years Journey

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Although enzymes have evolved over millions of years to achieve specific cellular functions, chemists must rely on the synthetic toolbox to create abiotic catalysts from the ground up. In this presentation, we will describe our decade-long effort to develop small-molecule intracellular metal catalysts (SIMCats) that can interface with biological systems. The key discovery that sparked our research was the finding that half-sandwich Ir picolinamidate complexes could catalyze the reduction of aldehydes to alcohols in living cells, which was surprising given that other structurally similar Ir complexes were incapable of doing so. Since then, we have learned how to engineer these Ir SIMCats with additional functions, such as H_2O_2 production, cell tracking, and subcellular targeting, while maintaining their catalytic performance. Understanding the Ir SIMcats' properties allowed us to exploit them for therapeutic applications. For example, we have shown that they are highly effective as detoxification agents against reactive aldehyde species, which are cytotoxic compounds that are implicated in numerous human diseases (e.g., cardiovascular disease, neurodegenerative disorders, and cancer). To expand the capabilities of our Ir SIMCats even further, we have developed the first selective method to convert aldehydes to primary amines in living cells using an Ir-promoted reductive amination strategy. We will discuss how these latest advances will open new research opportunities by offering unprecedented ways to manipulate biological systems. Based on our 10+ years journey in bioorganometallic chemistry, we believe that much is yet to be explored at the chemistry-biology interface and many more surprises are likely to emerge along the way.

Maria CONTEL

Brooklyn College, The City University of New York
United States

BIOGRAPHY

Maria Contel graduated from the University of Zaragoza in 1993 and completed her PhD (Chemical Sciences) at the Public University of Navarra in 1996. After postdoctoral stays at the Australian National University, and at Utrecht University in the Netherlands, she returned to Spain (Universidad de Zaragoza-CSIC) as senior researcher in 2000 and became “Ramon y Cajal” Fellow in 2002. In 2006, she joined the Chemistry Department at Brooklyn College (The City University of New York, CUNY) becoming a Full Professor in 2016, and Department Chair (2017-2020). She is a faculty member at the CUNY Graduate Center in three doctoral programs (Biochemistry, Biology, and Chemistry). Dr. Contel has been funded by the National Institutes of Health since 2010, and has published over eighty articles and chapter of books, and was issued three US patents. She has organized international, national, and regional meetings and symposia. Her current research focuses on the synthesis of inorganic compounds with medicinal applications, the study of the biological activity and modes of action of these agents, and the development of targeted therapies through the use of nanotechnology. She has mentored numerous researchers and faculty members at different stages in their careers (mostly women and members of underrepresented groups in biomedical research). As Director of the Brooklyn College Cancer Center (BCCC-CURE) that she co-founded in 2020, she has led the development of partnerships with cancer centers, medical schools, and research institutes in Brooklyn and in the NYC area (including SUNY Downstate Health Sciences University). She has secured institutional grants from American Cancer Society (Diversity in Cancer Research Institutional Development Grant (DICR IDG) Program) and the Gray Foundation to fund operations, research, educational and community outreach activities at BCCC-CURE.

PL2
Gold(I)-Based Compounds: Unlocking Their Potential as Anticancer Chemotherapeutic and Targeted Agents

Maria Contel[a-e,*]

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Gold compounds are now well-recognized for their anticancer properties, and their interactions with the immune system—particularly their ability to enhance immunogenicity—are increasingly being elucidated [1]. In this talk, I will present an overview of research carried out in my laboratory over the past 14 years on the anticancer activity of gold(I) and gold(I)-based heterometallic compounds, investigated in vitro, in cellulo, and in mouse models, including recent and unpublished results. Our studies encompass pharmacokinetic and histopathological analyses, which have demonstrated remarkably low systemic toxicity for several of the compounds evaluated [2]. I will also highlight recent findings on the ability of selected gold-based agents to induce immunogenic cell death.

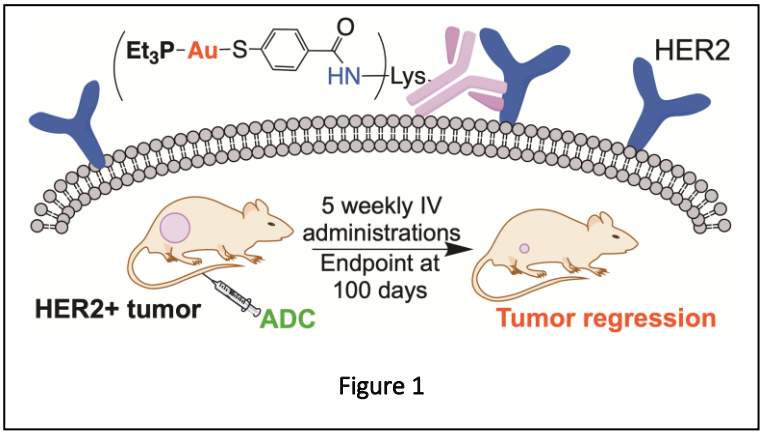

Figure 1

Additionally, I will feature strategies developed in my group to enhance the safe delivery and tumor-targeting capabilities of gold(I) compounds, one example of which is illustrated in Figure 1 [3–4]. Targeted therapies represent a cornerstone of personalized medicine, offering treatment approaches tailored to a patient's tumor's specific genetic and molecular features. These types of strategies are expected to play a pivotal role in advancing the translational potential of gold-based chemotherapeutics in oncology. Finally, I will present preliminary results on the development of gold-based targeted theranostic agents, which integrate therapeutic and diagnostic functions within a single platform.

References

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Kenneth Kam-Wing LO

City University of Hong Kong
Hong Kong

BIOGRAPHY

Professor Kenneth Kam-Wing Lo obtained his BSc and PhD degrees from The University of Hong Kong. He then worked as a Croucher Foundation Postdoctoral Research Fellow in the Inorganic Chemistry Laboratory at the University of Oxford. In 1999, he joined the Department of Biology and Chemistry (now the Department of Chemistry) at City University of Hong Kong as an Assistant Professor, and he has been a Chair Professor since 2023. His research interests include the utilization of luminescent inorganic and organometallic transition metal complexes as biomolecular probes, cellular imaging reagents, and photocytotoxic agents. He received the APA Prize for Young Scientist from the Asian and Oceanian Photochemistry Association in 2005 and the Distinguished Lectureship Award from the Chemical Society of Japan in 2011. In 2015, he was awarded a Croucher Senior Research Fellowship from the Croucher Foundation and was admitted as a Fellow of the Royal Society of Chemistry (FRSC) in 2018. He received the Elsevier Lectureship Award from the Japanese Photochemistry Association in 2024.

KL1
Photofunctional Bioconjugates with Transition Metal Complexes for Theranostic Applications

Kenneth Kam-Wing Lo*

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Site-specific bioconjugation plays a critical role in biochemistry and biomedicine by enabling the covalent attachment of functional moieties, such as fluorescent tags or cytotoxic agents, to biomolecules. We have a long-standing interest in photofunctional transition metal complexes for theranostic applications due to their attractive photophysical and photochemical properties. These properties include high photostability, large Stokes shifts, long emission lifetimes, and efficient reactive oxygen species generation. Conjugating these complexes to peptides or proteins produces new bioconjugates with interesting biological behaviors, such as receptor targeting, cell penetration, organelle targeting, enzyme responsiveness, and self-assembly capabilities, thereby enhancing their theranostic potential. In this lecture, I will describe our recent designs of photofunctional transition metal complexes as bioconjugation reagents for constructing peptide- and protein-based theranostic agents using various chemoselective strategies. The focus will be on elucidating the photophysical and photochemical properties, cellular uptake behavior, and photocytotoxic activity of the conjugates, highlighting their potential in precise cancer imaging and phototherapy.

References

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Hannah SHAFAAT

UCLA
United States

BIOGRAPHY

Hannah Shafaat's scientific career began at Caltech, where, in addition to earning a B.S. in Chemistry in 2006, she became enamored with the research enterprise while developing spectroscopic endospore viability assays with Adrian Ponce at NASA's Jet Propulsion Laboratory. She earned her Ph.D. in Physical Chemistry from the University of California, San Diego (UCSD) in 2011, under the direction of Professor Judy Kim, investigating amino acid radical intermediates in biological electron transfer reactions. Hannah was awarded a Humboldt Foundation Postdoctoral Fellowship and traveled across the ocean to Germany to study hydrogenase and oxidase enzymes and learn advanced EPR techniques working under Director Wolfgang Lubitz at the Max Planck Institute for Chemical Energy Conversion. She started her independent career in 2013 at The Ohio State University, initially developing hydrogenase mimics and expanding into the study of one-carbon activation reactions and organonickel proteins. Hannah's group also studies new classes of Mn/Fe oxidase enzymes. In recognition of her research on metalloproteins, Hannah was awarded the 2018 Sloan Research Fellowship. Hannah Shafaat and her group moved to UCLA in 2023 and have been enjoying the science, sun, and scenery of Southern California!

KL2

Nickel: A central element in Nature's organometallic toolkit

Alina Yerbulekova[a,b], Kathryn G. Woodburn[a], Kevin E. Rivera Cruz[a], Isaiah A. Ervin[a], Adam J. Jenkins[c], Hannah S. Shafaat[a,b,c,*]

[a] Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA USA
[b] Ohio State Biochemistry Program and [c] Department of Chemistry and Biochemistry, The Ohio State University, Columbus, OH USA
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Nickel-containing metalloenzymes catalyse challenging chemical reactions vital to microbial metabolism, including controlling global carbon and hydrogen gas cycles, where the generation of nickel-carbon bonds is considered to be essential. The cornerstone enzyme of the ancient Wood-Ljungdahl pathway, carbon monoxide dehydrogenase/acetyl coenzyme A synthase (CODH/ACS), catalyses the reduction of carbon dioxide to carbon monoxide at one nickel site and subsequent formation of new carbon-carbon and carbon-sulphur bonds at another nickel site to generate acetyl coenzyme A. However, the molecular mechanisms of catalysis in CODH/ACS remain relatively poorly understood owing to the presence of multimetallic active sites and auxiliary cofactors along with inherent enzyme fragility. We seek to understand how these small-molecule transformations are carried out and, more specifically, address the central role of nickel-carbon bonding in mediating enzymatic selectivity and efficiency. Towards this end, we have developed protein-based models of CODH and ACS that recapitulate key electronic structure elements along with reactivity, including substrate binding and conversion. By combining functional studies of our model proteins with diverse spectroscopic techniques and computational investigations, we can obtain a comprehensive understanding of how the electronic and geometric structures dictate reactivity in each system. Metal-ligand covalency is directly interrogated and an "inverted ligand field" has been identified within our biochemical model of ACS, where it has been implicated as a mechanism for mitigating unproductive but accessible side reactions. Looking forward, we hope to apply these principles towards engineering effective systems for energy conversion processes while learning about fundamental bioorganometallic transformations that may underlie the evolution of prebiotic carbon utilization in early life.

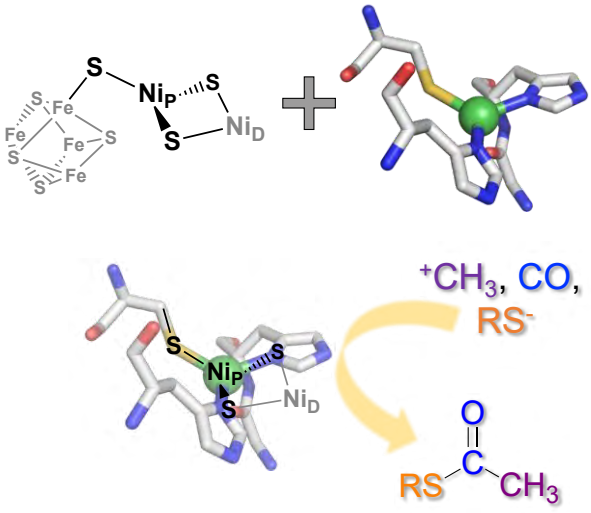

Figure 1 Mapping the metallocofactor of acetyl coenzyme A synthase (ACS) active site (*left*) onto the M121A Ni^{I}Az active (*right*) highlights the development of a protein-based model for catalyzing bioorganometallic transformations analogous to ACS.

Justin WILSON

University of California Santa Barbara
United States

BIOGRAPHY

Justin Wilson began his research career as an undergraduate in the lab of Prof. Jeff Long at UC Berkeley, where he investigated cyanide-bridged transition metal clusters as single-molecule magnets. After graduating in UC Berkeley with Highest Honors and the Departmental Citation in 2008, he began is PhD studies in Inorganic Chemistry at the Massachusetts Institute of Technology under the mentorship of Prof. Stephen J. Lippard. Justin's graduate research focused on the design and investigation of novel platinum-based anticancer drug candidates, for which he received the annual Davison Prize for best inorganic thesis.

From 2008–2013, Justin was a Seaborg Institute Postdoctoral Fellow at Los Alamos National Laboratory, where he worked with Dr. Eva Birnbaum on radioisotope production, separation, and ligand design.

In 2013, Justin began his independent career as an assistant professor in the Department of Chemistry and Chemical Biology at Cornell University, and was subsequently promoted to the rank of associate professor with tenure in 2021.

In 2024, Justin joined the Department of Chemistry & Biochemistry at UC Santa Barbara as a professor. His research program has been recognized by a number of awards including the Cottrell Scholar Award, the Jonathan Sessler Award for Emerging Leaders in Bioinorganic and Medicinal Inorganic Chemistry, the Ed Stiefel Young Investigator Award at the Metals in Biology Gordon Research Conference, and the National ACS Harry Gray Award for Creative Work in Inorganic Chemistry by a Young Investigator.

KL3
Cytotoxic Rhenium(I) Carbonyl Complexes with Novel Mechanisms of Action and Imaging Capabilities

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Since the discovery of the biological properties of cisplatin, there have been substantial efforts to find alternative cytotoxic metal-based drug candidates.[1] Because of limitations associated with conventional platinum-based drugs, researchers have investigated coordination and organometallic complexes of alternative metal centers. In this presentation, we discuss efforts to implement rhenium(I) tricarbonyl complexes as novel anticancer agents with the potential for imaging applications.[2] By modifying their structures, compounds with similar cytotoxicities as cisplatin can be obtained.[3] Mechanistic studies show that they exhibit distinct profiles of activity compared to the platinum-based drugs. This property is advantageous because they lack cross resistance with these drugs. Furthermore, the mechanism of action of these compounds were investigated.[4] The most potent candidates within this class were found to elicit endoplasmic reticulum stress, a consequence of their ability to induce protein misfolding.[5] Lastly, the results of in vivo antitumor studies are also described, and they highlight the promising therapeutic potential of these compounds.

References

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Ana PIZARRO

IMDEA Nanociencia
Spain

BIOGRAPHY

Ana M. Pizarro completed a PhD in Chemistry from the Universidad Autónoma de Madrid in 2004, focusing on trans-platinum cytotoxic compounds, under the supervision of Professor Carmen Navarro-Ranninger. She then received a Marie Curie Individual Fellowship to conduct research at The University of Edinburgh under Professor Peter Sadler FRS, exploring new ruthenium-based organometallics. She continued her work with Prof. Sadler at The University of Warwick, investigating how selected metallodrugs exert their anticancer effects in tumour cells. In 2014, she joined IMDEA Nanociencia (Madrid) as a Ramón y Cajal Fellow. She got tenure in April 2019.

Pizarro leads the Molecular Metallodrugs research group at IMDEA Nanociencia. Her main research interest lies in exploiting the extraordinary features of transition metal complexes inside the human cell to interfere and modulate its machinery: (i) at the molecular level, fully understanding metal-based chemistry inside the cell, (ii) at the organelle level, identifying chemistry confinement, and (iii) in a timeline.

KL4
Rhodium(III) tethered half-sandwich organometallic complexes with potent anticancer activity

Arturo Villechenous, Vanessa Rodríguez-Fanjul, Ana M Pizarro[a,*]

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Organometallic and coordination bonds possess accessible energy dynamics that make them powerful tools to interact with the components of a biological system. The metal-mediated chemistry of organometallic complexes can be finely tuned—either activated or suppressed—through careful selection of the metal centre and its surrounding ligands. It is the delicate balance between reactivity and inertness that gives metal complexes exceptional potential in the densely packed intracellular environment.

In our group, we synthesize half-sandwich complexes of rhenium, ruthenium, osmium, cobalt, rhodium, and iridium. Structurally, these complexes incorporate a tether ring capable of reversible opening and closing—a switch-like mechanism that enables controlled access to the metal's coordination sphere in the human cell, thus enabling substitution reactions and triggering an intracellular response. In previous work, we have used hemilabile ligands in Ru(II)- and Os(II)-arene complexes, as well as Ir-Cp*R systems, to this purpose with great success.[1,2]

Here, we present highly potent rhodium(III) tethered half-sandwich complexes (example in Figure 1) that exhibit unprecedented cytotoxicity. We propose that, much like their Ir(III) analogues, the rhodium centre is effectively shielded from excessive reactivity, allowing for selective accumulation at the target organelle—mitochondria—[3] and this results in potent cytotoxic effects.

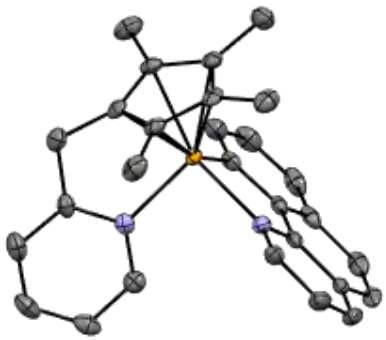

Figure 1 ORTEP diagrams for complex Rh(η^5:κ^1-$C_5Me_4CH_2py$)(Phpy)]$^+$

I will outline our current efforts to understand intracellular speciation and to unravel the cascade of events culminating in cell death, with a particular focus on the role of the mitochondrial, as we work toward mapping the full intracellular journey of our rhodium-based anticancer candidates.

References

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[3] Conesa, J. J.; Pizarro, A. M. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 1270-1278.

Bogna RUDOLF

University of Lodz, Faculty of Chemistry
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BIOGRAPHY

Bogna Rudolf obtained her PhD in 1998 at the University of Lodz (Poland). After a few post-doc positions in France (ICSN Gif-sur-Yvette, ENSCP Paris) she obtained her habilitation in 2011 at the Faculty of Chemistry, University of Lodz where she started her independent career. Her Team research interests encompass the synthesis of organometallic compounds and their application in biochemistry (anticancer drugs, antioxidants, metallocarbonyl labels, enzyme inhibitors, CO releasing molecules (CORMs).

IL01
Piano-stool Fe(II)/Ru(II) carbonyl complexes bearing 1,10-phenantroline or 2,2'-bipyridine ligands: Synthesis, characterization, and cytotoxicity studies

Bogna Rudolf*

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Organometallic complexes containing transition metals like Fe, and Ru are being massively investigated for their versatile biochemical applications. In the literature, there are many examples of ruthenium complexes having antitumor activity[1] and much less for iron ones[2]. Half-sandwich organoruthenium complexes are divided into two subtypes according to their structure-activity parameters, namely Ru(η^6-arene) and Ru(η^5-cyclopentadienyl) complexes. Ru(η^5-cyclopentadienyl)-derived complexes are less widely investigated comparing to Ru(η^6-arene) compounds, however, they have also shown promising activity against cancer cell lines.[3] The half-sandwich organoruthenium complexes of both types based on bidentate ligands were found to be potent anticancer agents.[4] Many of these complexes exert their antiproliferative activity via ligand-exchange mechanisms, having at least one labile ligand.[5]

Herein, we report a series of (η^5-cyclopentadienyl)M^{II}(CO) complexes (M = Fe, Ru) with 1,10-phenantroline or 2,2'-bipyridine ligands, their synthesis, characterization, X-ray diffraction analysis followed by their activity on breast cancer adenocarcinoma cells MCF-7, hepatocellular carcinoma HepG2 and lung carcinoma A549. To elucidate the potential mode of action of the investigated complexes, we treated MCF-7 cells with the compounds under study at a concentration corresponding to their IC_{75} for 24 h and proceeded to cell cycle analysis. We have also measured the DNA intercalation potential of the investigated compounds by capillary viscometry. In the search for new anticancer drugs, the selective activity of these complexes toward different cancer cells is of key importance. For this reason, iron(II) and ruthenium(II) complexes described here are expected to open new ways for anticancer research.

References

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BIOGRAPHY

Prof. José Ruiz received his PhD in Chemistry in 1984 at University of Murcia (UMU). Afterwards, he moved to the Sheffield University (UK), where he spent 2 years as a Post-doctoral Researcher in the P.M. Maitlis group, working in transition organometallic hydrides. In 1987, he got a permanent position as a Lecturer at UMU. Since 2002, he started his independent career and drove his interest towards the field of Medicinal Inorganic Chemistry. In 2007, he became Professor at UMU and founded the Metallodrugs Discovery Group. He is also leader of the Non- Conventional Anticancer Metallodrugs Group at the Murcian Institute of Biosanitary Research (IMIB). He has served as President of the Spanish Society of Bioinorganic Chemistry (AEBIN, 2017-2022). Throughout his scientific career, he has authored more than 130 publications in peer-reviewed international journals, leading to more than 4,600 citations. His h-index is 40. Prof Ruiz has supervised 13 Doctoral Theses. Since 2013 he secured over 750k € in funded research grants.

IL02

Novel heteroleptic iridium(III) complexes containing COUBPY ligands for effective and biocompatible photodynamic cancer therapy

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Cancer remains leading cause of morbidity and mortality worldwide, underscoring the need to develop more effective and selective treatment modalities. Photodynamic therapy (PDT) is an approved and promising medical treatment modality with high spatial and temporal precision and minimal invasiveness. The photogeneration of multiple reactive oxygen species (ROS) not only enhances PDT's effectiveness but also induces ferroptosis, particularly in tumors with imbalanced redox homeostasis. Iridium(III) complexes with the structure $[Ir(C^N)_2(N^N)]^+$ have been widely investigated as luminescent and photosensitizing materials. Although these photosensitizers (PSs) show great promise for cancer treatment, their relatively low molar absorption coefficients at long wavelengths make them ineffective for treating deep solid tumors. Very recentlv, Marchán et al. have described a family of potent PSs based on Ru(II) polypyridyl complexes (Figure 1B) incorporating 2.2'-bipyridyl ligands derived from COUPY coumarins, termed COUBPYs [1]. Herein, we describe for the first time the synthesis and biological evaluation of Ir-COUBPY complexes as new PSs.

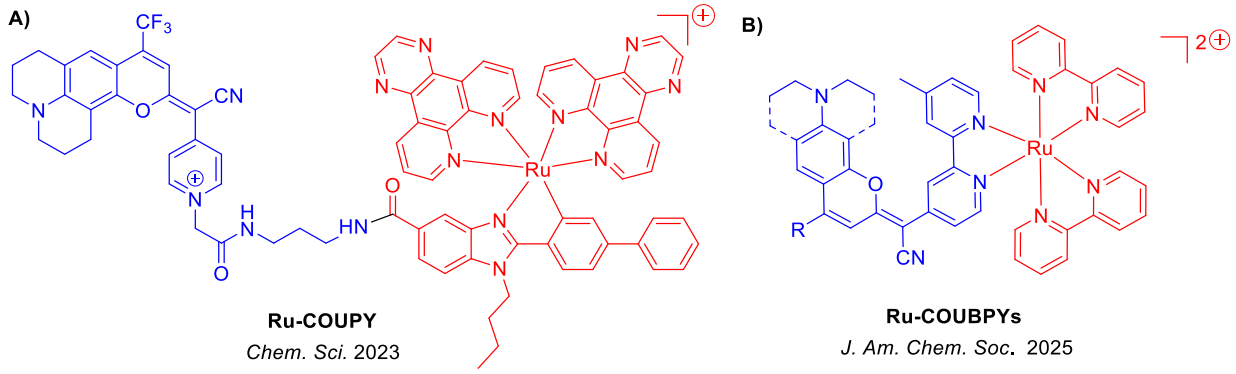

Figure 1. Chemical structures of Ru(II)-COUPY (A) and Ru(II)-COUBPY (B) reported by Marchán et al. [1]

Acknowledgments

This work This work was supported by funds from the Spanish Ministerio de Ciencia, Innovación y Universidades and Agencia Estatal de Investigación (MICIU/AEI/10.13039/501100011033) (PID2023-146161OB-I00 to V.M.; PID2021-122850NB-I00 to J.R.), by "ERDF A way of making Europe." (PID2023-146161OB-I00 to V.M.; PID2021-122850NB-I00 to J.R.), and Fundación Séneca-CARM (project 21989/PI/22 to J.R.) and the Fundació "la Caixa" (CaixaImpulse Innovation project LCF/TR/CI23/56000013 to V.M.). A.H.-G. thanks Fundación Séneca-CARM for a grant (project 21426/FPI/20).

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Anaïs PITTO-BARRY

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BIOGRAPHY

Anaïs Pitto-Barry was appointed as CNRS Researcher at the Institut Galien Paris-Saclay (Université Paris-Saclay, France) in 2021 after starting her independant scientific career at the University of Bradford (UK) in 2019. Previously, she obtained her PhD degree from the University of Neuchâtel (Switzerland) with Prof. R. Deschenaux where she focused on the mesomorphic or biological properties of dendritic and metallodendritic assemblies. In 2012, she joined the University of Warwick (UK) to work with Profs R.K. O'Reilly FRS and A.P. Dove on the synthesis, self-assembly, and characterisation of polymeric micelles. She then worked with Profs P.J. Sadler FRS and N.P.E. Barry on the applications of metallated compounds at the University of Warwick and the University of Bradford. Her research interests encompass the use of polymers for the transport of inorganic compounds for biomedical applications. Her research activities focus on the design of polymers used as cargo to carry organometallic complexes or boron atoms for cancer applications.

IL03
Using polymers for the delivery of organometallics

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Cancer is projected to claim up to 24 million lives worldwide by 2030, with economic costs expected to surpass 20 trillion euros by 2050 if no further investments are made in research and prevention.[1] Despite significant advancements in chemotherapy, major challenges persist, particularly drug resistance and toxicity, which hinder treatment efficacy and patient outcomes. Inorganic compounds, due to their diverse structural and electronic properties, offer promising alternatives to conventional organic drugs, enabling the design of therapeutics with specific functionalities.[2] Among them, organometallic compounds have gained increasing attention for their unique mechanisms of action and potential for targeted therapy. However, efficient delivery remains a crucial challenge in their clinical translation.

To address this, polymer-based systems are being increasingly explored as carriers for organometallic drug candidates, offering enhanced solubility, controlled release, and improved bioavailability.[3,4] We will present various strategies we have recently developed for the delivery of organometallics, including chemical binding to monomers or preformed polymers and ligand modifications on metal complexes. Additionally, we will discuss our latest syntheses of organometallic compounds, their biological properties, and their overall therapeutic potential. By leveraging polymeric delivery systems, these approaches may contribute to the advancement of more effective and targeted cancer treatments.

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James COVERDALE

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BIOGRAPHY

Dr James Coverdale is a Chartered Chemist (CChem) and Assistant Professor in Pharmaceutical Biology at the University of Birmingham, where team are developing new metalloproteomic and elemental mass spectrometry techniques to study the subcellular fate of catalytic anticancer metallodrugs in cells. James was part of the team awarded the Royal Society of Chemistry Horizon Prize for “pioneering work on catalysis of redox reactions by synthetic organometallic complexes” and received the 2024 Royal Society of Chemistry Spectroscopy Award for his contribution to the field.

IL04

Boron quantitation in live cells by single-cell inductively coupled plasma mass spectrometry

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Boron capture neutron therapy (BNCT) combines neutron irradiation with a boronated therapeutic which can undergo neutron capture to elicit a localised cell kill effect. Methods to quantify intracellular boron are limited: in vivo tumoral boron levels are inferred from circulatory concentrations, while in vitro sample preparations often overlook rapid boron pharmacokinetics. By considering both analytical sample preparation requirements and biological boron dynamics, two novel approaches to quantify intracellular boron have been developed: (1) rapid in situ tryptic and acidic digestion of treated cells to avoid premature B efflux (LOD = 0.2-0.4 µg/L) with method suitability confirmed by pre- and post-digestion spike recoveries of 102.5 ± 0.5% and 103 ± 3%, respectively; (2) real-time measurement of boron in live cells without the use of chemical fixation, using single-cell ICP-MS (scICP-MS) revealing real-time monitoring of boron efflux: biological half-life of ca. 6 min. These complementary approaches deliver unprecedented insight into boron influx and efflux and provide essential bioanalytical tools to advance BNCT therapeutic development.

Keywords: ICP, MS, boron, BNCT, single, cell, cancer, pharmacokinetics, efflux, SC, scICPMS

Éva Anna ENYEDY

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BIOGRAPHY

Prof. Dr. Éva Anna Enyedy is the Head of the Department of Molecular and Analytical Chemistry at the University of Szeged (Hungary) and Leader of the Bioinorganic Chemistry Research Group. Her research focuses on the development and characterization of anticancer metal complexes and organometallic compounds, with respect to their solution speciation and physico-chemical properties that influence their pharmacokinetics. Her studies combine spectroscopic, electrochemical and separation techniques in order to elucidate and understand the relationships between structure, stability, redox activity, interactions with target or transporter macromolecules and biological activity for different families of metal complexes. Correlation analysis of this type of thermodynamic and kinetic data can greatly contribute to a better understanding of the differences in anticancer effects of metal or organometallic complexes. She is the author of over 150 scientific publications with more than 3,000 independent citations.

IL05
Half-sandwich rhodium(III) complexes of bidentate ligands with enhanced drug-like properties against multidrug resistant cancer

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Multidrug resistance (MDR) poses a significant challenge in cancer treatment and is often marked by the overexpression of P-glycoprotein (P-gp), a key efflux drug transporter. MDR cells showed a surprising hypersensitivity to several metal chelating compounds, including 8-hydroxyquinoline (8HQ) and 1,10-phenanthroline (PHEN) derivatives [1]. The introduction of different substituents allows the fine-tuning of their pharmacological and physico-chemical properties. A correlation was found between MDR-selectivity and the pK_a values of the 8HQs, and their mechanism of action was suggested to be linked to intracellular metal complex formation, as they induced iron depletion in MDR cells due to the P-gp-mediated efflux of the iron complexes [2]. Despite the efficacy of these compounds, solubility issues often limit their use *in vivo*. Here, we present the development of half-sandwich Rh(III)(η^5-C_5Me_5) complexes of MDR-selective 8HQ-derived Mannich bases [3], and PHEN derivatives with improved drug-like properties (Figure).

Figure General chemical structure of the studied compounds

The complexes were comprehensively characterized by various spectroscopic methods regarding their structure, stability, co-ligand exchange processes and interaction with human serum albumin (HSA). The most promising complexes of PHEN derivatives possessing high stability, increased solubility and HSA binding were selected for nanoformulation studies, using cross-linked HSA and its combined version with TPGS and PLGA. Cytotoxicity of the complexes was assayed on parental and MDR mono- and cocultured human cancer cells. Some complexes and their encapsulated forms have been identified as optimal candidates for further application.

Acknowledgement: NRDI Fund ANN 149481, TKP2021-EGA-32, and FWF 10.55776/PIN1280424.

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Amanda JARVIS

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BIOGRAPHY

Dr Jarvis conducted her undergraduate studies at the University of St Andrews (Scotland) and received her PhD in Chemistry from the University of York (UK). She then joined the group of Dr Philippe Dauban (ICSN, Gif-sur-Yvette, France) to work on Rh(II)-catalysed nitrene chemistry, before moving back to St Andrews to work with Prof Paul Kamer on the development of artificial metalloenzymes. In 2017, Dr Jarvis started her independent career as a Christina Miller Fellow at the University of Edinburgh (Scotland), and was awarded a UKRI Future Leaders Fellowship in 2019. In 2022, she was promoted to Senior Lecturer. Her group works on combining traditional homogeneous chemistry with biocatalysis through the design of artificial metalloenzymes.

IL06
Engineered and Artificial Myoglobins: electrochemical and catalytic studies

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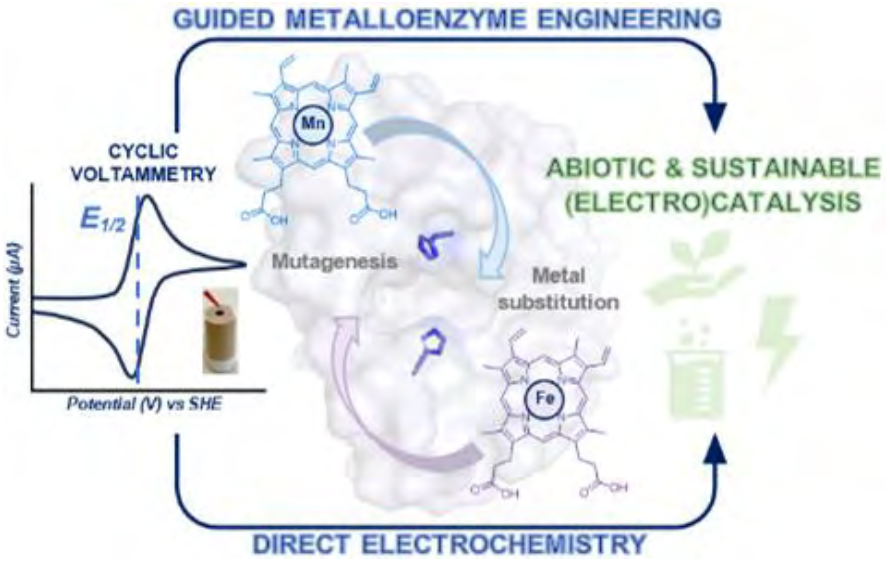
Myoglobin (Mb) is a 18 kDa monomeric globular hemoprotein with a native function in O2 storage. Its malleable architecture makes it an ideal scaffold for artificial metalloenzyme (ArMs) development.[1] Unnatural cofactors such as metalloprophyrins and salophen complexes can be introduced to these scaffolds giving rise to enzymes for abiotic reactions, such as carbene transfer.[2] It has been shown that electrochemical tools can be used to screen and tune the redox activity profile of Mb ArM mutant systems.[3] These tools demonstrate great potential in guiding further engineering of ArM libraries for target applications in redox transformations. We have developed a robust method for non-covalent immobilisation of myoglobin-based ArMs onto pyrolytic graphite electrodes allowing direct electrochemical measurements to determine the redox potentials of both metal-PPIX and salophen Mbs. Here we will present our method for direct electrochemical characterisation alongside catalytic studies focusing on carbene transfer which probed how changes in redox potential and the active site residues of the systems influence catalytic activity and product selectivity.



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BIOGRAPHY

Takashi Matsuo graduated from Kobe University in 1996 and received his Ph.D. degree from Kyoto University in 2001. He then had worked as a post-doctoral fellow at Kyushu University and Osaka University from 2001 to 2006. During this period, he also worked as a visiting scholar at University of Washington (USA) in 2003. In 2006, he was appointed as an assistant professor at Osaka University and was promoted to an associate professor at Nara Institute of Science and Technology in 2009. His current research interests include the application of olefin metathesis catalysts for bio-relevant chemical studies and the regulation of protein functions by protein-protein interactions. He has also conducted mechanistic studies of metal complex-catalysed chemical reactions and enzymatic reactions in terms of physical organic chemistry.

IL07
Chemical Modification of Biomolecules Based on Transition Metal-Olefin Specific Interactions

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Chemical modification of biomolecules using transition metal complexes is a popular strategy for regioselective introduction of synthetic molecules into biomolecules. Olefin metathesis reaction (carbon-carbon rearrangement reaction) catalyzed by Hoveyda-Grubbs 2nd generation (HG-II)-type complexes is a possible method to regioselectively modify biomolecules when the target biomolecules are equipped with olefin moieties. However, the hydrophobicity and reactivity reduction of the metal complexes in water often cause a difficulty in the chemical modification of biomolecules. We should address whether the ruthenium-olefin interaction, a key factor of HG-II-catalyzed olefin metathesis, works effectively in biochemical media.

We have reported ligand exchange reactions in nonpolar solvents between 2-alkoxybenzylide compounds and HG-II.[1] Accordingly, we have synthesized hydrophilic HG-II-type derivatives and investigated whether the ligand exchange also occurs in protic solvents, using an olefin-labelled tripeptide (see Figure 1). When HG-II was applied to Lys-Cys-Phe-OMe with an olefin moiety at the side chain of Cys residue in methanol, the NHC-coordinated ruthenium moiety was transferred onto the olefin moiety in the tripeptide with 80% yield. An HG-II-type complex with a cationic moiety accelerated the ruthenium complex transfer reaction. Furthermore, the complex transfer reaction was found to occur in aqueous media with 50–70% yields. This result indicates that the ruthenium-olefin interaction also occurs in aqueous media. The ruthenium complex transfer was found to occur at olefin-modified cysteine residues on proteins. In fact, the ruthenium complex can be immobilized onto the protein through the ruthenium-olefin interactions. We also attempted interpeptide cross metathesis reactions catalyzed by the cationic HG-II-type complex and confirmed the reaction course. In these reactions, addition of chloride salt is essential for smooth reactions.

In conclusion, ruthenium-olefin interaction (one of the organometallic interactions) can work in aqueous media. Olefin metathesis can be used a method of biomolecule modification.[1,2]

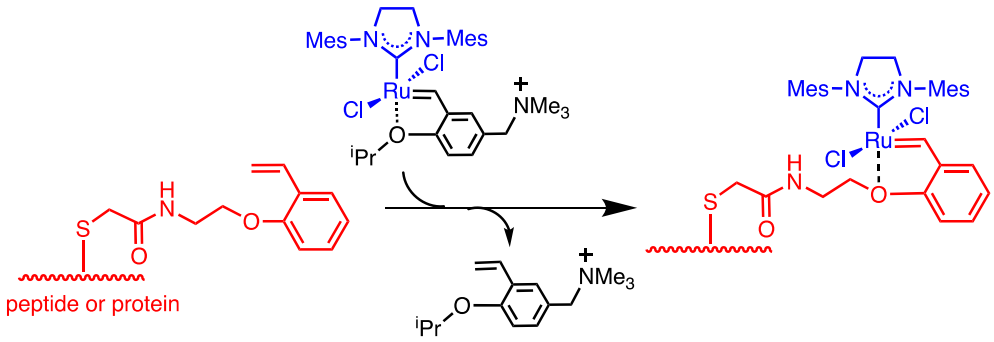

Figure 1 Ruthenium complex transfer reaction on biomolecules

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Malay PATRA

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BIOGRAPHY

Prof. Malay Patra is an Associate Professor with tenure at the Department of Chemical Sciences, Tata Institute of Fundamental Research (TIFR), Mumbai, India. He earned his PhD from Ruhr University Bochum, Germany, and subsequently worked as a post-doctoral researcher at the University of Zurich and the Massachusetts Institute of Technology. He later became a Senior Scientist at the University of Zurich before starting his independent career as a tenure-track Assistant Professor at TIFR, Mumbai. His research focuses on the rational design of multi-targeted anticancer agents, sugar chemistry, targeted drug delivery, and chemical biology. Prof. Patra has published 63 papers in top international journals and holds 10 patents.

IL08

A Single-Agent Strategy to Halt Proliferation, Combat Resistance, and Suppress Angiogenesis

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The intricate pathology of cancer, characterized by its uncontrolled proliferation, resistance to therapy, induction of angiogenesis & metastasis, etc., operating concomitantly, necessitates a paradigm shift from monotherapy using DNA-targeted chemotherapeutics to a multi-target strategy.[1] Multi-targeted drugs act simultaneously on multiple targets essential for the complex pathological processes. Moreover, this strategy reduces the probability of resistance emergence during the treatment cycle, as multiple damaged targets/pathways are difficult to modify and/or repair. Therefore, these drugs will provide an opportunity for prolonged treatment. In addition to this, targeting multiple machineries often leads to improved potency through synergism that is not achievable using single-target drugs. Worthy of note, although multi-targeting using combination therapies (i.e., drug cocktails) has become a well-established clinical approach, multi-targeted single molecule drugs offer numerous advantages, such as i) more predictable pharmacokinetics and pharmacodynamics, ii) reduced risks of drug-drug interactions, iii) simplified mechanistic studies.

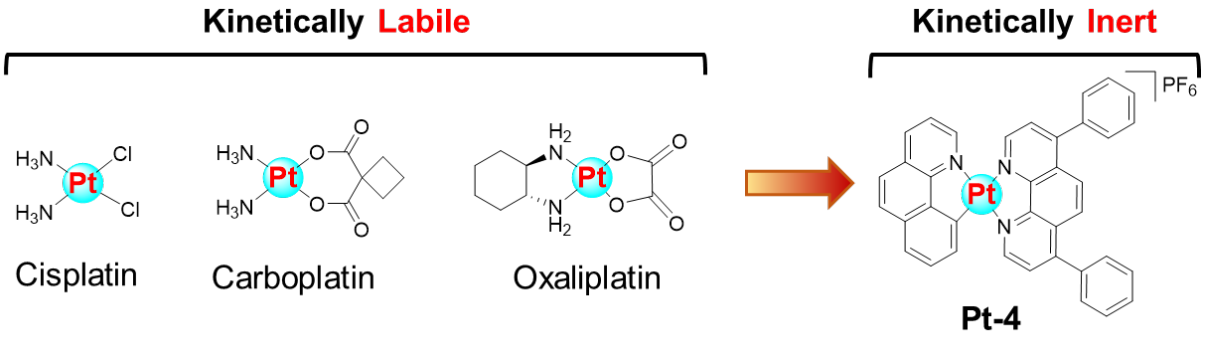

Figure 1: Structure of Kinetically labile platinum drugs and the kinetically inert organometallic Pt candidate drug.

Recognizing the strong correlation between kinetic lability and the shortcomings of current platinum-based chemotherapeutics, we rationally designed a class of kinetically inert organometallic platinum compounds with a multi-targeted mechanism of action (Figure 1).[2,3] Through extensive in vitro and in vivo investigations, we identified a lead candidate that exhibits potent antitumor activity, effectively overcomes cisplatin resistance, and suppresses angiogenesis. Moreover, in comparison to cisplatin, this kinetically inert compound significantly reduces nephrotoxicity. In this presentation, I will discuss the design and development of this single-agent strategy aimed at simultaneously addressing multiple cancer pathologies.

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Camilla ABBEHAUSEN

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BIOGRAPHY

Camilla Abbehausen has been an Associate Professor at the University of Campinas (Brazil) since 2022. She earned her Chemistry degree from the same institution in 2003, where she was awarded the Regional Chemical Council Prize for outstanding academic performance. Prior to her academic career, she worked at Dow Corning Co. in Technical Support for health and personal care applications, earning the prestigious Application Engineer and Technical Service Excellence Prize in 2009.Dr. Abbehausen completed her PhD in Chemistry at the University of Campinas in 2014. Her doctoral and postdoctoral research, under the supervision of Prof. Nicholas Farrell at Virginia Commonwealth University (VCU), focused on the interaction of gold compounds with zinc fingers. In 2015, she joined the University of Campinas as an Assistant Professor, where she established the Research Group on the Study of Metalloenzymes and Metallodrugs (GREMMLENZ). Her research focuses on the intersection of inorganic chemistry and biology, particularly the interaction of metal compounds with proteins and the medicinal applications of metal-based compounds. Currently, she is investigating the effects of organometallic compounds as antiparasitic and antiviral agents.

IL09

Designing Au(I) and Cu(I) Organometallic Therapeutics: Tuning Ligand Exchange for Enhanced Antiviral and Antiparasitic Activity

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In this presentation, we will showcase our systematic efforts to develop therapies for leishmaniasis and viral infections, including arbovirus and SARS-CoV-2, using Au(I) and Cu(I) organometallic compounds. Our recent publications highlight how ligand exchange reactions and lipophilicity in linearly coordinated Au(I) and Cu(I) organometallics play critical roles in designing effective drugs.[1–4]. We investigated a systematic series of four $[AuLL']^{n+}$ (n = 0, +1) complexes, where L is either 1,3-bis(mesityl)imidazole-2-ylidene (IMes) or triphenylphosphine (PPh_3), varied L', always referenced to chloride. In our antiviral assays, the PPh_3-based derivatives inhibited viral replication by 99%, compared to 50% for IMes derivatives. This difference may be attributed to the higher lipophilicity of the PPh_3 derivatives. Although L' dissociates faster than chloride in solution for both IMes and PPh_3 derivatives, this does not significantly affect in vitro activity, suggesting that the biological effects are more influenced by L than by L'.[2] For Cu(I) complexes with NHC ligands ([Cu(I)(NHC)Cl]), we observed that disproportionation in solution generates $[Cu(I)(NHC)_2][Cu(I)Cl_2]$. This product is more lipophilic and consequently more toxic to host cells in infections involving Chikungunya virus or *Leishmania*, which decreases the selectivity index. Using hindered wingtip groups helps control disproportionation, reducing host cell toxicity and improving selectivity. Further, substituting chloride with pyrimidines and thiazolidines enhances ligand exchange in solution, which, while increasing toxicity, also improves antiviral efficacy, but not antiparasitic activity.[5] The best leishmanicidal compounds were screened for trypanothione reductase inhibition and $[Au(Ph_3P)Cl]$ and [$Au(Ph_3P)$(thiazolidine-2-thione)] highlighted among them. *In vivo* studies using Balb/c mice infected with *L. amazonensis* treated with the most selective candidates have shown promising outcome[6]. This body of work illustrates how we can optimize the chemical properties of organometallic compounds to achieve favorable biological results, emphasizing their potential in therapeutic applications.

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Felix ZELDER

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BIOGRAPHY

Felix Zelder is an adjunct professor at the University of Zurich. His research interests focus on fundamental and applied chemistry studies of vitamin B12 derivatives and the development of new analytical rapid tests. In 2009, he was awarded the Mercator Prize of the University of Zurich and a 2nd prize “Emerging Technologies 2016 Food and Water” of the Royal Society of Chemistry.

IL10

Expanding Tetrapyrrole Chemistry: Novel Ni-Substituted B_{12} Analogues for Mimicking F_{430} Reactivity

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Our group is deeply engaged in exploring the structure and function of tetrapyrrole cofactors, with a particular focus on vitamin B_{12} and cofactor F_{430}. Cofactor F_{430}, a nickel-containing hydrocorphinate, plays a central role in the enzymatic formation and oxidation of methane under anaerobic conditions.

In the first part of this lecture, I will present our pioneering efforts to develop a chemical strategy for synthesizing vitamin B_{12} derivatives incorporating metals other than cobalt—specifically nickel, copper, and rhodium.

The second part of the lecture will focus on nickel-substituted B_{12} analogues as biomimetic catalysts for F_{430} function. I will highlight recent electrochemical model studies that replicate key steps of the radical-based mechanism involved in the anaerobic oxidation of methane.

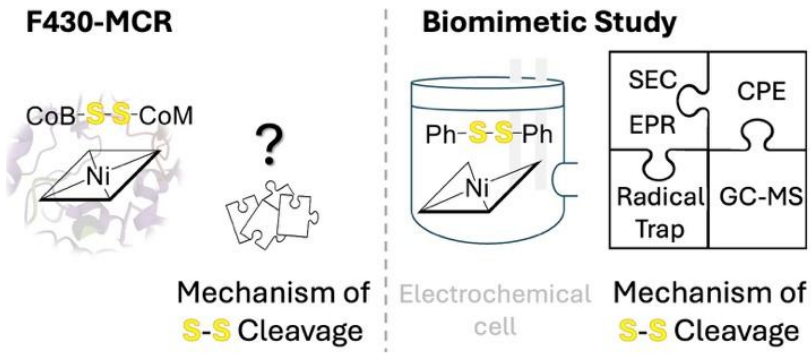

Figure Biomimetic Study (right) of F430-catalysed enzymatic reactions (left).

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BIOGRAPHY

Alessandro studied and started up his academic career in "Università Gabriele d'Annunzio di Chieti-Pescara" (UdA). He took degree in "Medicinal Chemistry and Technology" in 2000 and graduated in Drug Sciences in 2005. Since 2018, Alessandro is associate professor and teaches General and Inorganic Chemistry at the Department of Pharmacy (UdA). His research activity is mainly focused on the application of several computational chemistry methods, ranging from pure QM to empirical methods or based on their combination, to the investigation of inorganic and organometallic systems.

IL11

Computational studies of the parallel β-sheet nucleation by Fe-W bimetallic scaffolds

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Manipulation of peptides' conformation is an intriguing structural challenge. Beside the structural imprinting imparted by the amino acid sequence, peptides are shaped towards functional structures by the interaction with chaperones; such a mechanism suggests that peptide sculpting may be feasible. Recently, Curran et al. synthesized and tested cyclic tungsten bis-alkyne complexes derived from a 1,1'-ferrocenyldialkyne (Figure) as scaffolds for the nucleation of β-sheet structures [1-3]. These bimetallic scaffolds bear two η^2-alkyne ligands on the tungsten center acting as suitable anchoring points for the nascent C-to-N or N-to-C peptides, and warranting the steric constraint for their β-sheet pairing. In this communication, we report and discuss the results of DFT-based computational studies addressed on three Fe-W bimetallic complexes appended by different peptide chains [2,3]. Theoretical results corroborated the experimental data, and provided for atomistic interpretations to either occurring or not occurring peptide pairing in the investigated complexes.

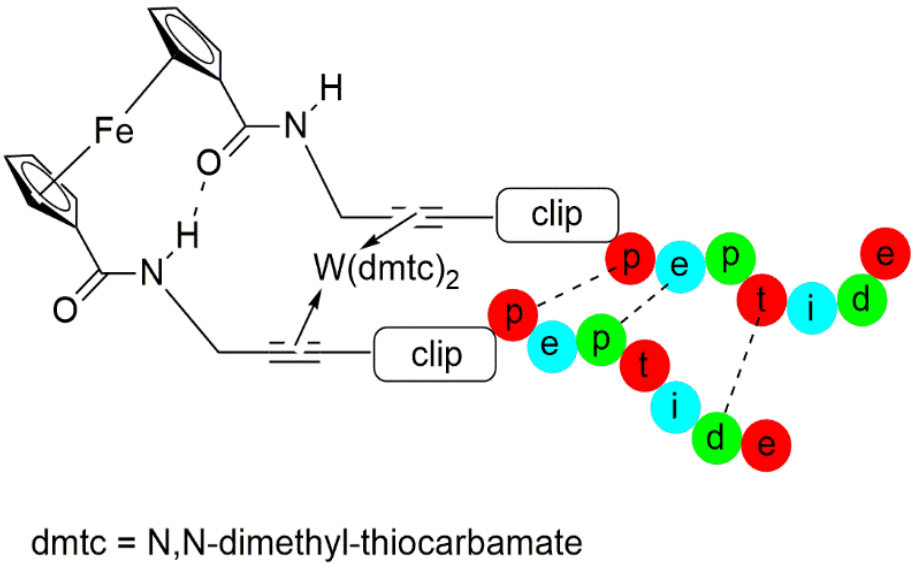

Figure Rendition of the bimetallic Fe-W complex equipped by two peptide chains. The clip fragment can be used to vary the anchoring of the peptide chains to the bimetallic scaffold.

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Toshiyuki MORIUCHI

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BIOGRAPHY

Toshiyuki Moriuchi received his doctoral degree in 1995 from Osaka University. He became Assistant Professor at Osaka University and was a postdoctoral fellow at California Institute of Technology (Professor Jacqueline K. Barton group, 1996–1997). Dr. Moriuchi was promoted to Lecturer in 2004 and Associate Professor in 2008. He was appointed Professor at Osaka City University in 2018 and Osaka Metropolitan University in 2022. His current research interest focuses on the development of functional molecular systems based on self-organization programs of biomolecules. Dr. Moriuchi received the Inoue Research Award for Young Scientists (1997), AJINOMOTO Award in Synthetic Organic Chemistry, Japan (2004), HGCS Japan Award of Excellence 2011 (2012), The 15th Kansai Branch Award of the Society of Synthetic Organic Chemistry, Japan (2017), and Nagase Foundation Award 2018 (2018).

IL12
Chirality Organization in Bioorganometallic Conjugates

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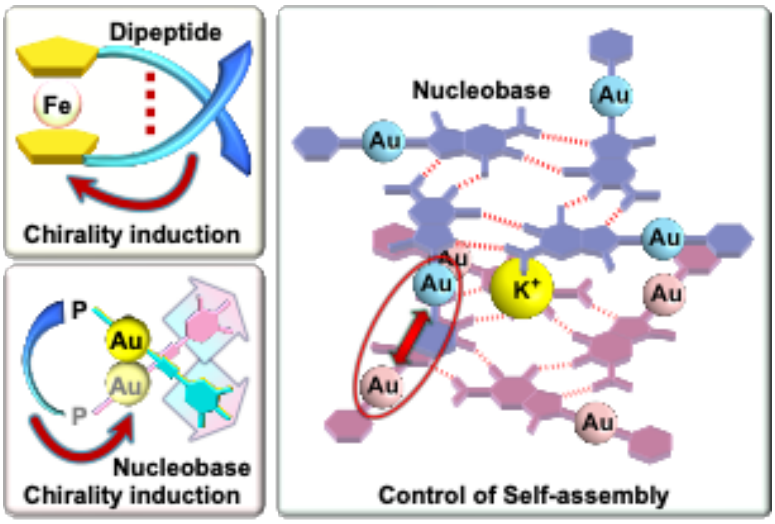
Chirality-organized structures are formed in proteins and DNA by self-assembling properties of biomolecules such as amino acids, peptides, and nucleobases. Conjugation of biomolecules and functional organometallic compounds is expected to create novel bioconjugates depending on both properties. In this presentation, I wish to present Prof. Toshikazu Hirao's achievements in bioorganometallic chemistry. Especially, chirality organization in bioorganometallic conjugates with dipeptides [1-2] or nucleobases [3-6] will be focused on.

The introduction of -L-Ala-L-Pro- dipeptide chains into the ferrocene organometallic scaffold was demonstrated to induce the helical chirality of the ferrocene moiety through the formation of the interchain intramolecular antiparallel *b*-sheet-like hydrogen bonds. Furthermore, controlling helical chirality and creating protein secondary structures in ferrocene–dipeptide bioorganometallic conjugates were achieved by adjusting the conformational flexibility of the dipeptide chains.

Guanosine-based Au(I) isonitrile complex was performed to form G-octamer via self-assembly in the presence of a potassium ion, exhibiting a specific emission based on Au(I)-Au(I) interaction.

Chirality induction into the Au(I)-Au(I) axis of the dinuclear organogold(I)-uracil conjugate was achieved by using (R)-BINAP as a bridging diphosphine ligand, inducing a helical molecular arrangement in the crystal packing.



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BIOGRAPHY

Thomas Scattolin completed his PhD in Chemistry in 2019 under the supervision of Prof. Fabiano Visentin at University of Trieste. In 2019 he was a visiting scientist in the laboratories of Prof. Antonio Togni at the ETH in Zurich. Throughout this period, he developed a straightforward route to allyl palladium complexes stabilized by N-trifluoromethyl NHCs which proved to restrain the growth of high grade serous ovarian cancer tumoroids. One year later, he joined the group of Prof. Steven P. Nolan at Ghent University as a postdoc researcher. In 2021, he worked as postdoc researcher at CRO Aviano, Italy, within the CaTHENa project (Cancer THErapy by Nanomedicine). Since 2022, he is assistant professor in Inorganic Chemistry at the University of Padova. His research activity, which is documented by more than 80 articles and two patent applications, primarily focuses on the synthesis and reactivity of late transition metal complexes with applications in medicinal chemistry and homogeneous catalysis.

IL13

A Chemical Journey Through the Medicinal Chemistry of Organopalladium Compounds: From Palladates to Butadienyl Complexes in Ovarian Cancer Therapy

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Organopalladium complexes have emerged as promising candidates in the development of next-generation anticancer agents, particularly for addressing resistance associated with platinum-based drugs like cisplatin. Among these, palladate and Pd(II)-butadienyl/vinyl complexes stand out due to their unique mechanisms of action and potent cytotoxicity.

Palladate complexes incorporating azolium ligands and Pd(II)-η^3-allyl fragments have shown exceptional stability and activity across various cancer cell lines, including those resistant to cisplatin (Figure 1). These compounds demonstrate low micromolar to sub-micromolar IC_{50} values and operate via multiple mechanisms, most notably the inhibition of thioredoxin reductase (TrxR)—a redox enzyme overexpressed in tumors. This TrxR inhibition disrupts cancer cell antioxidant defences and contributes to the induction of immunogenic cell death (ICD), a form of regulated cell death that enhances antitumor immune responses. Palladates were shown to trigger ICD more effectively than standard inducers like doxorubicin, positioning them as strong candidates for chemo-immunotherapy approaches.

Parallel research into Pd(II)-vinyl and Pd(II)-butadienyl complexes has introduced additional therapeutic possibilities. While vinyl derivatives suffer from limited stability, the butadienyl analogues exhibited high cytotoxicity and novel biological behaviour. The most active compound, which bears two PTA ligands, was found to induce ferroptosis, an iron-dependent, lipid peroxidation-driven form of cell death that is especially valuable in targeting apoptosis-resistant cancers, such as high-grade serous ovarian carcinoma (HGSOC). This marks the first report of a palladium complex acting through this pathway, significantly expanding the known repertoire of metal-based anticancer mechanisms.

Together, these findings highlight the potential of palladates and butadienyl complexes as innovative anticancer agents.

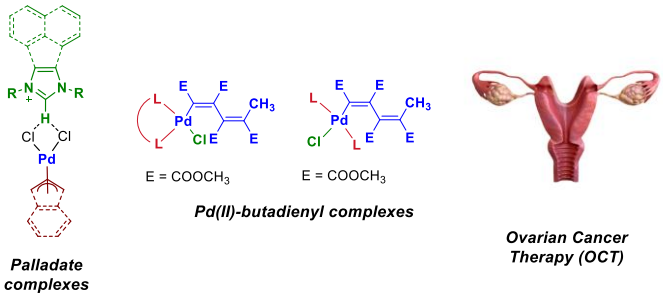

Figure 1. Palladate and butadienyl complexes with promising anticancer activity

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SL01
Gold Phosphonium Ylides: A Promising Tool for Selective Mitochondrial Targeting

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The use of gold compounds in cancer treatment has surged over the past decades, with numerous studies highlighting the potent antitumor properties of gold complexes. A key distinction between the antitumor activity of cisplatin and gold(I) compounds lies in their mechanisms of action: while cisplatin primarily interacts with DNA, gold complexes exert their antiproliferative effects through enzyme inhibition, particularly targeting thiol- and selenol-containing enzymes. The strong binding affinity of gold for sulfur and, even more so, selenium makes critical enzymes such as thioredoxin reductase (TrxR), glutathione reductase (GR), and cysteine protease prime targets for gold-based anticancer therapies [1].
Moreover, lipophilic cationic salts, also known as delocalized lipophilic cations, can selectively accumulate in the mitochondria of cancer cells, especially human-derived ones, due to the differences in trans-mitochondrial membrane potential between malignant and healthy cells. This unique property has sparked significant interest in the field of medicinal chemistry. Among these, phosphonium salts have been extensively studied for their promising role as selective chemotherapeutic agents [2]. Building on this, our research focuses on functionalizing phosphonium salts by incorporating biologically relevant ligands or chromophores. Subsequent deprotonation of these phosphonium ligands leads to the formation of gold ylide derivatives (see Figure 1), which exhibit diverse functionalities, enabling precise targeting of cancer cell mitochondria. The mechanism of action is being systematically explored using advanced techniques, including intracellular drug monitoring, to unlock their full therapeutic potential.

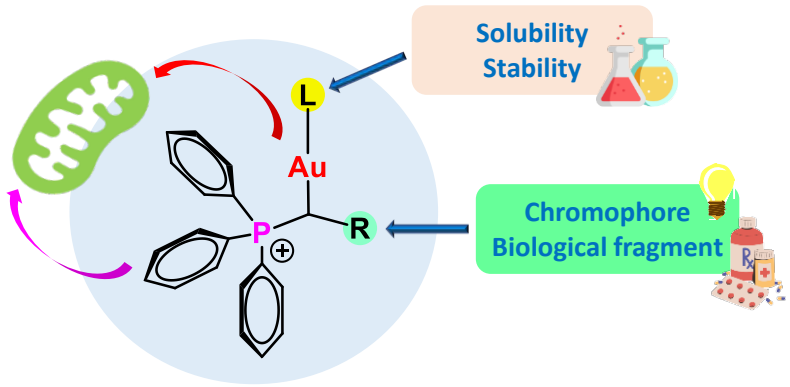

Figure 1. General structure of the gold complexes

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SL02
Photoactivable Group 8 Metals Complexes for Anticancer Studies

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Our research team has investigated iron, ruthenium, and osmium metallocycles as a novel class of efficient anticancer agents. The effects of these organometallic derivatives on various biological targets have been evaluated, revealing modes of action that differ from those of platinum derivatives commonly used in chemotherapies [1,2]. Additionally, the cytotoxic activity of complexes with π-expanding ligands was significantly enhanced upon visible light irradiation through the formation of singlet oxygen [3]. To improve the selectivity and cytotoxicity of the compounds towards their application in photodynamic therapy (PDT), a series of porphyrins and chlorins were synthesized and coordinated to ruthenium and osmium. Experiments on human gastric cancer cells demonstrated exceptional activity upon light irradiation, with the photocytotoxicity index exceeding 1000 in some cases. Biological studies, along with EPR and UV-vis spectroscopy, enabled us to identify potential modes of action. The complexes can generate singlet oxygen and superoxide anion radicals, with cell death induced via a caspase 3-mediated apoptotic pathway and via CHOP, an endoplasmic reticulum stress transcription factor. These results underscore the potential of our complexes as promising multi-target therapeutic alternatives that may mitigate tumor resistance mechanisms.

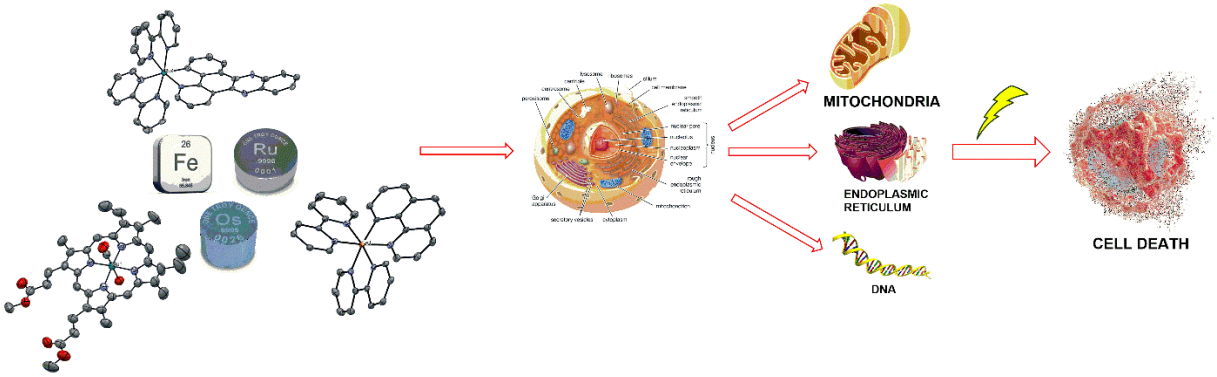

Figure 1. Examples of cytotoxic complexes studied and potential biological targets.

Acknowledgments
Financial support from DGAPA-UNAM (IN211522 and IN207725) is acknowledged.

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SL03
Targeting Malaria via Bioorganometallic Hybridisation

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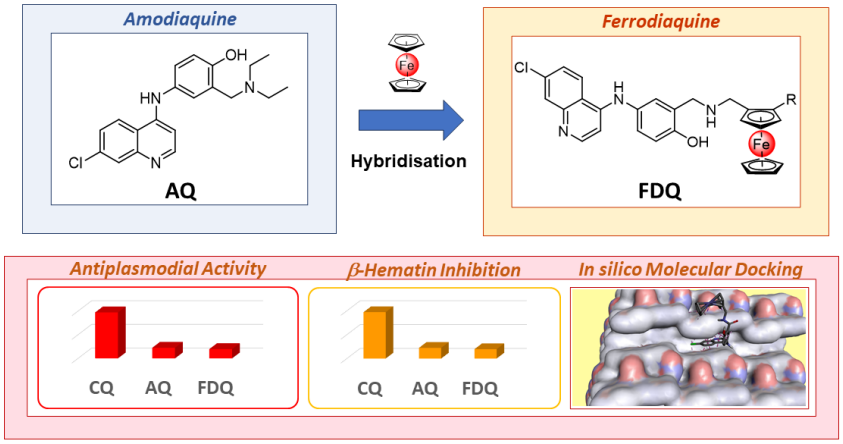
Malaria continues to be a globally prevalent parasitic disease, impacting millions of individuals. It is primarily caused by the protozoan parasite *Plasmodium*, which targets and invades human red blood cells. Although significant strides have been made in controlling the disease, the rising incidence of drug-resistant strains underscores the limitations of existing antimalarial therapies. Ongoing research is crucial to overcoming resistance and identifying new compounds with strong antiplasmodial activity.

Ferroquine, a derivative of the conventional antimalarial chloroquine modified by incorporating a ferrocene moiety into its side chain, has shown effectiveness in overcoming resistance associated with the original drug. This highlights the promising potential of metal-based complexes in malaria therapy, especially in the context of rising drug resistance. As a result, there is increasing interest in designing novel metal-containing compounds with improved antimalarial activity to combat resistance more effectively.

This presentation will highlight our recent endeavours in developing hybrid bioorganometallic compounds with antiplasmodial activity, some of which have shown notable potency, especially against drug-resistant *Plasmodium falciparum* strains. Our research consistently indicates that incorporating sandwich-type organometallic structures, such as ferrocene, can enhance biological activity. Furthermore, the presentation will explore investigations into microsomal metabolic stability and putative mechanisms of action.



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SL04
Multifunctional Anticancer Metal Complexes as Selective HDAC6 Inhibitors

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The inhibition of histone deacetylase 6 (HDAC6) has emerged as an efficient strategy in treating cancer and neurodegenerative disease.[1] The combination of different biologically-active groups has been widely applied in developing anticancer metal complexes. In this project, we combined the HDAC inhibitor SAHA[2] with bioactive 8-hydroxyquinoline or 1,10-phenanthroline moieties to develop metal complexes with multimodal activity. The obtained ligands show strong binding affinity to metal ions and the Ru(II), Os(II), Ir(III), and Rh(III) half-sandwich complexes have been prepared. *In vitro* antiproliferative activity studies revealed high potency of the ligands against cancer cells, including human colon, non-small cell lung, ovarian and cisplatin-resistant ovarian cancer. While decreased activity was observed for monometallic complexes, the HDAC inhibitory activity of the ligands **1** and **4** (Figure 1, left) and their corresponding Ru(II) complexes was determined. Ligand **4** featuring a benzyl linker exhibited the highest selectivity factor (SF = 176), while most complexes showed moderate selectivity.

Furthermore, the hydroxamic acid in the obtained complexes was coordinated to Co(III) chaperones, affording novel heterobimetallic prodrugs which we hypothesise can undergo one-electron reduction to the labile Co(II) and dissociate in hypoxic tumour environments (Figure 1, right)[3]. Aqueous stability testing, cell uptake studies and cyclic voltammetry experiments will reveal the suitability of the approach and help elucidate the mode-of-action of these novel complexes.

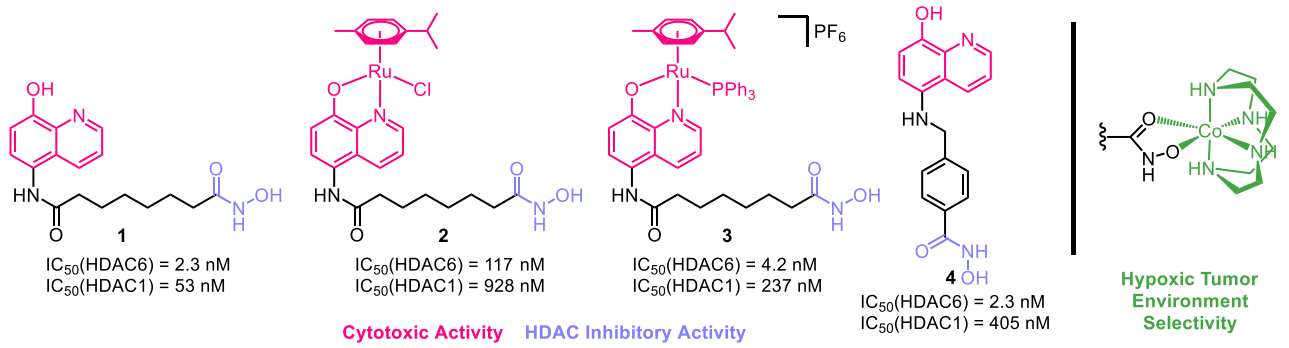

Figure 1. Structure of HDAC inhibitory multifunctional metal complexes

References

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SL05
Gold Porphyrin Metallacages Multifunctional Drugs Interacting with Non-Canonical DNA Structures

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Self-assembled metallacages are promising supramolecular systems that have shown potential in different fields of chemistry, including being developed as versatile platforms for biomedical applications, such as drug delivery, tumour therapy, bioimaging, and biosensing.[1] Such 3-dimensional metal-containing assemblies possess cavities that can accommodate various guest molecules (e.g. anti-cancer drugs, radiopharmaceuticals or imaging agents). By correctly designing the ligands and exploiting the predictable and well-defined coordination geometries of transition metal ions, the cage's size, and chemical-physical properties can be tuned to promote specific host-guest interactions [2].
Furthermore, bioactive building blocks can embed the 3-dimensional structures with further therapeutic and diagnostic properties. Recently, we have developed the first gold(III) porphyrin-based self-assembled metallacage (**AuCg**), exploring its potential as a bioactive agent [3] and highlighting its selectivity as a guanine-quadruplex (G4) stabilizer (Figure 1). Importantly, our results unveil the until-now overlooked significance of the host-guest chemistry in stabilizing non-canonical DNA structures. More recently, our studies have expanded to other systems presenting enhanced DNA binding properties when gold is coordinated in the porphyrin. These findings support the positive effects of including gold porphyrins in metallacages designed as selective binders for secondary DNA structures of therapeutic relevance.

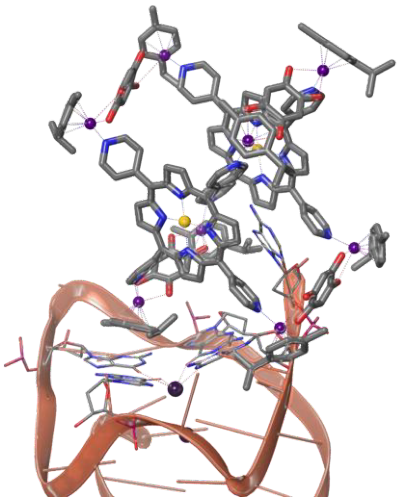

Figure Interaction of **AuCg** with the C-KIT1 promoter G4.

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SL06

N-Heterocyclic Carbenes as Ligands to ^{198}Au(I) Radiolabeled Compounds: a New Platform for Radiopharmaceutical Design

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The application of Au(I) ions in pharmaceuticals, including in nuclear medicine, is limited by their instability towards reduction *in vivo*. The gold radionuclide ^{198}Au, with a half-life of 2.7 days, emits gamma radiation ideal for diagnostic purposes and generates β^- particles suitable for effective cancer radiotherapy, making it a perfect nuclide for 'theranostics'. Here, we explore N-heterocyclic carbene (NHC) organometallic chemistry to stabilize ^{198}Au(I) in radiopharmaceuticals.[1] Thus, Au(I) NHC compounds featuring different scaffolds have been selected for ^{198}Au radiolabeling. Two new benzimidazol-2-ylidene Au(I) complexes bearing peptide ligands enabling blood-brain barrier translocation *in vitro* have also been synthesized, and their radiolabeling attempted. The obtained proof-of-concept results showed that NHCs are suitable ligands to achieve isotope exchange in Au(I) complexes, with imidazole derivatives being particularly stable, also in the presence of AuCl(THT) (THT = tetrahydrothiophene) and human serum albumin. Overall, our work reveals the still untapped potential of organometallic chemistry in radiopharmaceutical design.

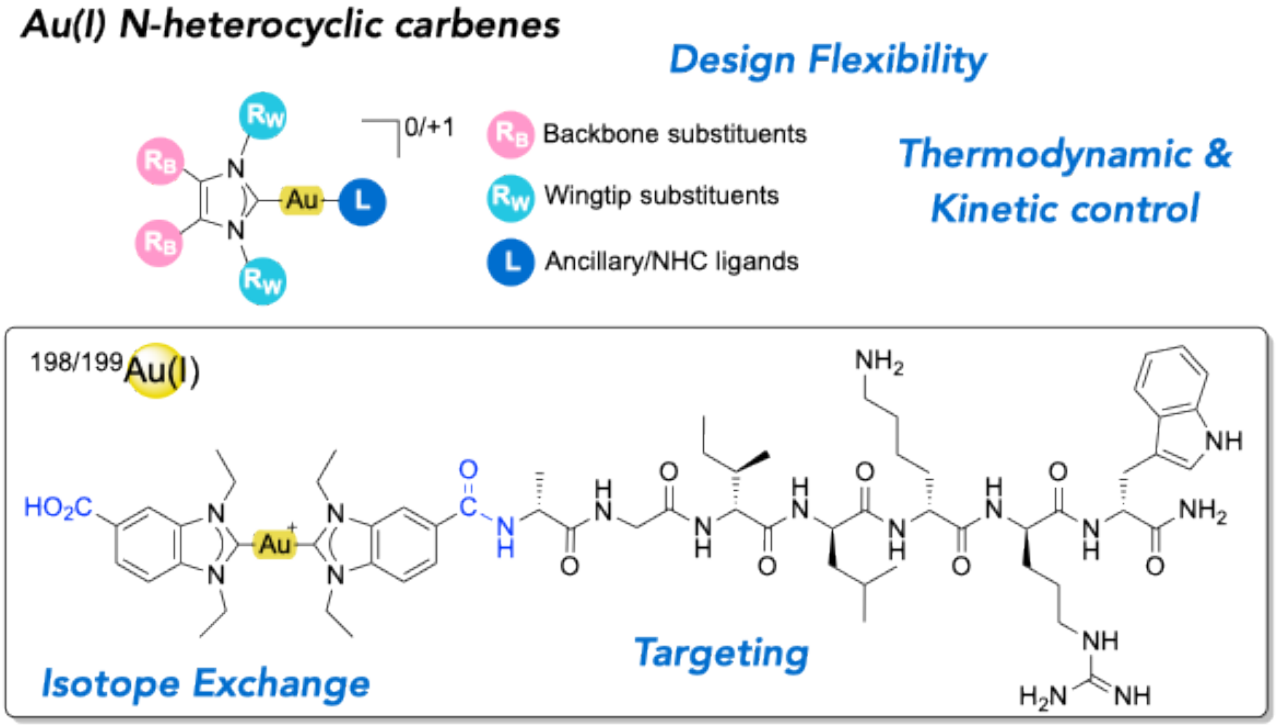

Figure 1: Au(I) NHCs as a platform to radiopharmaceutical design.

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SL07

The design of phenyl arsine anti-cancer complexes specific to neurological cancer cells

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With the exception of leukaemia, arsenic-containing cancer therapies require increased arsenic concentrations, potentially leading to serious side effects, necessitating dose-reduction or cessation.[2] An emerging method to improve treatment efficacy is the conjugation of a drug to a tumour-homing peptide.[3] Dillon and Carrall have previously patented a phenyl arsine-tumour-homing peptide that exhibits 1000 times greater toxicity in leukemia cells over healthy blood cells.[4] The aim of the present work was to develop PhAs(RGD), an arsenic-tumour-homing peptide designed to target neurological cancers. Following the optimisation of reaction conditions and purification, PhAs(RGD) was characterised using electrospray ionisation mass spectrometry (ESI-MS), and nuclear magnetic resonance (NMR) spectroscopy, and, displayed promising stability in DMSO (98%, 24 h) and cell media (86%, 24 h, IMDM). Good stability was also observed in human plasma supplemented with HEPES buffer (93.51%, 24 h). Uptake studies performed using graphite furnace atomic absorption spectroscopy (GFAAS) demonstrated 904 times greater arsenic uptake in U-87 MG cells and, 830 times greater uptake in SH-SY5Y cells in comparison to healthy blood cells. In a monolayer cell model, PhAs(RGD) exhibited significantly lower IC_{50} values in U-87 MG cells (3.9 ± 0.2 µM) and in SH-SY5Y cells (0.61 ± 0.04 µM) in comparison to healthy blood cells (30.2 ± 0.4 µM). This preliminary work demonstrates the successful synthesis, characterisation, uptake and cytotoxicity of a phenyl arsine-tumour-homing peptide, which exhibits potential for improved selectivity towards neurological cancer cells.

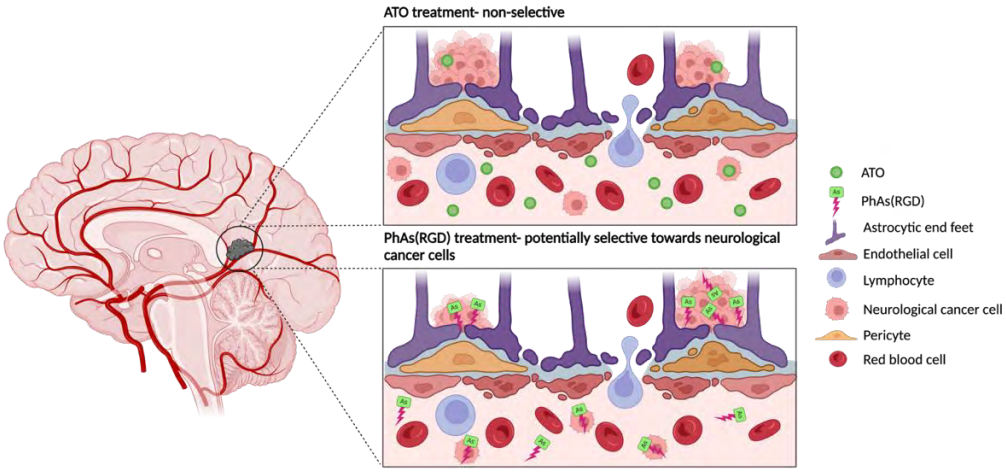

Figure 1: Hypothesised selectivity of PhAs(RGD) for neurological cancer cells in comparison to ATO (the frontline treatment for acute promyelocytic leukemia). Figure created using BioRender

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SL08
[(C^C)Au(P^P)]$^+$ organogold(III) complexes: intracellular speciation and mitochondrial accumulation

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Keywords: Gold; cancer, reactivity, speciation, localization

To circumvent platinum-based drugs limitations such as a narrow spectrum action, appearance of resistances to the treatments and heavy side effects, the investigation of complexes based on other transition metals appeared crucial. Within this context, the isoelectronic and isostructural Au(III) ion has been envisaged as a potential replacement for Pt(II) complexes. However, while Pt(II) is stable in physiological medium, Au(III) gets easily reduced in those conditions. The development of ligands stabilizing the +III oxidation state was the first aim to achieve which could be efficiently done by using cyclometallated ligands and especially (C^N^C) pincers.[1] As such, the quest of stability was achieved at the cost of the derivatization possibilities by blocking three out of the four coordination sites. We decided to reorganize the coordination of the complexes by using a (C^C) biphenyl chelate which will ensure the redox stability of the Au(III) cation while leaving two coordination sites functionnalizable in soft conditions opening the way to a much broader variety of structures.[2] We will present here our recent work on the intracellular speciation studies of [(C^C)Au(P^P)]$^+$ complexes involving the investigation of the metabolite present inside the cells using cryo-synchrotron radiation-X-ray fluorescence (cryo-SR-XRF) and X-ray absorption spectroscopy (XAS) and the its mitochondrial accumulation by cryo-SR-XRF and confocal microscopy.[3]

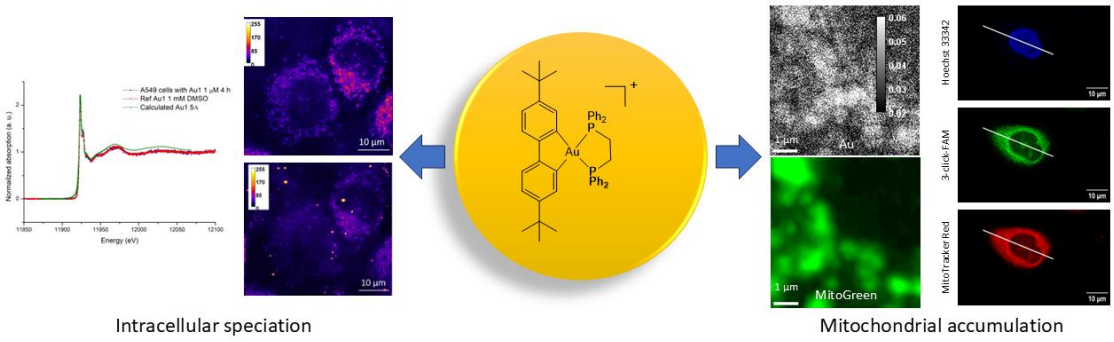

Figure 1 Intracellular determination of the speciation of and mitochondrial accumulation of a [(C^C)Au(P^P)]$^+$ complex.

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SL09
Ferrocenyl quinoline-benzimidazole molecular hybrids as antileishmanial agents

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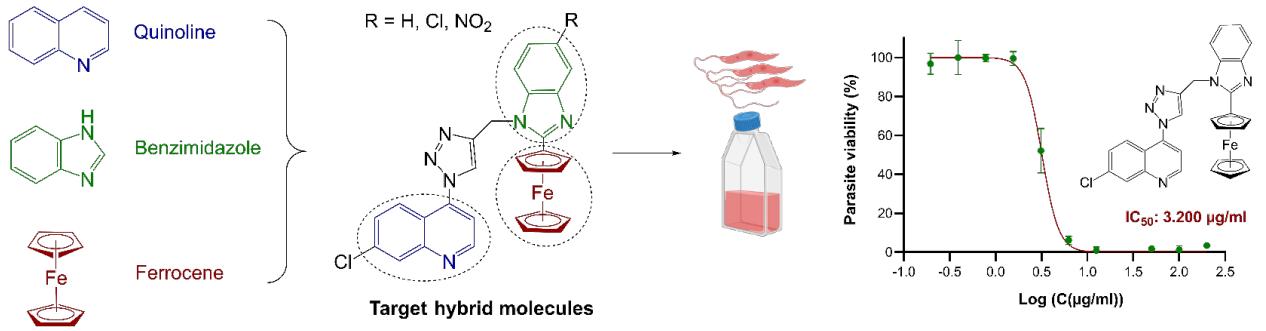
Cutaneous leishmaniasis, the most widespread clinical form of the vector-borne parasitic disease leishmaniasis, is principally caused by *Leishmania major* (*L. major*). Transmission occurs through the bite of infected female phlebotomine sandflies. Clinically, the disease manifests as ulcerative lesions with indurated margins, often leaving disfiguring and permanent scars. In the absence of an effective prophylactic vaccine, pharmacological intervention remains the cornerstone of treatment. However, the increasing incidence of drug resistance, coupled with the pronounced toxicity and high cost of current therapies, necessitates the exploration of alternative strategies — particularly the repurposing of pharmacophoric frameworks with established efficacy against other parasitic infections.[1]

Among such frameworks, the quinoline and benzimidazole scaffolds are privileged in medicinal chemistry. Quinoline constitutes the core structure of classical antimalarials like chloroquine, while benzimidazole has emerged as a versatile motif with applications in both anticancer and antimalarial drug development.[2] In parallel, the strategic incorporation of metal centres into organic architectures represents a promising and evolving frontier, often endowing compounds with additional redox-based mechanisms of action. A notable exemplar is the ferrocenyl moiety, which has been shown to enhance antimalarial activity.[3] Accordingly, this study integrates the principles of molecular hybridisation and metal incorporation to synthesise a series of ferrocenyl-containing benzimidazole-quinoline hybrid compounds. Following assessments of chemical stability and cytotoxicity, their *in vitro* antileishmanial efficacy was evaluated against both intracellular and extracellular forms of *L. major* (LV39 strain), resulting in promising and noteworthy findings.



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SL10
Unlocking the Potential of Transition Metal Complexes in Protein-Protein Interaction-Targeted Drug Discovery

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Transition metal complexes have emerged as promising candidates for biomolecule probes due to their unique photophysical properties and protein interaction capabilities. Octahedral metal complexes, in particular, offer distinct advantages owing to their tunable inertness, stability, and geometries compared to traditional organic molecules. In this presentation, we describe our group's efforts in developing transition metal complexes to target protein-protein interactions (PPIs) and their application in high-throughput drug screening. We have developed iridium (Ir) and rhodium (Rh) complexes that target PPIs involved in critical cellular processes, including cell signaling pathways, gene regulation, and mitochondrial function. By utilizing the unique luminescent and subcellular targeting properties of these metal complexes, we have established methods for competitive protein-protein interaction-based drug screening. Through conjugation with specific ligands, these complexes can serve as probes for screening inhibitors of protein-protein interactions. Our findings demonstrate that metal complexes hold significant potential not only as drug candidates but also as powerful tools for drug discovery.

SL11

N-Heterocyclic Ligands in Bimetallic Complexes: Synthetic Strategies and Biological Activities

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Since the discovery of the anticancer properties of cisplatin in the 1970s, transition metal complexes have garnered significant attention for their potential as metallodrugs [1]. Among the various strategies explored, combining biologically active N-heterocyclic frameworks with organometallic fragments has shown great potential. Isoindole-based scaffolds, derived from both natural and synthetic sources, have emerged as versatile scaffolds for the design of pharmaceutical and bioactive compounds [2].

In this study, we report on the synthesis, characterization, and biological evaluation of homobimetallic scaffolds (Co-Co, Pt-Pt) as well as Platinum(0) complexes incorporating an isoindole moiety. These metal-metal bonded species and the Pt(0) p-complexes were prepared using alkyne-functionalized isoindole ligands, characterized by IR, multinuclear NMR spectroscopy, and single-crystal X-ray diffraction [3]. Biological assays were also conducted to evaluate their cytotoxic, anti-Alzheimer, and anti-diabetic activities [4].

Preliminary cytotoxicity tests indicate notable efficacy against several cancer cell lines (HCT116, MCF-7, WM266-4 and LS174T), with IC50 analyses. Promising anti-butyrylcholinesterase (BChE) activity was also observed, suggesting a potential application in Alzheimer's disease treatment. However, no significant inhibition was noticed in the a-glucosidase assay, highlighting the selective bioactivity of these complexes.

Our results reveal the ability of bimetallic complexes as multifunctional platforms for the development of innovative metallodrugs with improved biological efficacy.

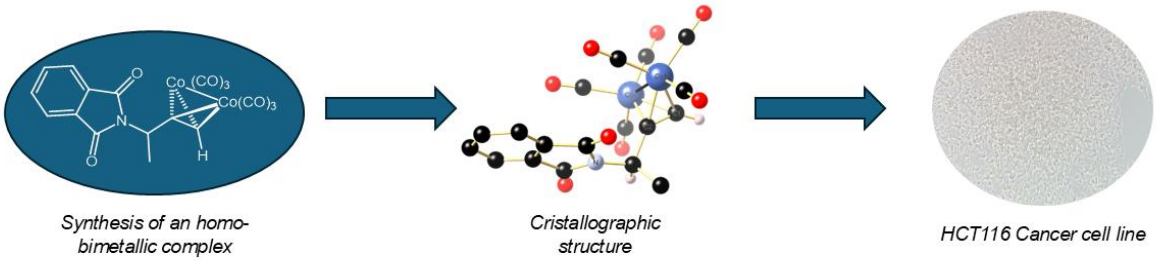

Figure 1 Crystal structure of a homo-bimetallic Co-Co dimetallatetrahedrane complex and microscopic imaging of a HCT116 cancer cell line.

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SL12
Bioconjugated organometallics for targeted chemotherapy

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Inspired by the success of platinum-based drugs in cancer treatment, the field of bioorganometallic compounds has risen to explore the unique properties of organometallic compounds, which offer diverse mechanisms of action and broader targeting strategies. Organometallic-peptide conjugates are a growing field featuring conjugates formed by attaching metal centers via metal-carbon bonds to peptides at the N- or C-terminus, on side chains, or even within the peptide backbone. Different synthetic strategies have been applied to create stable and biologically active organometallic-peptide hybrids to this aim.[1-2]

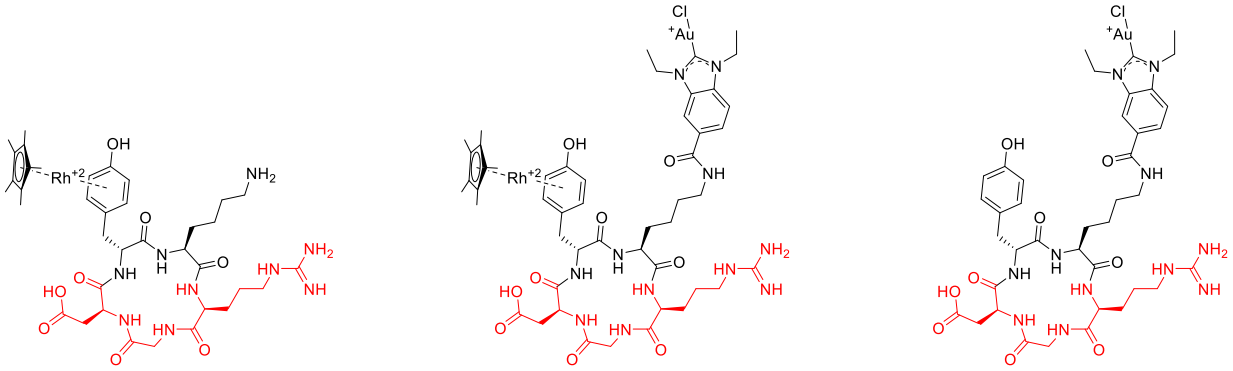

Figure 1: Integrin-binding cyclic peptide (RGD-recognition moiety highlighted in red) bearing bioactive organometallic moieties based on Rh and/or Au.

This work aims to combine two different organometallic moieties with integrin-binding ligands to obtain novel targeted bioorganometallic drugs. To this end, a cyclic RGD peptide, targeting αvβ3 and αvβ5 integrins overexpressed in cancer cells, was modified by incorporating a tyrosine residue into the backbone, enabling conjugation to a rhodium(II)-arene moiety (Cp*Rh) via previously demonstrated chemoselective bioconjugation.[3] On the other hand, an Au(I) N-heterocyclic-carbene (NHC) moiety can be integrated into the same peptide sequence via the functionalization of the robust NHC scaffold. Au(I) NHC complexes exhibit high stability, tunability, and potent anticancer activity through mechanisms such as seleno-enzyme inhibition and ROS generation, which enable them to overcome drug resistance of classical chemotherapeutics.[4] Overall, the tethering of Rh(II) or Au(I) centers to the targeted peptide may enhance their cellular uptake and therapeutic efficacy while reducing side effects. Preliminary data on the new compounds will be presented and critically discussed.

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SL13

Synthesis and Conformational Evaluation of Beta-Sheet Models Derived from a Rigid Tungsten-Iron Organometallic Ring

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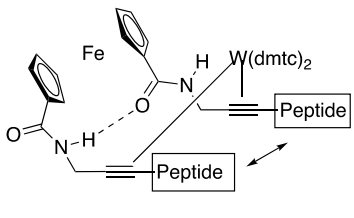
Protein-protein interactions drive many biological events. For example, in Alzheimer's disease and other amyloid diseases oligomerization of b-sheet proteins has been implicated in disease initiation and propagation. To study, control or reverse oligomerization of b-sheet structures, it would be useful to employ b-sheet peptidomimetics. Organic chemists have developed a variety of b-sheet peptidomimetics, but because these molecules have flat (sheet-like) structures, they form oligomers with limited solubility, making them difficult to use for probing protein-protein interactions. Our lab has postulated that peptides appended to the two alkynes in a tungsten-ferrocene ring system (general structure **1**) will form b-sheets, and that because the organometallic ring system here lies perpendicular to the parallel peptide chains, it will act to prevent oligomer formation, possibly making this b-sheet peptidomimetic more soluble and tractable for studying protein-protein interactions. In addition, the presence of the two metals would provide a useful spectroscopic tool for probing where such molecules might accumulate in vivo. Two systems are currently under study, depicted in **2** and **3**. Details about the preparation and conformational analysis of **2** and **3** and related structures will be presented.



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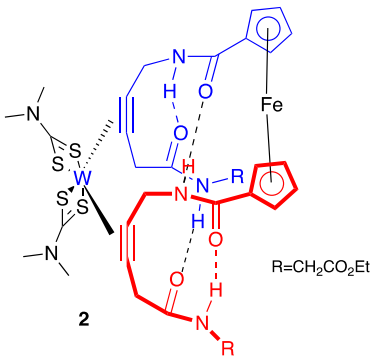

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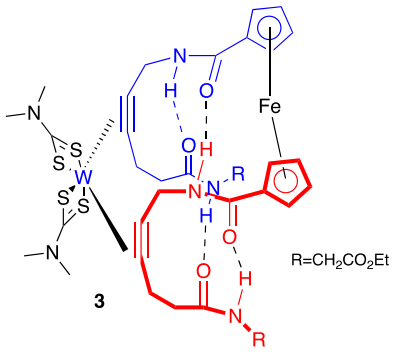

3

SL14

Syntheses, structures, CO release properties and biological studies of new neutral Mn(I) tricarbonyl complexes

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Carbon monoxide (CO) is known in the popular culture as a lethal gas, earning its name of "silent killer". Since the past decade, CO has emerged as a promising therapeutic agent for cancer treatment when administrated at optimal concentrations.[1] However, due to its gaseous form, CO remains difficult to handle. To overcome this issue, Carbon Monoxide Releasing Molecules (CORMs) have been introduced as a more convenient mode of administration.[2] These molecules are mostly organometallic complexes, enabling the release of CO upon a given external stimulus, such as visible light. These complexes, named photoCORMs, remain the most widely developed so far.[3] Despite some recent advances, efforts are still ongoing to synthesize new carbonyl complexes combining light absorption in the visible region and high potency of vectorization for the site-selective, controlled delivery of CO.[4] In this context, we present a new series of photo-activatable complexes [Mn(8-hydroxyquinoline)(CO)3(Imd)] with Imd = imidazole derivatives. We developed an expedite synthetic route from the dimeric structure [Mn2(8-HQ)2(CO)6] and applied a series of imidazole ligands (Fig. 1a). The use of various imidazole-based ancillary ligands allows the synthesis of a wide range of complexes with a high degree of modularity due to the presence of allyl, hydroxyl, or amine groups on the imidazole ring. Moreover, *N,C*-diprotected histidine was successfully applied, opening the way to further functionalization with peptides[5] (Fig. 1b).

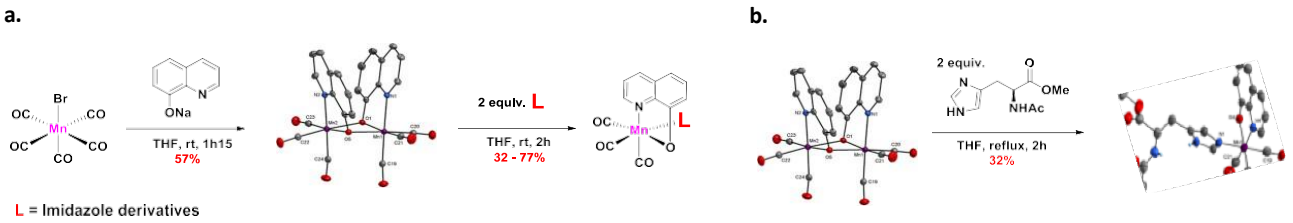

Fig.1 *Synthetic pathway to these new photoCORMs. a) General synthesis pathway b) Synthesis of [Mn(8-HQ)(CO)3NAc-His-OMe] with corresponding X-ray structures.*

Finally, we successfully developed a series of new glycoconjugated CORM (GlycoCORMs) to allow targeted delivery of CO to cancer cells (Fig. 2). The first biological results showed an enhanced cytotoxicity for the GlycoCORMs compared to [Mn(8-HQ)(CO)3Me- Imd] with IC50 in the µM range, respectively 5 µM and 9 µM, assessing the positive role of the carbohydrate moiety in the biological activity of the glycoCORMs.

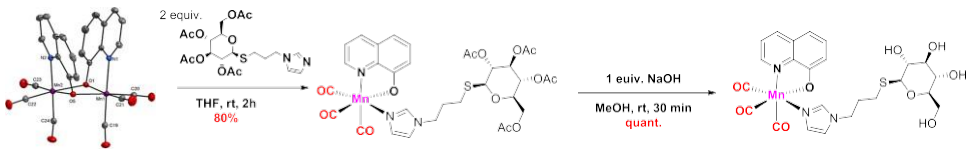

Fig. 2 *Synthesis of [Mn(8-HQ)(CO)3GluSImd]"GlycoCORM-1".*

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SL15
High-throughput Combinatorial Click Chemistry for the Development of Novel Metalloantibiotics

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Due to the rise in antibiotic-resistant bacteria, new classes of antibiotics are required to counter the upcoming public health emergency.[1] Previously, our group has focused on exploring transition metal complexes chemical space to identify promising antibiotic candidates,[2] primarily utilising Schiff-base ligand chemistry.[3] Here, we demonstrate a new avenue for diverse metal complex libraries utilising triazole-based bidentate ligands, prepared by Cu-catalysed Alkyne-Azide "Click" reactions. In tandem with high-throughput experimentation, we were able to prepare ~200 ligands and over a thousand novel metal complexes at once, with excellent reaction efficiency. All reactions have been confirmed by LC-MS, and all complexes have been tested for antibacterial activity and toxicity in a High-Throughput capacity, with promising candidates resynthesised. Additionally, select libraries have also been tested for photophysical properties and catalysis in high-throughput assays, demonstrating applications of these metal complex libraries beyond antibacterial screening.

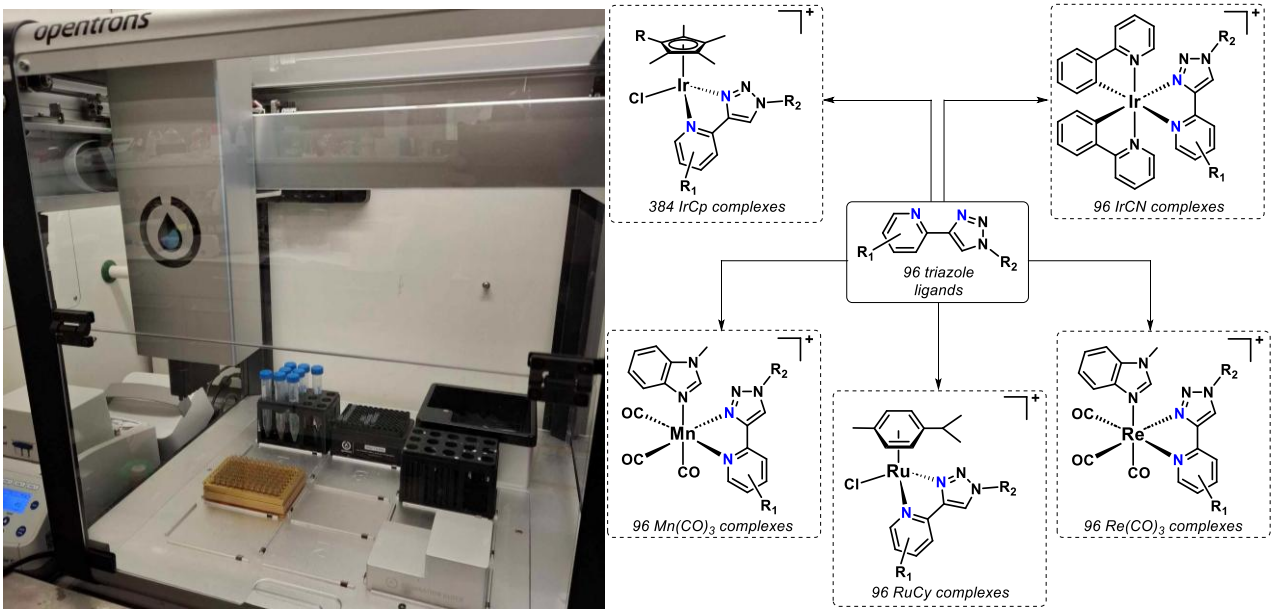

Figure: Left – Opentrons OT2 robot setup for high-throughput experimentation, using a 96-well plate; Right – examples of novel metal complex libraries prepared in this work

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SL16
Biscyclometalated Ir(III) Complexes and Their Encapsulation for Enhanced Anticancer PDT

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Photodynamic therapy (PDT) is a selective and promising alternative to conventional cancer treatments. In this therapy, a photosensitiser, ideally innocuous in the dark, is activated upon light irradiation, generating reactive oxygen species (ROS) such as $O_2^{\bullet-}$ and $^1O_2$, which induce cell death. Octahedral Ir(III) complexes are well studied in medicinal chemistry for their emissive and anticancer properties [1]. In this work, two biscyclometalated Ir(III) complexes with π-extended C^N ligands were obtained, encapsulated in polymeric nanoparticles (NPs), and evaluated for anticancer PDT (Fig. 1). The introduction of π-extended C^N ligands (pbpz and pbpn) aims to enhance excited state lifetimes and ROS photogeneration [2].

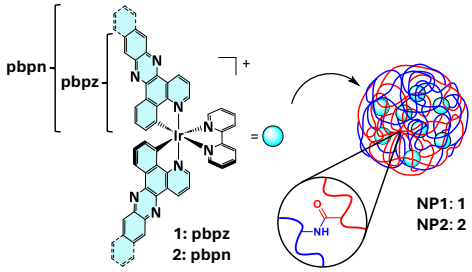

Figure 1. Structure of the Ir(III) complexes and its encapsulation into polymeric nanoparticles.

Complexes **1** and **2**, differing by a fused ring in the C^N ligand, showed different photophysical properties. While **1** showed delayed fluorescence, **2** was almost non-emissive, probably due to π–π aggregation, as observed in solution and in the solid state. Both efficiently generated not only $^1O_2$ but also $O_2^{\bullet-}$ upon light irradiation. TAS measurements revealed the presence of long-lived excited states responsible of ROS photogeneration. TD-DFT studies explained the photophysical properties. Biological studies in cancer cell lines showed high cytotoxicity for both complexes ($IC_{50,dark} \leq 3$ μM), which was strongly enhanced under blue light in both cases (PI = $IC_{50,dark}/IC_{50,light}$ up to 140). However, low cellular uptake was observed probably due to their tendency to aggregate. In order to address this issue, the complexes were encapsulated in polymeric nanoparticles (D ≈ 180 nm, 5-7 % of Ir loading), which improved the cellular uptake, especially in 3D cancer spheroids, and maintained or even increased the phototoxicity of the free complexes. Confocal microscopy revealed that the emissive **1** and **NP1** accumulated in mitochondria. Light irradiation caused an increase in intracellular ROS, which led to mitochondrial dysfunction and photocatalytic oxidation of NADH, ultimately inducing cell death. Wound healing and clonogenic assays demonstrated their potential as antimetastatic agents. Notably, **NP1** exhibited one of the lowest reported IC_{50} values in Ir(III)-based systems (0.86 nM), highlighting these complexes and their nanoparticles as potent PDT agents with strong theragnostic promise.

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SL17
Design of biologically active ruthenium-based organometallic complexes

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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 unique ability to undergo reversible cycloaddition reactions with cell-penetrating/targeting agents. This talk will provide an overview of our most recent findings.

SL18
Novel organometallic chalcones as anticancer and anti-inflammatory agents

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Organometallic complexes have proven to be an interesting structural feature for the design of new metallodrugs. [1-3] In this work, we present the synthesis and biological evaluation of a family of novel ferrocene (**Fc**) (**Ia**), cyrethrene (**Cy**) (**IIa**), and ruthenocene (**IIIa**) organometallic chalcones as potential anti-inflammatory and anticancer agents (Figure 1). Preliminary molecular docking studies were performed to understand how **Ia**-**IIIa** might interact at the binding pocket of COX-2 and 5-hLOX, using the potent dual inhibitor curcumin as a reference. Interestingly, both organometallic complexes are located near the aromatic core (TYR181 and PHE177) present in the active site of 5-hLOX, positioning themselves in opposite directions. For COX-2, complexes **Ia**-**IIIa** and curcumin are similarly located within the enzymatic pocket, specifically between residues ARG513 and TYR385. In all cases, a better affinity for the organometallic complexes (**Ia**, **IIa**, **IIIa**, **A**, **B**, **C**) is observed (between -5.8 and -7.8 kcal/mol) compared to their organic analogues (**4a**, **IVa**, **D**) (between -2.2 and -3.6 kcal/mol). Furthermore, cytotoxicity studies were carried out on HT-29 and MCF-7. Our results indicate that chalcones **Ia**-**IIIa** exhibit the highest cytotoxicity (IC_{50} < 5 μM) compared to non-thiazole organometallic analogs (**A**, **B**, **C**) (IC_{50} < 30 μM) and organic analogs (IC_{50} < 50 μM).

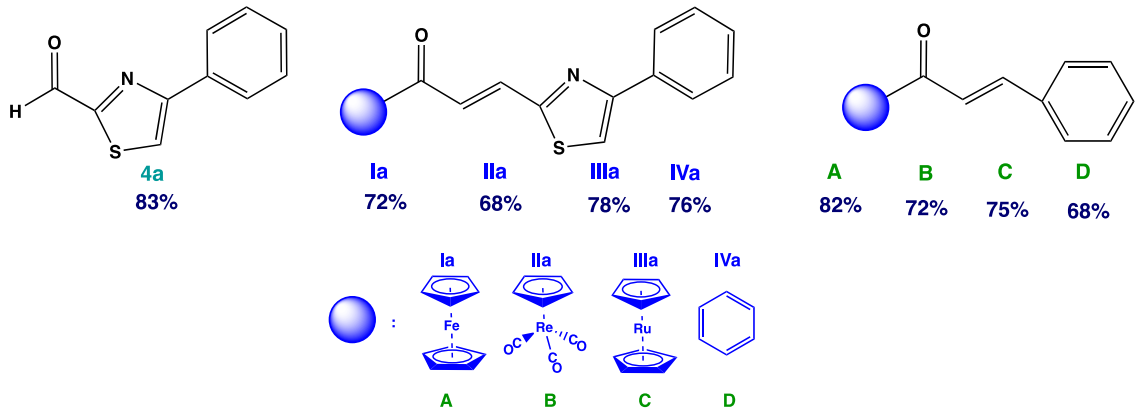

Figure 1. Organometallic and organic chalcones as new anticancer and anti-inflammatory agents.

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SL19
From the Synthesis to the Anticancer activity of Diiron Vinyliminium Complexes and their Derivatives

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Since the discovery of cisplatin and its anticancer properties, research on transition metal complexes for cancer treatment has exploded.[1] One of the new frontiers explores endogenous metals like iron to develop more effective and less toxic chemotherapeutics. In this respect, bis-cyclopentadienyl diiron complexes with a bridging hydrocarbyl ligand have revealed as promising anticancer compounds.[2,3] These complexes display favourable pre-requisites for drug development: straightforward, multigram scalable and inexpensive synthesis, adequate water solubility for biological applications, balanced lipophilic-hydrophilic character, considerable stability in physiological-like conditions. This work discusses the whole path from the design and synthesis to the *in vitro* testing of diiron vinyliminium complexes and their derivatives. Indeed, the vinyliminium bridging ligand is a useful scaffold, whose reactivity can be exploited to prepare diverse derivatives through C-H bond activation reactions (Figure 1). This chemistry and the related anticancer studies will be discussed.

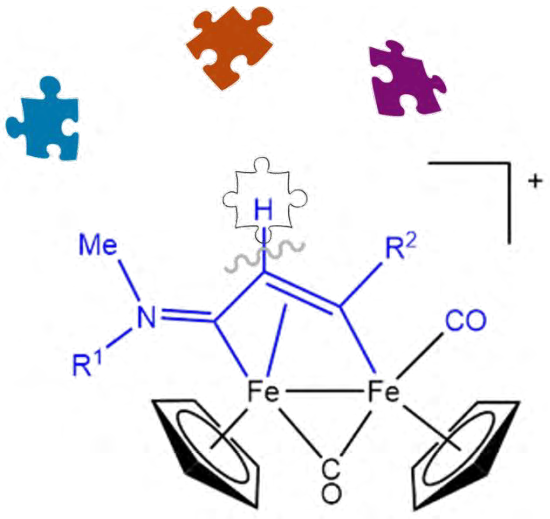

Figure 1. Diiron vinyliminium complexes are easily available. They display potentially unlimited combination of substituents and offer broad opportunity for functionalization.

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SL20

Influence of structural variations in Ag(I) *N*-Heterocyclic carbene complexes on the antibacterial activity against *Escherichia Coli*

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Silver compounds are well-known antibacterial agents, effective at low concentrations with limited cytotoxicity to human cells. Their activity is primarily linked to interference with bacterial nucleic acids and inhibition of key enzymes such as thioredoxin reductase (TrxR).[1] Since the concentration and the rate of silver ion release are crucial for antibacterial activity, strongly coordinating ligands should be used to improve stability and selectivity under physiological conditions. In this regard, *N*-heterocyclic carbenes (NHCs) have emerged as effective ligands for silver(I), offering tunable lipophilicity and strong metal coordination.

Silver NHC complexes of the type [(NHC)AgX] (X = Cl, Br, I) are commonly synthesized due to their stability and simplicity. In solution, they exist as either neutral monocarbene species or ionic biscarbene forms $[(NHC)_2Ag][AgX_2]$. Our earlier work showed that halide ligands significantly influence both structure and antibacterial activity. Notably, replacing chloride with iodide enhances activity against Gram-negative ESKAPE pathogens, including *E. coli*, *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii.*[2] Further mechanistic studies revealed that iodide complexes improve cellular uptake in *E. coli*, likely due to differing interactions with bacterial membranes compared to chloride analogues.[3]

Herein, we summarize how structural modifications to Ag(I) NHC complexes — specifically variations in side chain (**red**), backbone (**blue**), and ancillary ligand (**cyan**) (see Figure 1) — affect their antibacterial activity against *E.coli*, resulting in MIC values ranging from 10 to 100 µM.

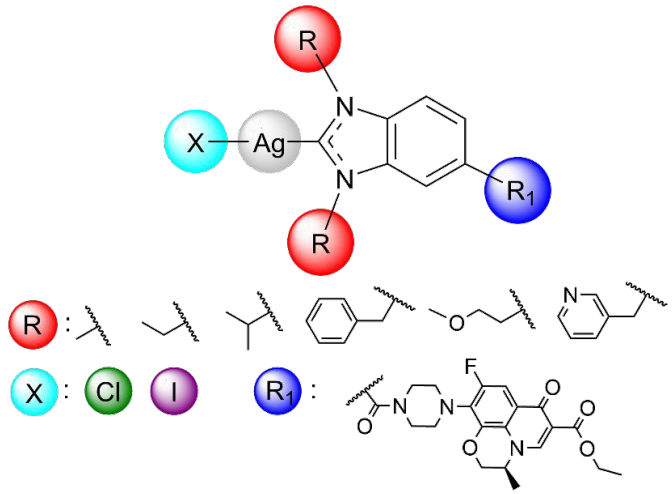

Figure 1. Different modification sites of Ag(I) NHC complexes, which can affect antibacterial activity

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SL21

Ferrocenyl β-Diketonate Compounds: A Versatile Platform for Increased Anti-Cancer Activity

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Functionalizing anti-cancer drugs with ferrocenyl groups has emerged as an effective approach to enhance their activity and overcome drug resistance through a dual mode of action.[1] However, modifying existing anti-cancer agents in this way can be synthetically demanding, often involving complex, multi-step procedures. An alternative strategy involves the synthesis of ferrocenyl-functionalized chelators, which can then be incorporated into metallodrugs. For instance, we previously developed a straightforward method to introduce ferrocenyl groups into β-diketonates, resulting in compounds with >18-fold increase in cytotoxicity against cancer cell lines.[2] Furthermore, coordination of these ligands with Ru(II) bipyridine or arene complexes produced highly potent anti-cancer agents, with activities in the nanomolar range.[3,4]

Despite these advances, a systematic investigation to identify the most active ligand frameworks has been lacking. To address this, we report herein a series of aryl- and benzyl-substituted ferrocenyl β-diketonate compounds. These have been fully characterized and evaluated for their biological activity against multiple cell lines.[5] The results confirm a dual mode of action, including the generation of reactive oxygen species. Notably, the anthracenyl derivative (inset, **Figure 1**) yields a fluorescent degradation product, which has enabled visualization of its intracellular localization using confocal microscopy.

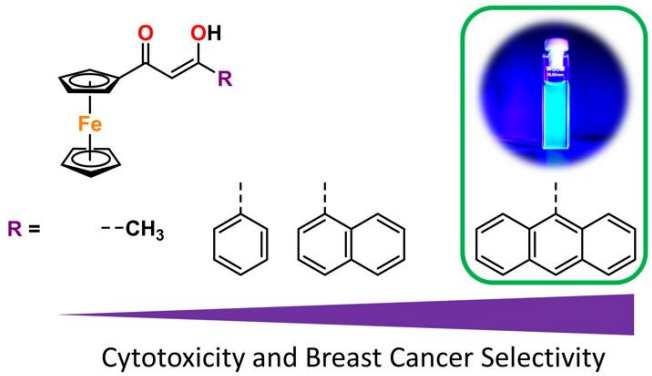

Figure 1: General structure of the presented ferrocenyl β-diketonate derivatives, highlighting the fluorescence of the decomposed anthracenyl derivative.

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SL22
Synthesis and Biological Evaluation of Ferrocene-Based Multitarget Antimitotic Agents

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Microtubule-targeting agents (MTAs) are among the most effective chemotherapeutic drugs for treating various cancers. Their mechanism of action involves disrupting microtubule dynamics, leading to mitotic arrest and cell death. However, despite their clinical success, MTAs suffer from major limitations, including systemic toxicity toward healthy proliferating cells and the emergence of multidrug resistance (MDR), often mediated by ABC transporters.

A promising strategy to overcome these limitations is the design of multitarget agents that can bypass resistance mechanisms or reduce the required therapeutic dose. One approach involves structural modification of known MTAs with organometallic fragments. We focus on introducing organometallic moieties into low-molecular-weight antimitotic compounds to enhance their biological activity, reduce toxicity, and potentially introduce novel mechanisms of action. We will present the synthesis and biological activity evaluation of newly developed ferrocene-containing analogues of selected MTAs.

Acknowledgments: These studies were financially supported by the National Science Centre (NCN), grant no. 2024/53/B/NZ7/04162.

SL23
From Dino Doom to Bio-Boom: Iridium Tagging Strategies for Detection and Imaging

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The element iridium, once famously linked to the asteroid impact that led to the extinction of the dinosaurs, is now paving the way for a new era of molecular exploration.

In this work, we explore the use of cyclometalated iridium(III) complexes as luminescent tags for the detection of enzymatic activity in live cells [1]. These organometallic complexes display ideal photophysical properties for bioimaging, including long-lived phosphorescence, high quantum yields, excellent photostability, and large Stokes shifts, enabling efficient background suppression via time-resolved emission techniques.

Our strategy relies on the metabolic incorporation of chemically modified sugar derivatives bearing a bioorthogonal reactive handle. Upon enzymatic cleavage by endogenous glycosidases, these masked sugars are unmasked and subsequently labeled with an azide-functionalized iridium(III) complex via strain-promoted click chemistry. The resulting conjugates generate a bright and selective luminescent signal at the site of enzymatic activity. This modular approach allows for spatiotemporal control of signal generation, leveraging the unique spectral fingerprints of iridium to overcome background autofluorescence and improve signal-to-noise ratios through time-resolved emission microscopy (TREM).

This work highlights the synergy between organometallic chemistry, metabolic engineering, and bioorthogonal strategies to develop next-generation imaging tools for cellular biology.

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SL24

A nanoencapsulated Ir(III)-phthalocyanine photosensitizer for hypoxia-tolerant photodynamic therapy

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Photodynamic therapy (PDT) faces significant limitations in treating hypoxic tumors due to the oxygen dependence of conventional photosensitizers.[1] In this study[2], we investigated a novel nanoencapsulated Ir(III)-phthalocyanine conjugate (**Ir-ZnPc-NCs**), designed to overcome such challenges by combining red-light activation with dual Type I and Type II reactive oxygen species (ROS) generation. Encapsulation in amphoteric redox-responsive polyurethane-polyurea nanocapsules improved water solubility, photostability, and cellular uptake, particularly enhancing endocytosis-mediated internalization into HeLa cells. Fluorescent imaging confirmed efficient intracellular delivery and lysosomal localization, key for controlled phototoxic activation.

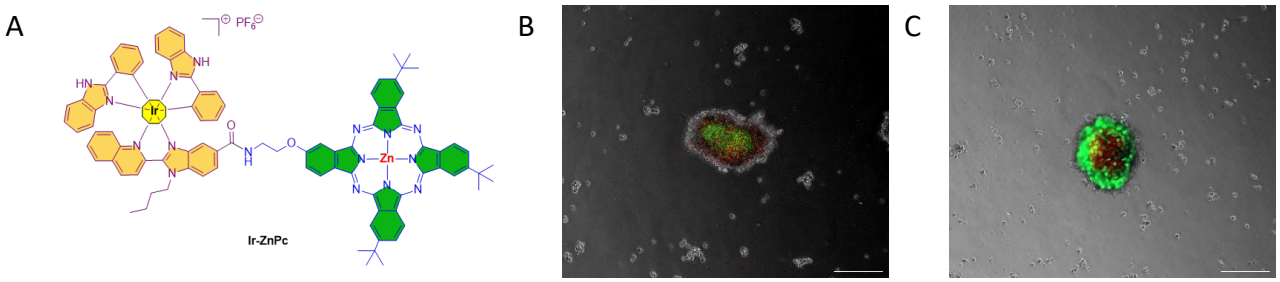

Figure 1. (A) Structure of the Ir(III)-phthalocyanine conjugate (**Ir-ZnPc**). HeLa spheroids treated with (B) **ZnPc-NCs** and (C) **Ir-ZnPc-NCs**, irradiated with red light and double-stained with Calcein AM and propidium iodide. Scale bar: 200 µm.

According to *in vitro* evaluations, **Ir-ZnPc-NCs** exhibited potent photocytotoxicity in both normoxic and hypoxic environments, attributed to the combined production of singlet oxygen, superoxide, and hydroxyl radicals. Notably, treatment led to significant ROS-induced stress and growth inhibition in 2D cultures and 3D multicellular tumor spheroids, simulating the tumor microenvironment. These findings demonstrate the potential of **Ir-ZnPc-NCs** as biologically effective nano-PDT agents, particularly valuable for targeting solid tumors with low oxygen levels.

Financial support from MICIU/AEI (RTI2018-096891-B-I00, PID2020-117508RB-I00, PID2020-117855RB-I00, PID2021-122850NB-I00), FEDER, EU funds (PID2021-122850NB-I00) and Generalitat de Catalunya (2017 DI 072) is acknowledged.

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SL25
A Trojan Horse Approach for Overcoming Antibiotic Resistance using Nature's Most Beautiful Cofactor

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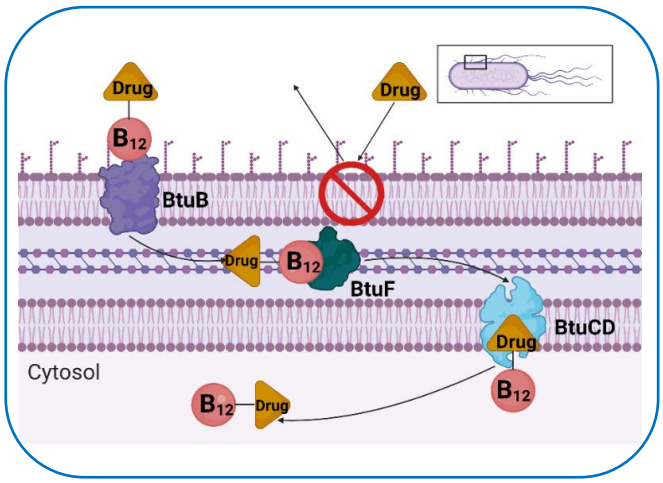
Increasing resistance of infection-inducing bacteria to antibiotics has now reached pandemic levels. Treating Gram-negative bacterial infections is especially challenging. This is because Gram-negative bacteria have an additional protective outer membrane which prevents the uptake of numerous antibiotic classes. Most major antibiotics active against Gram-negative pathogens enter the bacterial cell through passive processes. There is an urgent need for new strategies to treat these infections beyond this traditional approach.

The active uptake system of the deep, red-coloured micronutrient vitamin B_{12} which has been referred to as "Nature's most beautiful cofactor", can be exploited to deliver peptide nucleic acids and the antibiotic ampicillin into Gram-negative bacteria.[1-4] Vitamin B_{12} is essential for humans and most bacterial species. Even bacteria that synthesise B_{12} prefer to scavenge B_{12}. Gram-negative bacteria actively import B_{12} and B_{12} analogues, via the highly conserved BtuBFCD pathway.[5]

In proof-of-principle experiments we have synthesized a series of fluorescent vitamin B_{12} and vitamin B_{12} analogue cobinamide complexes and investigated their uptake and intracellular localisation in bacterial and mammalian cells. Vitamin B_{12} conjugates of antibiotics that are currently in use have also been synthesized and their antibiotic properties assessed.



The vitamin B_{12} specific uptake system in *E. coli*, involving BtuB, TonB (not shown), BtuF and BtuCD.

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SL26

Ferrocene Correlates with Ferroptosis: Multiple Approaches to Explore Ferrocene-appended GPX4 Inhibitors as Anticancer Agents

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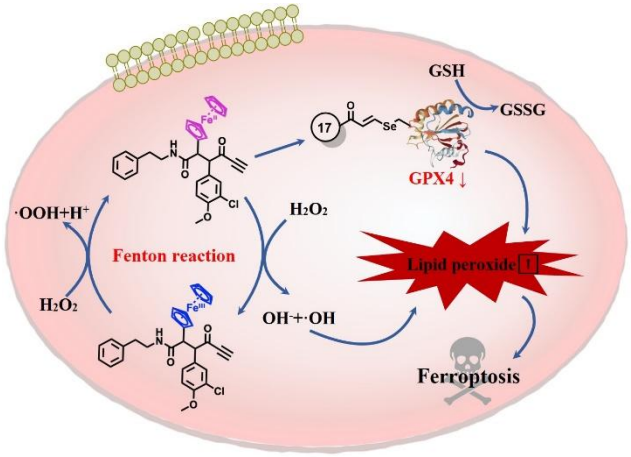
Ferroptosis, which was defined in 2012 as an iron-dependent form of programmed cell death caused by increased cellular reactive oxygen species (ROS) and lipid peroxidation (LPO), exhibits remarkable promise for anticancer therapy.[1] The driving force of ferroptosis arises from the iron-catalyzed Fenton reaction, making it worthwhile to explore the effect of ferrocene in the framework of ferroptosis. Initially, we have carried out the ferroptosis-based phenotypic screening of our in-house organometallic compound library and found that, none of those organometallics could induce ferroptosis selectively. These unexpected results contradicted the conventional perception of ferrocene for ferroptosis and drove us towards the rational design of ferrocene-based ferroptosis inducers.



We report two series of ferrocenyl-appended GPX4 inhibitors as ferroptosis induces rationally designed in a "one stone kills two birds" strategy.[2,3] Ferroptosis selectivity assays, GPX4 inhibitory activity and CETSA experiments validated the inhibition of novel compounds on GPX4. These data confirmed the dual role of ferrocene as both the bioisostere motif maintaining the inhibition capacity of certain molecules with GPX4 and also as the ROS producer to enhance the vulnerability to ferroptosis of cancer cells, thereby attenuating tumor growth in vivo. This proof-of-concept study of ferrocenyl-appended ferroptosis inducers via rational design may not only advance the development of ferroptosis-based anticancer treatment, but also illuminate the multiple roles of the ferrocenyl component, thus opening the way to novel bioorganometallics for potential disease therapies.

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SL27
Stimuli-responsive Prodrug Activation in Mitochondria for Improved Chemotherapy

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Mitochondria, the 'powerhouse of the cell' or 'local energy gradients' serve as highly dynamic organelles and arbitrators of cell's life and death. Incessant proliferation and undaunted growth of cancer cells are nourished by the immensely exploitation of the mitochondria. The design of mitochondria-demolishing anticancer agents can, therefore, be the significant weapons for efficiently treating the cancer. But chemoresistance and systemic toxicity are inexorable issues associated with the traditional chemotherapy. To securely cut-off the energy source of the cancer cells, contriving of the mitochondria-targeting prodrugs will be "kill of two birds with one stone" strategy, where prodrugs remain inactive at the outset and liberate active form of the drugs either by internal stimuli like copious thiols, acidic pH, and reactive oxygen species (ROS) in tumour tissue microenvironment or by external stimuli like localised light, ultrasound, electric impulse, magnetic field and radiation after reaching at the target-site. To abate the world-wide rampant prevalence of cancer, recently we have developed organelle targeted Ru(II)/Ir(III)/Re based half-sandwich and cyclometallated complexes for ROS mediated selective dynamic therapy with or without visible light irradiation (CDT or PDT) enhancing the therapeutic potential against the distinct tumour microenvironment (TME) (**Figure 1**).

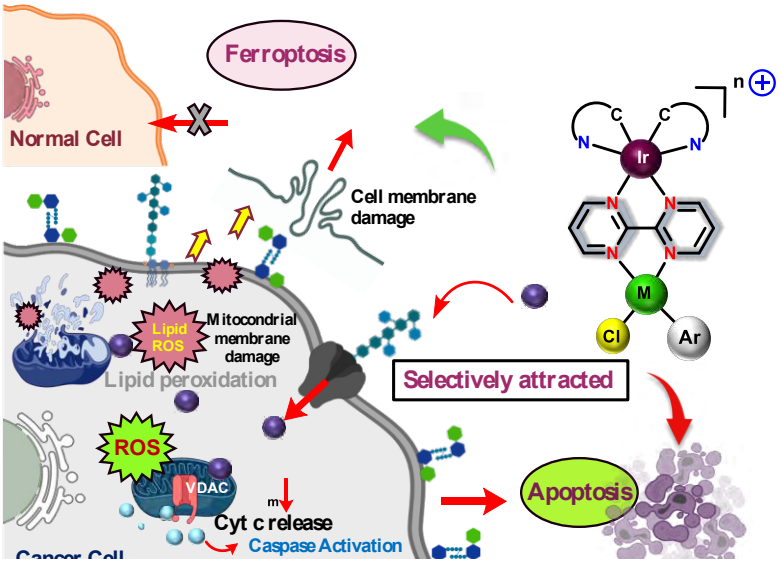

Figure 1: Mechanistic pathway of metal complexes in mitochondria for cell death

SL28
Theranostic clinical study with 188 Re P2045 in lung cancer expressing SSTR and well differentiated Neuroendocrine tumours

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Abstract

Despite recent advances in cancer therapy, there continues to be significant medical need for molecular level targeted cancer treatments. Peptide receptor targeted radiotherapy is a selective therapeutic approach demonstrated to be effective in the treatment of certain solid tumors. Labeling targeting peptides with radionuclides can achieve both noninvasive diagnosis and targeted radiotherapy, which is the essence of theranosis. Somatostatin receptor subtype 2 (SSTR2) is widely up-regulated in many lung cancers, well differentiated neuroendocrine tumors (NETs) as well as in tumoral (but not mature) vasculature. To evaluate the biodistribution, efficacy, and safety of Rhenium 188 Re P2045, a radiolabeled somatostatin analog specific for SSTR2, to both image and treat lung cancer and neuroendocrine tumors in patients overexpressing the somatostatin receptor, a phase I trial of was performed.

Methods: In an open label, single arm study, refractory lung cancer and metastatic neuroendocrine tumor patients were first identified by image analysis. 25 Patients received an imaging dose of 7-10mCi of 188 Re and 265ng of peptide by intravenous injection. Three patients were selected, based on high SSTR expression levels, to receive a therapeutic dose of 30-50 mCi of 188 Re P2045 within 14 days after imaging. Patients were followed for 12 weeks post treatment.

Results: Imaging revealed a high density of somatostatin receptor expression in well differentiated NETs of patients. Images obtained using 188 Re P2045 demonstrated accurate detection of lung cancers with SSTR expression in a subset of patients with refractory lung cancer. The scans obtained with 188 Re P2045 were of sufficiently high quality to enable identification of receptor expression at the tumor site. Image-based analysis revealed that patients who received the therapeutic dose of 188 Re P2045 had a reduction in tumor mass compared to patients receiving the standard of care. No adverse events or signs of toxicity were reported by patients in either the imaging or treatment group.

SL29
Synthesis and Investigation of Monometallic and Heterobimetallic Re(I)/Au(I) Complexes for Cell Imaging Applications

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Over the past few years, metal complexes have attracted increasing interest for their potential in medicinal applications. In addition to their therapeutic potential, metal complexes have also been explored for diagnostic purposes. To combine both properties within a single molecule, heterobimetallic complexes have emerged as promising candidates for theranostic applications.[1] In this context, the investigation of biological targets, biodistribution, and subcellular localization is essential. The insights into the mode of action of heterobimetallic complexes can guide strategic synthetic modifications to enhance both their therapeutic efficacy and diagnostic performance. This study presents the synthesis and *in vitro* evaluation of two heterobimetallic complexes containing Re(I) and Au(I) as metal centers. Inspired by the work of the Wilson group on tricarbonyl rhenium isonitrile polypyridyl (TRIP) complexes, a monometallic Re(I) complex was initially designed.[2] Additionally, a monometallic Au(I) complex and two heterobimetallic Re(I)/Au(I) complexes were synthesized. Notably, the novel heterobimetallic Re(I)/Au(I) complexes demonstrated promising results compared to their monometallic counterparts, while remaining easily traceable within cells. The intracellular integrity of the heterobimetallic complex and the maintenance of both metal centers within the complex were explored by confocal fluorescence microscopy and X-ray fluorescence (XRF) imaging. We are currently investigating the potential of our metal complexes as cell imaging agents.

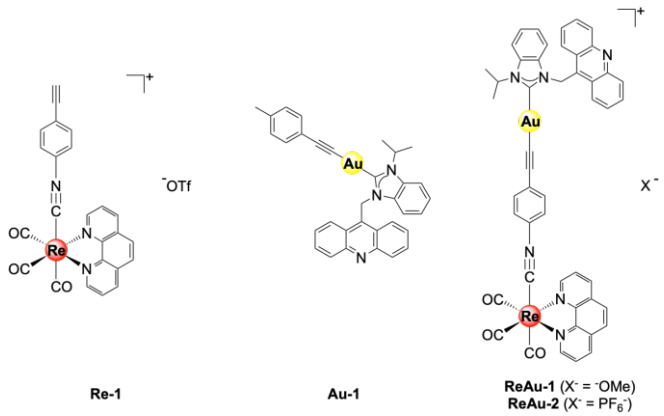

Figure 1. Structures of the monometallic Re(I) and Au(I) complexes and the heterobimetallic Re(I)/Au(I) complexes.

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SL30
Modulation of Redox potential in Ferrocene-peptide conjugates with potential antitumor activity

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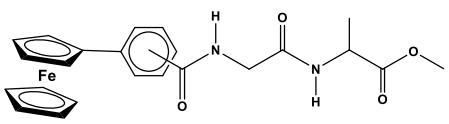
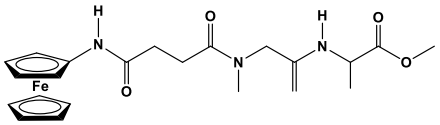
New anticancer therapies are currently much needed. Our contribution aims at synthesizing and studying ferrocene-peptide conjugates to be tested as anti-tumor agents. The peptide is intended to selectively address over-expressed integrins of cancer cells, whereas ferrocene is expected to display anti-proliferative activity through the production of reactive oxygen species (ROS) and its potential (0.40 V vs SCE) is compatible with the intracellular potential which varies from +0.40 V to -0.44 V. A concentration of ROS higher than normal favors carcinogenesis, but if this exceeds a certain value then a cytotoxic effect is observed. The exogenous production of ROS, consequently, represents a possible strategy to induce apoptosis in diseased cells.
We synthesized compounds made up of three components: i) a ferrocene unit as an electroactive element; ii) a linker to adjust the oxidation potential of Fc to the physiological conditions; iii) a di- or tripeptide, including the well-known RGD, capable of interacting with over-expressed receptors of the cancer cells.
The role of the linker consists in modulating the oxidation potential of ferrocene in order to make the structure more easily oxidizable in a cellular environment. In an attempt to modulate the redox potential appropriate to physiological conditions, we followed different strategies synthetizing linkers containing (a) Fc-benzoil-CONH-peptides, in which the aromatic group is able to reduce the oxidation potential of Fc by compensating the electron-withdrawing effect of the carbonyl, (b) a ferrocene unit linked to the peptide via an amide bond, but N-linked to the ferrocene and not the carbonyl, as reported in the literature so far. The transition from an electron-withdrawing group (-CO-NH-) to an electron-donating one (-NH-CO-) involves a significant change in the redox potential, with probable notable effects also on biological behavior.



(a)



(b)

On these molecules we carried out conformational studies in solution (^{1}H NMR, IR and CD) and an in-depth electrochemical investigation by cyclic voltammetry. Furthermore, we performed enzymatic degradation tests through treatment with human serum. As expected, the ferrocene unit acts as a protector of the peptide portion. After 24 hours from the start of the treatment, significant amounts of the conjugates are still detected. The shortest spacers gave the best results as ferrocene is closer to the peptide.

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SL31

Luminescent organometallic iridium(III) complexes as affinity-based probes for imaging subcellular biomolecule biomarkers

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Recent advancements in bioimaging have highlighted the critical need for robust molecular probes capable of visualization of subcellular biomolecule biomarkers. Traditional fluorescent dyes often suffer from limitations such as photobleaching or insufficient specificity. In this context, luminescent organometallic iridium(III) complexes have emerged as promising alternatives due to their unique photophysical properties, including long-lived phosphorescence, large Stokes shifts, and tunable emission wavelengths. Here, we present the design, synthesis, and application of iridium(III)-based affinity probes for real-time imaging of subcellular biomolecule biomarkers. We systematically modified iridium(III) complexes with targeting moieties, such as small-molecule ligands or peptide sequences, to achieve selective binding to specific biomolecules, including membrane epidermal growth factor receptor (EGFR), prostate-specific membrane antigen (PSMA), and mitochondrial glutathione *S*-tranferase (GST), pyruvate dehydrogenase kinase 1 (PDK1) and G-quadruplex (G4). Spectroscopic characterization revealed that the complexes exhibited luminescence enhancement against these biomolecules in aqueous media. Confocal studies confirmed their subcellular location, while competitive binding assays and siRNA knockdown experiments confirmed the affinity-driven targeting mechanism, with minimal off-target binding observed. These work establish luminescent iridium(III) complexes as versatile, affinity-based tools for subcellular biomolecule imaging, and these findings hold significant potential for advancing diagnostics, drug screening, and fundamental studies of biological process.

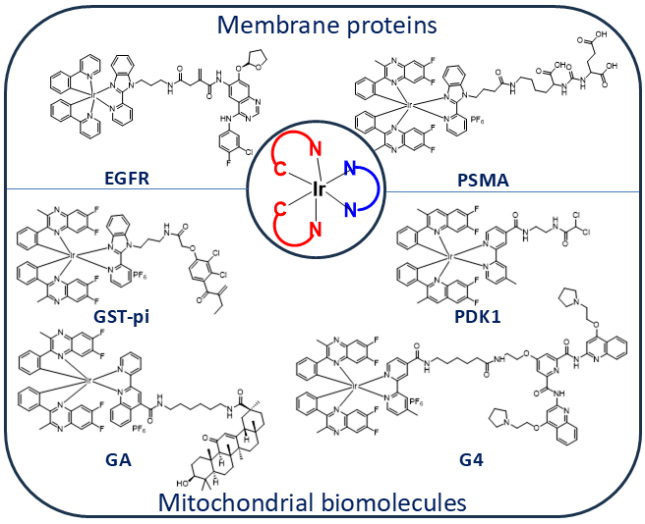

Figure Luminescent iridium(III) complexes as affinity-based probes for imaging subcellular biomolecule biomarkers

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SL32
Unveiling the in vitro/in vivo potential of Co(III)-cp complexes

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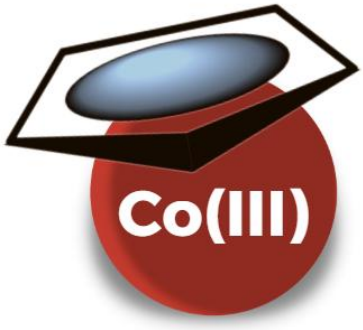
Cancer remains a burden in society, with 19 M new cases and 10 M deaths only last year.[1] Platinum metallodrugs are among the most used anticancer chemotherapeutics. Nonetheless, they show limited efficacy, acquired drug resistance, and severe side effects. Alternative therapeutic approaches are of urgent need. Within this, one important strategy is based on designing new complexes containing endogenous metals, which may lead to lower systemic toxicity than conventional metallodrugs and reach specific biological targets more easily. Cobalt is an essential element for life, playing a key role in several biological processes of the human body. Inorganic complexes of cobalt have shown promising therapeutic proprieties, yet the anticancer potential of Co(III) organometallic complexes remains scarcely studied and exploited.[2]



Herein, we report the synthesis and structural characterization of a new family of organometallic Co(III)(η^5-C_5H_5) complexes.[3] Their cytotoxic activity was evaluated *in vitro* using the MTS assay in colorectal, ovarian, and breast cancer cell lines, as well as in healthy fibroblasts. Cellular uptake was assessed by ICP-AES. Additionally, the mechanisms of cell death and ROS production will be discussed. To further explore their biological effects, an ex ovo chick embryo yolk sac membrane (YSM) assay was conducted to investigate their potential to modulate angiogenesis and assess *in vivo* toxicity.

Acknowledgments
We thank the Fundação para a Ciência e Tecnologia (FCT), I.P./MCTES for the financial support through the projects UIDB/00100/2020 (CQE, DOI 10.54499/UIDB/00100/2020), LA/P/0056/2020 (IMS, DOI 10.54499/LA/P/0056/2020), UIDP/04378/2020 (DOI 10.54499/UIDP/04378/2020), and UIDB/04378/2020 (10.54499/UIDB/04378/20209, LA/P/0140/2020 (i4HB), UIDB/50006/2020 | UIDP/50006/2020 (LAQV-REQUIMTE). TSM also thanks FCT POPH and FSE-European Social Funds for the Individual Call to Scientific Employment Stimulus 2022.00028.CEECIND/CP1722/CT0005 project (DOI 10.54499/2022.00028.CEECIND/CP1722/CT0005).

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SL33

Gold Acyclic Diaminocarbene Complexes: A Promising Class of Multitarget Anticancer Agents

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In the development of gold chemotherapeutics, ligand design plays a important role. Acyclic diaminocarbene (ADC) ligands are emerging as a promising class of ligands due to their flexible, open-chain structure and high electron density. While gold-based NHCs have been extensively studied for their antitumor potential, research on ADC gold complexes in biological applications remains limited. Existing studies on gold(I) and gold(III) ADC derivatives exhibit variable cytotoxicity and their mechanisms of action are not well understood.[1] Further research is needed to explore their biological targets and improve selectivity for tumor cells.

To address this gap, we synthesize chiral and achiral gold-ADC complexes with varying stoichiometries and ancillary ligands. Three types of complexes gold-chloride-ADC, bis(carbene), and thiolate-gold-ADC were evaluated to assess how ancillary ligands affect. Most of these complexes exhibit remarkable cytotoxic activity, with IC50 values ranging from the nanomolar to low micromolar range against highly resistant cancer cell lines. Notably, some complexes demonstrate high selectivity, causing minimal toxicity in healthy lymphocytes, achieving a selectivity index of 74. Mechanistic studies reveal that these complexes induce mitochondrial damage, generate ROS, and, in the case of bis(carbene) species, exhibit DNA-binding properties. Experiments with caspase inhibitors and concentration-dependent assays indicate that these complexes trigger apoptotic cell death at low concentrations while activating alternative cell death pathways at higher doses. Additionally, they show strong TrxR inhibition, with potency comparable to Auranofin. Their multitargeted mechanism combining ROS generation, mitochondrial damage, DNA binding, and TrxR inhibition along with their high selectivity and effectiveness, highlights their strong potential as anticancer agents.

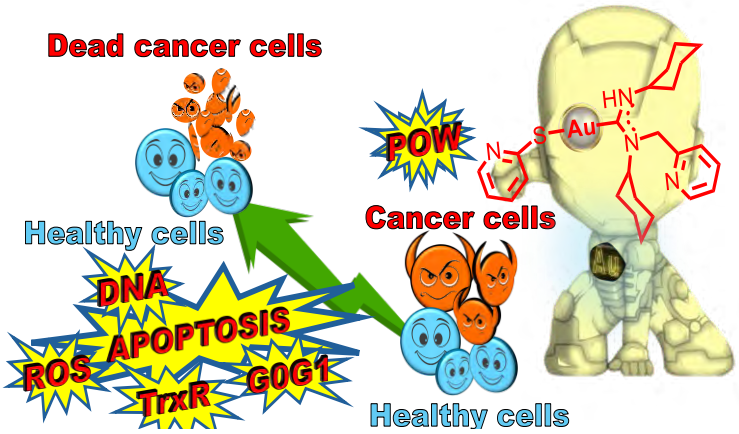

Figure 1: Mechanism of ADC gold complexes

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SL34
Towards Atomically Precise Gold Nanoclusters Application in Nanomedicine

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Despite the late appearance of molecular gold nanoclusters (Au NCs) stabilized by N-heterocyclic carbene (NHC) ligands,[1] we have successfully reported a new synthetic methodology to obtain three new classes of mixed PPh_3 and NHC ligated AuNCs through a controllable reaction sequence.[2] Exploiting the strict stoichiometric control on the ligand sphere, a precise structural regulation at atomic level of these nanometric supramolecules is derived, also reflected in their chemical physical properties.
Exhibiting strong optical absorption in the visible region and equally strong luminescence in solution, Au NCs are frequently reported as contrast agents in bioimaging or photodynamic therapy (PDT) agents in the medicinal field, directing the synthetic efforts in reaching good stability in biological media and nontoxicity at the working concentrations[3].
In our case, relying on a robust synthetic approach, a systematic study in complex biological media is accessible, aimed at assessing their stability, optical properties, and possible interactions with biomacromolecules, up to clarify the impact of NHC ligated AuNCs on cellular recognition and response. Supported by the promising results of gold-based species as potential anticancer agents and their actual involvement in medicine as anti-inflammatory drugs, we present here the results of our first systematic investigation on the potency and efficacy of AuNCs as antitumoral agents, which demonstrate that these clusters can display very high activity (in the micromolar to sub-micromolar range) and/or selectivity for particular strains of tumoral cells. Whereas ligand Au_{11} clusters display the lowest IC_{50}s, Au_{13} clusters can exhibit preferential cytotoxicity for some cancer cell lines, while remaining nontoxic towards healthy cells.
If differences in nuclearity can exquisitely tune NCs activity, selectivity against tumoral cells is ensured only by the right choice of L-type ligands which is constrained to the use of mixed phosphine and carbene donors for NCs stabilization.
The mechanism of action of these clusters has been preliminarily investigated and it surprisingly appears not to conform to the commonly assumed one for gold compounds (i.e. thioredoxin reductase inhibition). More-in-depth, these investigations speak against cytotoxicity arising from gold complexes slowly being released upon controlled Au NC decomposition after having been internalized by cells.

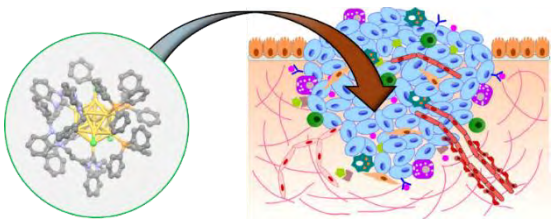

Figure Type **3** cluster $[Au_{13}(di\text{-}NHC)_3(PPh_3)_3Cl_3]^{2+}$ as potential anticancer agent.

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SL35
Chemistry and Bioactivity of Ferrocenyl Quinone Methides

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The antiproliferative behaviour of the ferrocifens, derived by replacing a phenyl substituent in tamoxifen by ferrocenyl, and also in their diphenol counterparts, against both ER+ and ER- breast cancers may be attributed to two key factors: the redox-mediated formation of reactive oxygen species (ROS), and the formation of ferrocenyl quinone methides (Fc-QMs) that inhibit the ability of thioredoxin reductase to function, thereby weakening the cell's defence towards ROS [1].
Metabolites arising from the reactions of these Fc-QMs are generated from a variety of novel reactions and molecular rearrangements. These include the generation of spiro-bonded dihydro- and tetrahydro-furans and pyrans, ferrocenyl-indenes, and ferrocenyl migrations, all arising in a stepwise manner via the intermediacy of ferrocenyl quinone-methide cations (Figure 1).

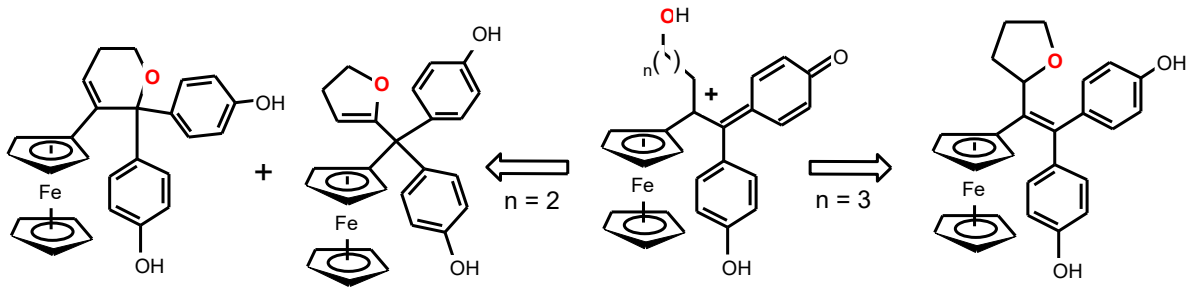

Figure 1. Molecular rearrangements of hydroxyalkyl-ferrocenyl QMs.

X-ray crystal structures of Fc-QMs bearing alkyl-imido substituents reveal the existence of novel lone pair-π* interactions, exemplified in Figure 2, that enhance their stabilities and lifetimes and allow a rationalisation of their effectiveness against a wide range of tumours.

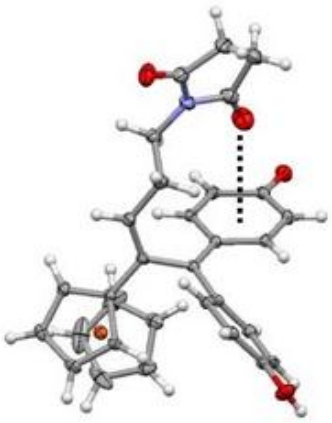

Figure 2. The lone pair-π* interaction of a succimidyl oxygen with the quinone methide moiety in a ferrocenyl-QM.

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SL36
Metalloantibiotics - Starting to Understand How They Work

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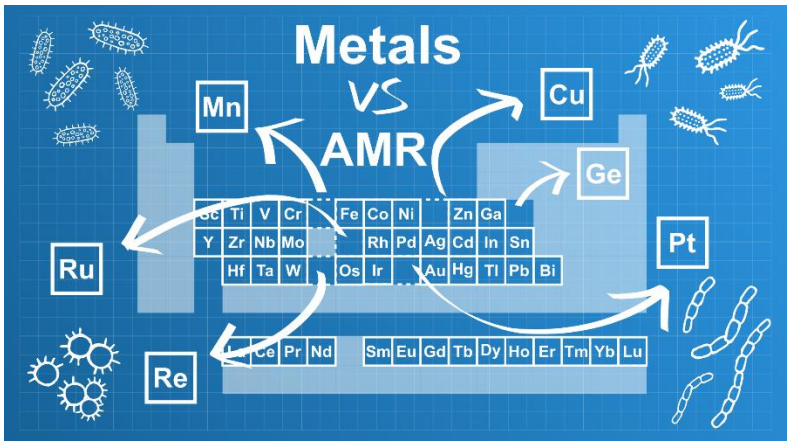
While current antibiotics are failing with increasing rates, the pipeline for new effective drugs is sparse with <50 compounds in clinical trials. In comparison, there are over 1000 drugs in clinical trials for the treatment of cancer. As conventional approaches to bacterial infections are failing to provide novel and effective drugs, alternative treatment modalities need to be considered. Over the last decade, metal-based compounds (metalloantibiotics), have gained attention as potential new antimicrobial agents.[1] Despite this rise in interest the number of studied metalloantibiotics is still low and our understanding of how metalloantibiotics elicit their biological effects is extremely limited.[2]

In this talk I will highlight some of the metalloantibiotic compound classes we have discovered in recent years and the progress we have made towards understanding their biological effects utilizing both state-of-the-art techniques and applying metal-specific approaches to the task.



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SL37
Rational design of multifunctional organometallics as prospective agents against Neglected Diseases

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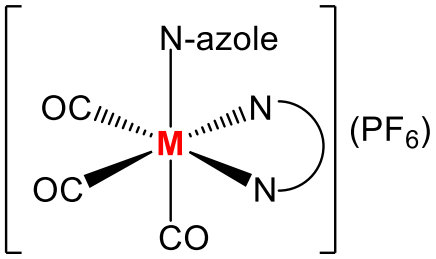
Diseases caused by the trypanosomatid parasites *Trypanosoma cruzi* and *Leishmania infantum* are considered neglected by the World Health Organization. The lack of suitable chemotherapy underscores the pressing need for the development of novel, potent, and non-toxic drugs. The exploration of organometallic compounds has emerged as a promising strategy in the quest for enhanced and safer chemotherapy for addressing these illnesses. Our team has played a role in showcasing that the hybridization strategy involving an organometallic center and a bioactive organic ligand often results in antiparasitic compounds with enhanced biological properties compared to the free ligands and efficacy against multiple parasite targets.[1] Our recent work has focused on the development of multifunctional Re(I) tricarbonyls and their Mn(I) counterparts, *fac*-[M^{I}(CO)$_3$(NN)(CTZ)](PF$_6$) (see Figure). These compounds incorporate two distinct bioactive ligands with proven activity against *T. cruzi*: a bidentate 1,10-phenanthroline derivative (NN) and the monodentate azole Clotrimazole (CTZ).[2,3] Their activity on *T. cruzi* and *L. infantum*, stability in biological media, lipophilicity, inhibitory effects on ergosterol biosynthesis, potential as carbon monoxide-releasing molecules, parasites uptake and proteomic impact have been thoroughly compared.[3] Although the Re series exhibited good antiparasitic activity, it also displayed relatively high nonspecific toxicity in VERO cells, a mammalian cell model. To enhance antiparasitic efficacy while reducing cytotoxicity, we pursued rational structural modifications, including replacing Re by Mn, changing the azole ligand or counterion, and incorporating a non-phenanthroline bioactive bidentate ligand. The outcomes of some of these strategies will be discussed.



fac-[M^{I}(CO)$_3$(NN)(CTZ)](PF$_6$)

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SL38

Antibiotic Rhenium Carbonyl Complexes: Key Molecular Features Mediating *in vivo* Antimicrobial Activity and Toxicity

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Antimicrobial resistance (AMR) is a major emerging threat to public health, causing serious issues in the successful prevention and treatment of persistent diseases. Rhenium carbonyl complexes have emerged as promising antimicrobial agents due to their critical combination of low in vivo toxicity and potent activity against Gram positive pathogens. Beyond the phenomenological models, much remains to be understood in terms of their mechanism(s) of action and the key molecular features modulating their *in vivo* antibiotic effectiveness and toxicity. With a focus on methicillin-resistant *S. aureus*, we have investigated the antimicrobial effects of hundreds of compounds. Our study allowed the identification of potent and non-toxic complexes active *in vivo* against *S. aureus* infections at MIC doses as low as 300 ng/mL, while showing no sign of cardio-, hepato-, hematotoxiciy or teratogenicity.[1, 2] Fundamental to the identification of such complexes is the understanding of the key molecular features of the compounds.[3, 4] In this contribution we present the antibiotic rhenium complexes identified, the inorganic and organometallic chemistry that allowed us to understand how to design the species, and aspects of the mechanism of action of the molecules in relation to bacterial membrane disruption, peptidoglycan synthesis and electron transport interference.

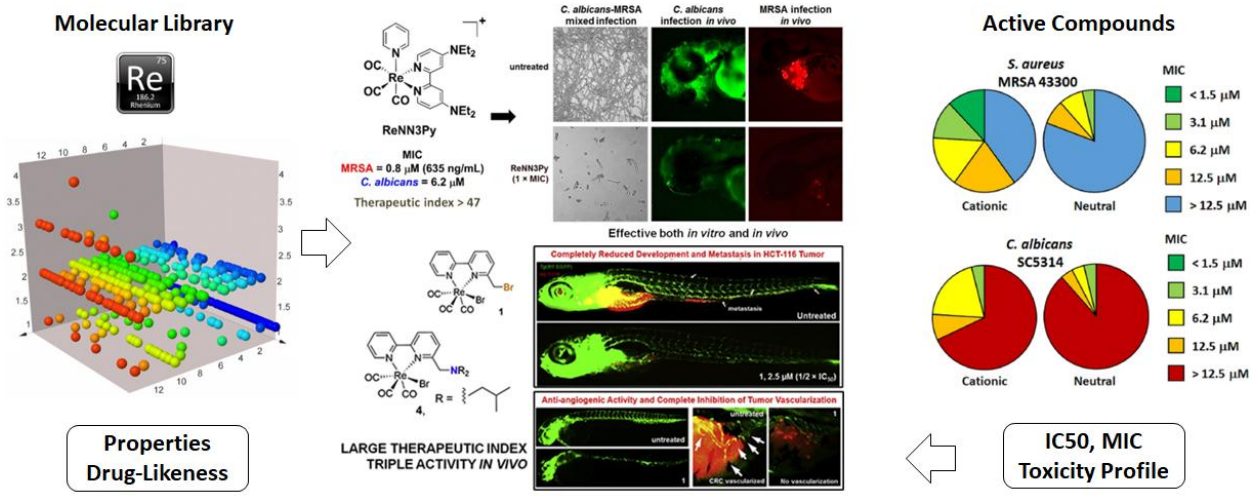

Figure From a molecular library of Rhenium complexes to key molecular features mediating potent and non-toxic complexes active *in vivo* against S. aureus infections.

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SL39

BiFcT a new ferrocene-based ferroptosis inducer to cancer cells

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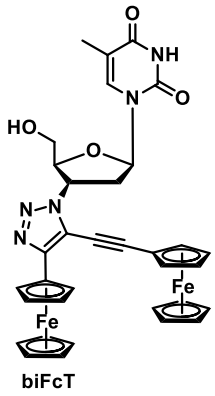
Ferroptosis[1] holds great promise for medicinal applications, including the development of new anticancer therapies and drugs. Ferroptosis is primarily linked to iron/ROS-induced accumulation of lipid peroxides in cell membranes. This deleterious lipid peroxidation is circumvented by the GSH/GPX4 and the cystine transporter system X_c-.



biFcT

Figure Structure of ferroptosis inducer **biFcT**.

Using a combination of *in vitro* assays, we demonstrated that our recently reported[2] **biFcT** nucleoside is a remarkably active anticancer agent against non-small cell lung cancer (NSCLC) A549 and H1975 cells. It acts as an ROS generator, causing oxidative damage to mitochondria and lipids.[3] Cancer cells treated with **biFcT** exhibit high levels of malondialdehyde (a lipid peroxidation endpoint marker) and protein carbonylation products. The membrane-targeting luminescent lipid ROS probe C11-BODIPY 581/591 also confirmed membranes damage. Notably, the deleterious effects of **biFcT** are alleviated by ferrostatin-1 which is an established ferroptosis inhibitor. Furthermore, the anticancer activity of **biFcT** in H1975 and A549 cells is not associated with caspase-3 activation. Collectively, these results show that **biFcT** functions as a ferroptosis inductor in NSCLC cancer cells. Its activity is based on two electronically coupled Fc^{2+}/Fc^{3+} entities acting as a "ROS-generating warhead."

Acknowledgments
K.K. thanks the National Science Center in Cracow, Poland (grant OPUS UMO-2024/53/B/ST5/00040) for financial support.

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SL40

Preparation, stability, photochemistry and anticancer study of photoactivatable Pt(IV) prodrugs bearing axial alkoxido Ligands

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Platinum-based drugs are widely used to treat various cancers in clinical settings, but their side effects and the development of resistance limit their efficacy. Photoactivatable Pt(IV) prodrugs can selectively activate within tumours, releasing Pt(II) agents and reactive oxygen species. The synergistic action of both components effectively kills tumour cells, offering a novel approach to mitigate the side effects and resistance associated with platinum drugs.[1] Yet, current photoactivatable Pt(IV) prodrugs, based on carboxylato axial ligands, are spontaneously activated by cellular reductants, causing toxicity in normal tissues. In this study, we employed ligand exchange reactions to synthesize Pt(IV) prodrugs with axial alkoxido ligands. These alkoxido Pt(IV) prodrugs demonstrated greater kinetic resistance to hydrolysis and reduction compared to their carboxylato Pt(IV) analogues, resulting in significantly reduced cytotoxicity.[2] We then conjugated a photosensitizer to the alkoxido Pt(IV) prodrug, which exhibited exceptional stability and resistance to reduction. Under light irradiation, the photosensitizer catalytically reduced the alkoxido Pt(IV) prodrug. Compared to conventional carboxylato photoactivatable Pt(IV) analogues, the alkoxido photoactivatable Pt(IV) prodrug showed a threefold reduction in dark toxicity while retaining comparable phototoxicity. This study advances the development of novel Pt(IV) prodrug scaffolds for controlled activation, providing new strategies to reduce toxicity associated with platinum drugs.

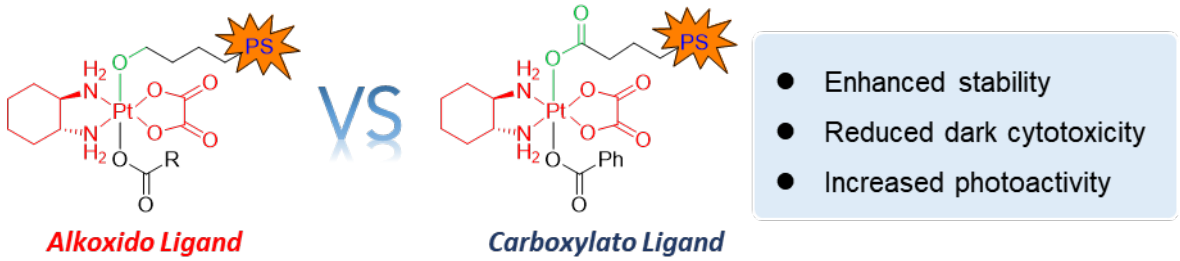

Figure Advantages of photoactivatable Pt(IV) complexes with axial alkoxido ligands compared to carboxylato ligands in photochemotherapy

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P01
Structure and Bonding in *fac*-Tricarbonylrhenium(I) Organometallic Complexes: A Theoretical Perspective

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In this work, a series of *fac*-tricarbonylrhenium(I) complexes derived from bipyridine analogues [1] were studied computationally. The crystal structures of the complexes were initially optimized using density functional theory (DFT) at the BP86/def2-TZVPP level of theory with the Gaussian 16 program. Since the complexes can adopt different rotamers and conformers, the Conformer–Rotamer Ensemble Sampling Tool (CREST) was employed to identify the most abundant conformers at the semi-empirical level of theory. The lowest-energy conformation was then refined using dispersion-corrected DFT calculations at the BP86-D3/def2-TZVPP level. Frequency calculations were carried out on the optimized geometries, and the absence of imaginary frequencies confirmed the location of the lowest-energy conformation of the complex.
The nature of the metal-to-ligand bonding was investigated using the Ziegler–Rauk-type energy decomposition analysis (ETS-EDA) method, as implemented in the ADF engine of the Amsterdam Modeling Suite (AMS), at the BP86/TZ2P level using the optimized geometries, which revealed the dative nature of the interactions. ETS-NOCV (Extended Transition State-Natural Orbitals for Chemical Valence) was used to decompose the orbital interactions into pairwise contributions, providing insight into the extent of forward donation and backdonation between the metal and ligands [2]. Additional bonding analyses were carried out using Natural Bond Orbital (NBO) analysis and Wiberg bond indices.

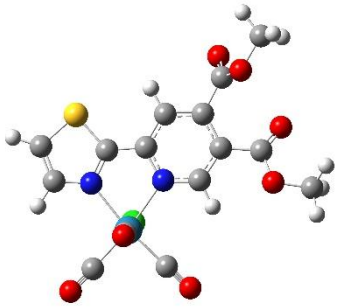

Figure: Optimized geometry of a selected Re(I) complex at the BP86-D3/def2-TZVPP level of theory

Funding information: This work was supported by the Marie Skłodowska-Curie EUTOPIA-SIF program under the EU Horizon 2020 grant No. 945380, with additional support from Vrije Universiteit Brussel (Belgium) and the University of Ljubljana (Slovenia)

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P02
Designing Cold Plasma Cleavable RGD-Metal Peptide Bioconjugates for Targeted Tumor Therapy

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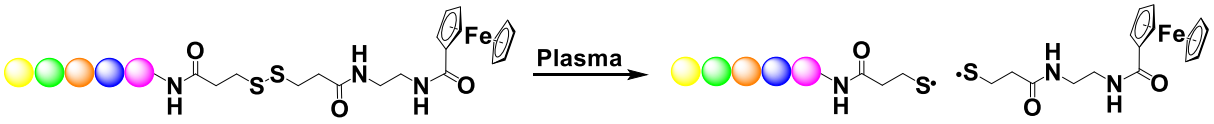
Cancer is a multifactorial disease resulting from various genetic and environmental factors. Metal based anticancer drugs are widely used for chemotherapy of various cancers. However, current therapies harbor several significant limitations such as poor selectivity and emergence of tumor resistance. Therefore, enhancing the tumor selectivity has become a major goal for the development of novel cytotoxic agents with drug delivery systems (DDS) for metallodrugs gaining increasing significance. Within this arena, so-called cell-targeting peptides (CTP) can be utilized to target specific receptors. Highly favored are RGD peptides with an amino acid sequence of Arg-Gly-Asp, which are widely known for their selectivity and affinity towards the tumor-associated $\alpha v\beta_3$ integrin receptor. A few of these RGD peptide derivatives, such as Cilengitide, have shown impressive results in preclinical trials.[1] In the past years, the effectiveness of drug delivery systems has been enhanced by adding physical energy to conventional DDSs. These techniques can potentially be utilized in different biological and medical applications as an advanced targeted drug delivery system, decreasing the current limitations and undesired side effects. Atmospheric pressure cold plasmas (APCP) are gaining increasing interest in biomedical trials for enhanced wound healing and skin disinfection. A typical plasma source for wound healing is a dielectric barrier discharge (DBD), which allows direct contact between the skin and the active plasma zone. In our previous studies, we investigated the time-dependent chemical modifications of GSH and GSSG in the presence of Fe(II) and Fe(III) complexes by DBD under ambient conditions.[3] In our current studies, we are focusing on the development and the synthesis of novel RGD peptide bioconjugates and their activation through cold atmospheric pressure plasma treatment. Therefore, a disulfide bridge linker will be inserted between the peptide and metal complex for plasma treated activated S-S bond cleavage. The peptide RGDfK will be synthesized in linear and cyclic versions to compare stability and activity under cold plasma conditions. Ferrocenecarboxylic acid was selected as the metal complex of interest for bioconjugation. We will report our efforts to optimize the cleavage conditions on the linear and cyclic metal peptide bioconjugate by APCP with several treatment times.



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P03
Multi-targeting Ir(III) Catalysts for the Treatment of Ovarian Cancer

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Cancer remains a leading cause of morbidity and mortality worldwide, necessitating continuous research into its etiology, early detection, and innovative treatment strategies. Ovarian cancer poses a significant challenge due to its late-stage diagnosis and limited therapeutic options[3], highlighting the need for advanced research and targeted interventions. Resistance to conventional cytotoxic platinum-based chemotherapy is commonly observed, and typically emerges within six months post-treatment[3]. To overcome this challenge, catalytic metal-based anticancer complexes have gained interest due to there ability to carry out reduction chemistry inside cancer cells[1,2,4]. Their mechanism mirrors the function of naturally occurring redox enzymes, which utilize coenzymes like NADH to transfer hydrides to acceptor molecules[1,2,4]. Three metal complexes [M(arene)Cl(diamine)] have been prepared, Ru-1 and Ir-1 [M(arene)Cl(TsEN)] with one example containing a known inhibitor of casein kinase 1 (CK1) as the diamine ligand.

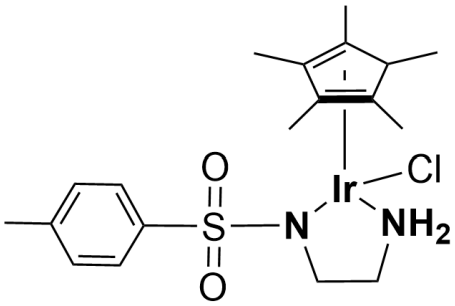

Figure Chemical structure of Ir-2 catalyst.

All three showed promising selectivity for cancer cells over normal cells, and interestingly, the catalyst containing a CK1 inhibitor also overcomes cisplatin cross-resistance. When the Ir complexes co-administered with a non-toxic dose of sodium formate, cell viability was decreased by ~ 46% and 51%, while no activity modulation was observed in non-cancerous cells (HOF).

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P04

Deciphering the cellular behaviour of organoruthenium(II)-pyrithionato complexes in ovarian cancers

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Ovarian cancer is an important societal burden which kills approximately one woman every two hours in the UK[1]. Innovations in treatments are limited, and chemotherapeutic regimes still heavily rely on the use of platinum drugs. This is particularly relevant for the up to 20% of patients who develop Pt-resistant recurrences[2]. Ruthenium piano-stool complexes have shown great promise to overcome this drawback and may well be developed as viable alternatives. In this work, we have used pyrithionato ligands, which have already been reported to have great potential for clinical use [3-4]. This time, we have focused in understanding the effect of fluoro- and cyano- substitutions on pyrithione cores, paying particular attention to the importance of their position on the aromatic ring. We have also investigated the contrasting cellular behaviour between complexes with triphenyl phosphite $(PhO)_3P$ and triphenylphosphine (Ph_3P) as monodentate ligands instead of the halogen.

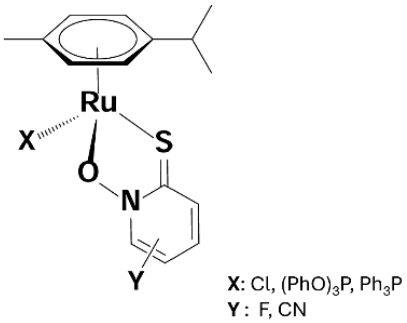

Figure Organoruthenium(II)-pyrithionato complexes

PPh_3-derived complex demonstrated significant anticancer activity, limiting the proliferation, migration, and aggregation of A2780 cells. In addition, it disrupted the cellular membrane integrity, altered mitochondrial membrane potential, increased the production of ROS, and induced an irregular nuclear morphology consistent with DNA packaging alterations. Phosphorus-containing complexes significantly induce late apoptosis populations and cell cycle arrest in the G2 phase with an increased sub-G1 population. No significant non-apoptotic alternate mechanisms of cell death have yet been identified with these complexes.

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P05

Expanding the Horizons of Organometallic Redox Intracellular Chemistry To Half-Sandwich Cobalt(III) Complexes

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Intracellular redox chemistry mediated by half-sandwich complexes of Ru(II), Os(II), Rh(III), and Ir(III) has emerged as a powerful strategy to monitor and modulate biological processes at the molecular level, with impactful applications in medicine and diagnostics.[1] The results obtained so far, provide a strong foundation for expanding the scope of organometallic-mediated intracellular redox chemistry to other metal complexes and substrates. Cobalt is a biologically essential first-row transition metal found in various cofactors and redox enzymes.[3] Compared to rhodium and iridium analogues, half-sandwich organometallic Co(III) complexes display distinct properties: different thermodynamic and kinetic stabilities, greater electronegativity, a harder Lewis acid character, and a richer redox chemistry, with accessible oxidation states ranging from 0 to +4 via one- or two-electron processes.[4] These properties make cobalt-based systems not only a more economical and biocompatible alternative to noble metal complexes but in some cases a unique platform for unlocking redox pathways inaccessible to their heavier counterparts.[4]

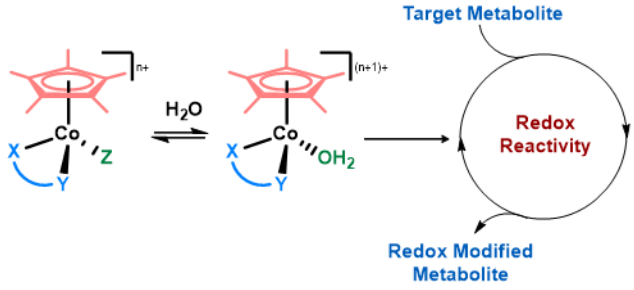

Figure Redox reactivity of the Co(III) complexes in aqueous systems

Herein, we report the development of a library of half-sandwich Co(III) complexes with the general formula [CoCp*(X-Y)Z]. These complexes were synthesized and fully characterized, incorporating diverse bidentate ligands (X-Y = N-N'; N-O; or N-C) and monodentate anions (Z = Cl^- or I^-). The variation in chelating and anionic ligands is designed to modulate the stereo-electronic properties and fine-tune the reactivity–stability balance in aqueous biological environments. The hydrolysis and stability of the complexes were systematically investigated, along with the pH speciation to support their application in biological systems. Cytotoxicity assays were conducted on various human cell lines to evaluate their potential bioactivity. Additionally, preliminary studies on their redox mediated reactivity in aqueous media were performed, laying the groundwork for translating Co-based redox catalysis into cellular systems.

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P06

Organometallic Modification of Letrozole with Cymantrenyl and Cyrhetrenyl Fragments: Exploring Hybrid and Full Organometallic Aromatase Inhibitors

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Hormone-dependent cancers are characterized by the presence of receptors that respond to sex hormones such as estrogen. Among current treatments, aromatase inhibitors (AIs) [1] have gained attention because, unlike selective estrogen receptor modulators (SERMs), they present a lower risk of endometrial cancer and thromboembolism. Letrozole [2] is one of the most active AIs in clinical use; however, it is associated with adverse effects such as hot flashes and fibromyalgia. This highlights the need to explore new AIs with improved safety profiles.

Inspired by the structure of letrozole, particularly its electronic features, we synthesized a series of compounds containing one or two organometallic fragments—cymantrenyl or cyretrenyl—known for their electron-withdrawing properties, along with a 1,2,4-triazole moiety, which is key to aromatase inhibition. The compounds were characterized using ^{1}H and ^{13}C NMR spectroscopy and, when possible, single-crystal X-ray diffraction (Figure 1). Their cytotoxicity and aromatase inhibition activities were evaluated.

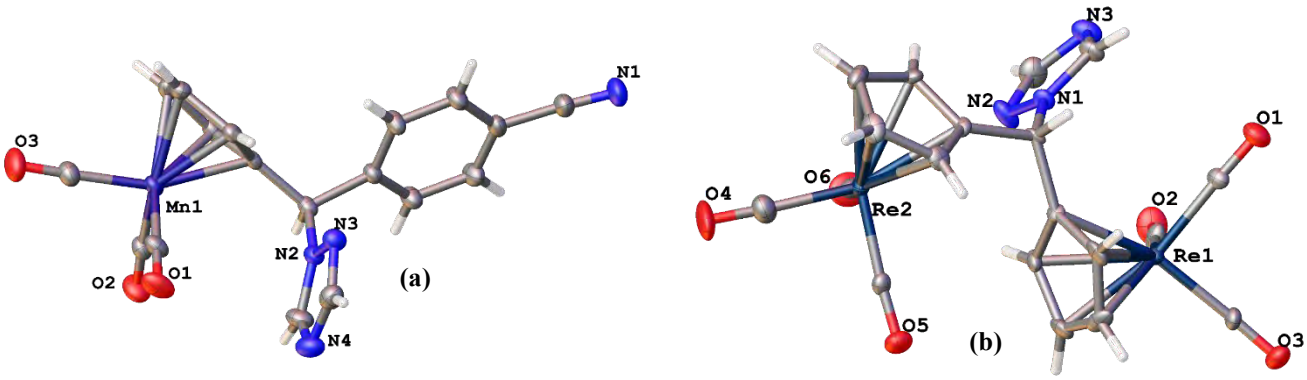

Figure 1. ORTEP diagram of the new bioorganometallic letrozole derivates.

Acknowledgements
We gratefully acknowledge funding from the FONDECYT project (1230296), which made this research possible.

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P07
Stereochemical Influence of Halogenated Iron(III) Complexes on Anticancer Activity

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Stereochemistry plays a critical role in drug design, as enantiomers can exhibit distinct differences in potency, pharmacodynamics, pharmacokinetics, as well as toxicity.[1] Chirality also influences the anticancer properties of non-platinum-based metallodrugs, including compounds based on gold and ruthenium.[2]

So far, only limited information of the influence of stereochemistry of iron complexes is available. In our group, we have already examined several meso-configured iron complexes.[3] In this study, new complexes were designed, chemically characterized, and biologically tested to investigate the influence of stereochemistry on biological activity.

A series of novel chlorido[*N*,*N*'-bis(chloro-/bromosalicylidene)-1,2-diarylethylenediamine)]iron(III) complexes, which differ in the diarylethylene backbone (*meso*, *racemic*, *SS*) and with 5-Br or 5-Cl substituents as well as 3-Br, 5-Cl substituents in the salicylidene moieties, were synthesized.

Complexes with 5-Br or 5-Cl substituents in the salicylidene moieties inhibited the proliferation and metabolic activity in the mammary carcinoma cell line MDA-MB 231, the cisplatin-sensitive and cisplatin-resistant ovarian carcinoma cell lines A2780 and A2780cis, and the acute myelogenous leukemia cell line HL-60 in a concentration-dependent manner, while sparing out non-malignant HS-5 stromal cells. Treatment with complexes with 5-Cl substituents in the salicylidene moieties and a *racemic* or *SS* diarylethylene backbone, induced mitochondrial reactive oxygen species, a loss of mitochondrial membrane potential and lipid peroxidation. The mode of action involves apoptosis, ferroptosis, and necroptosis. A clear stereochemical structure–activity relationship was observed with activity ranked as follows: *meso* < *racemic* = *SS*.

These findings highlight *racemic* and *SS* stereoisomers with 5-Br or 5-Cl substituents in the salicylidene moieties as promising candidates for further development as anticancer agents.

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P08
Design and Evaluation of Ferrocene–Peptide Conjugates as Potential Anticancer Agents

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Cancer remains one of the most significant health challenges in modern society. Existing therapeutic strategies often suffer from limited selectivity and numerous side effects. In this study, we aim to design, synthesize, and evaluate peptide–ferrocene conjugates as potential anticancer agents. The peptide component is intended to selectively target integrins, proteins that play a crucial role in cancer initiation and progression, while the ferrocene moiety is expected to exert cytotoxic effects through the generation of reactive oxygen species (ROS) [1].

Inspired by previous studies [2,3], we designed and synthesized conjugates composed of three key components: (i) a ferrocene moiety serving as an electroactive unit; (ii) an aromatic linker to modulate the oxidation potential of ferrocene to physiological conditions; and (iii) a short peptide sequence, including the well-known RGD motif, capable of interacting with overexpressed receptors on cancer cells.

The synthesized compounds were subjected to conformational analysis in solution using 1H NMR, IR, and circular dichroism (CD) spectroscopy, as well as detailed electrochemical characterization via cyclic voltammetry. In addition, we assessed their resistance to proteolytic degradation both by individual enzymes and in human serum. As expected, the ferrocene moiety provided protective effects for the peptide segment, with significant amounts of the conjugates remaining intact after 24 hours. Notably, the best stability was observed in constructs featuring the shortest linker, likely due to the closer proximity of the ferrocene unit to the peptide.

The evaluation of the potential anticancer activity of these compounds is currently ongoing on different cancer cell lines.

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P09

Exploring the synthesis and cytotoxicity of Pd(I) dimers bearing phosphine and isocyanide ligands

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Cancer is currently a very widespread malignancy, and its treatment is still one of the major challenges of our days. Among others, ovarian cancer has one of the higher percentages of death because of a combination of late diagnosis and low treatment options. In fact, this tumor is often characterized by nonspecific symptoms and first line therapy is still represented by surgery and cisplatin chemotherapy. The latter has issues related to general toxicity and development of resistance [1]. Thus, the development of new anticancer drug is of primary relevance. In the landscape of metallodrugs for cancer therapy, organopalladium complexes have emerged as promising candidates. Interestingly, the presence of an organic ligand that allows the formation of a strong Pd-C bond can both stabilize the metal center and work as new active site, possibly leading to a multitarget approach. Different Pd(II) and Pd(0) compounds were synthesized and tested in the last years, leading to interesting results in terms of activity and sometimes selectivity towards cancer cells [2]. Instead, Pd(I) complexes were further less explored, especially from a biological point of view [3].

In this presentation, we describe the synthesis and characterization of new Pd(I) dimers bearing phosphine and isocyanide ligands. The compounds were obtained by simply adding an excess of the isocyanide ligand to [Pd(Ind)(P(Ar)$_3$)(CNR)] precursors (Ar = C_6H_6, *p*-F-C_6H_5, *p*-Cl-C_6H_5, *p*-OMe-C_6H_5, Py; R = *t*-Bu, Cy, adamantyl) [4], leading to the selective formation of only one among the possible isomers. All complexes were fully characterized via NMR and IR techniques and, when possible, the X-ray diffraction structure was also obtained, thus confirming the corner-sharing geometry of these compounds, which contains a Pd-Pd bond and no bridging ligands. Moreover, the obtained complexes were tested against 4 ovarian cancer cell lines (A2780, A2780*cis*, KURAMOCHI, OVCAR-5) and a normal one (MRC-5), pointing out an interesting cytotoxicity, that most of the time is higher than cisplatin, with a certain selectivity toward cancer cells.

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P10

Exploring Organometallic Complexes as Antibacterial Agents

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Antimicrobial resistance poses a serious threat to public health, and there is an urgent need for alternatives to currently available antimicrobial drugs.[1] Among the most promising options are organometallic complexes, which offer great structural diversity, rich stereochemistry, and tunable kinetic properties.[2] Numerous examples of promising organometallic complexes for medical applications have been reported in the literature, including organoarsenical compounds as antimicrobials and ferrocene derivatives with antimalarial or anticancer activity.[3] In this context, our research focuses on exploring the antibacterial potential of two different families of organometallic compounds. Specifically, we are investigating gold(I) and silver(I) N-heterocyclic carbene (NHC) complexes, which are well known for their antibacterial properties. Gold complexes often act by inhibiting thioredoxin reductase, an enzyme involved in bacterial redox balance, while silver complexes exert their activity by releasing silver ions that target multiple bacterial sites.[4,5] To further enhance the activity of the gold compounds, we have incorporated the gold carbene moiety into a Ru(II)-polypyridyl system designed for controlled, light-triggered release of the gold fragment (Figure a). In parallel, we are exploring ruthenium(II)-arene complexes, which have recently shown promising antimicrobial properties.[6] In particular, we report the synthesis, characterization, and biological studies of a series of five structurally related Ru(II)-arene complexes, whose differences in activity may provide useful insights into structure–activity relationships (Figure b). Collectively, these studies testify to the growing interest in metal-based antibacterial agents, highlighting the potential of organometallic scaffolds to address the urgent need for novel treatments capable of bypassing bacterial resistance mechanisms.

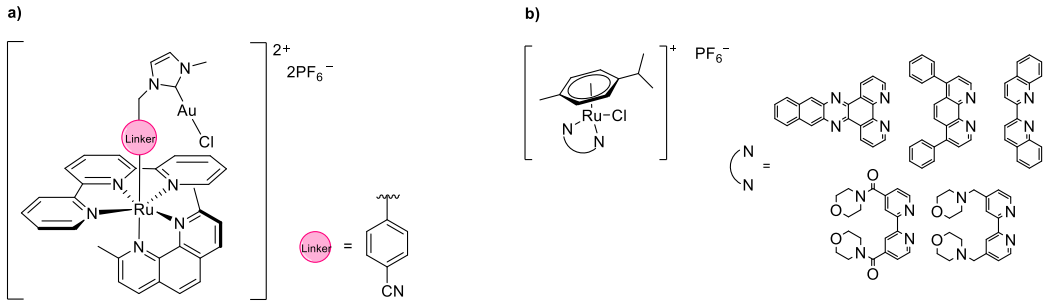

Figure Synthesized Organometallic Compounds Overview.

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P11
Investigation on Di-nuclear Ru(II) Complexes as Potential Antibiotics

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Antimicrobial resistance (AMR) has been a rising health concern with the emergence of drug-resistant strains and our slow development on new antibiotics. Recently there has been an increased interest in developing metal complexes as new antibiotics, amongst which ruthenium complexes have garnered significant attention.[1-3] It was reported that multi-nuclear Ru(II) complexes have a higher potency compared to their mono-nuclear analogues.[4,5] Herein, we report a synthesis of a range of structurally diverse di-nuclear Ru(II) complexes via combinatorial chemistry. These complexes are then screened against a panel of bacterial strains of critical interest to look for hit complexes.

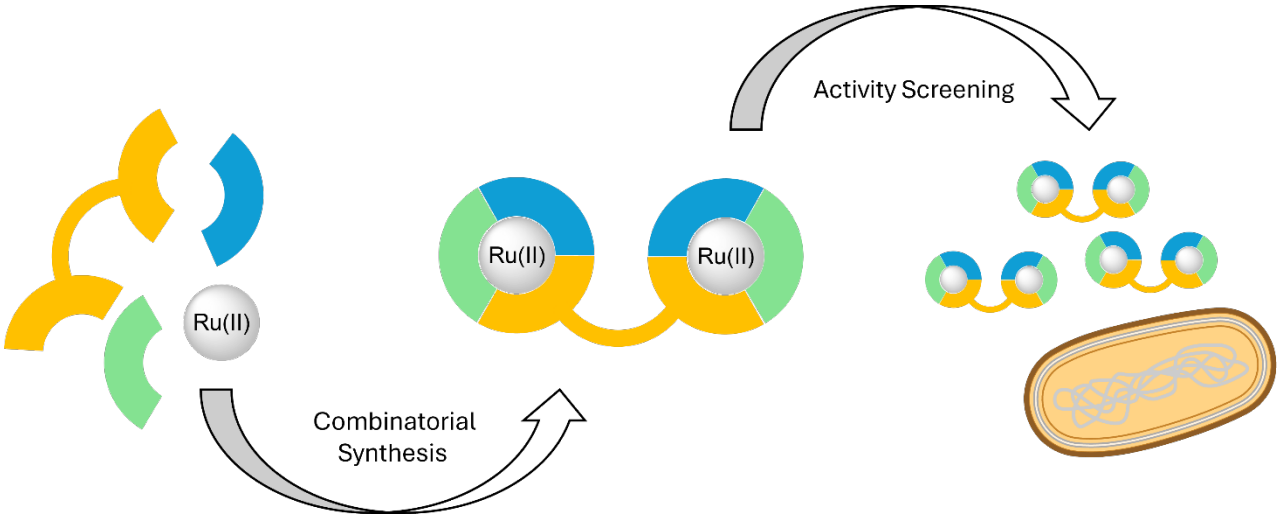

Figure Schematic diagram of combinatorial synthesis of di-nuclear Ru(II) complexes and screening for their antimicrobial activity.

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P12

Design and Characterization of Ferrocene–Peptide Hybrids Targeting Integrins: Impact of Amide Bond Orientation on Redox and Biological Properties

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Cancer is one of the major causes of mortality worldwide and typical therapeutic approaches consist of highly invasive methods with numerous deleterious side effects. In this context, ferrocene hybrids have attracted attention for their excellent cytotoxic features. The cytotoxic activity of ferrocene is related to its ability to induce the generation of reactive oxygen species (ROS) [1]. The ferrocene hybrids studied in this contribution are characterized by a ferrocene unit, as the electroactive component, conjugated to a peptide moiety through a spacer. The peptide moiety considered is the well-known RGD sequence capable of recognizing integrin receptors overexpressed in many tumor cells.

Notably, in the ferrocenyl compounds investigated here, the ferrocene moiety is linked to the rest of the molecule by an amide bond, with the NH group attached to the ferrocene, in contrast to the more commonly reported molecules where the carbonyl group is linked to the ferrocene. Previous studies conducted by this research group evidenced that the replacement of an electron-attracting group (C=O) with an electron-donor one (-NH-CO-) leads to a significant change in the redox potential of ferrocene, with likely significant effects on the biological activity as well.

A conformational investigation of the synthesized compounds was carried out using circular dichroism (CD), ^{1}H-NMR and X-ray diffraction techniques, as well as detailed electrochemical characterization via cyclic voltammetry. The stability of these compounds against proteolytic degradation was also investigated

Studies to assess the cytotoxic activity of these compounds on tumor cell lines are under scrutiny.

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P13
Photochemical reaction of $CpFe(CO)_2I$ with β-diketones and biological activity of the resulting products

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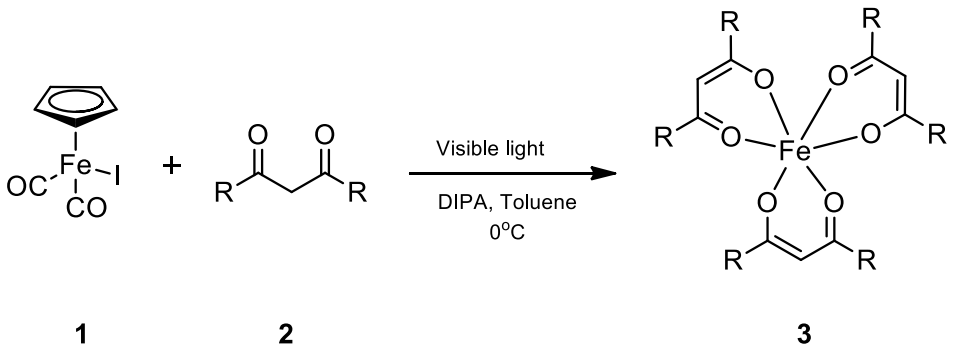
Complexes containing metals such as platinum, ruthenium, iron and others have garnered significant interest due to their unique physicochemical, photochemical and electrochemical properties. In recent years, there has been a significant increase in the applications of metal complexes in medicinal chemistry to treat many diseases, including cancer. [1]

The main objective of the research presented was to develop effective and efficient procedures for obtaining metal tris(acetonates) (**3**) in the photochemical reaction of $CpFe(CO)_2I$ (**1)** with *β*-diketones (**2**). The metal tris(acetonates) were obtained by irradiation with visible light of an argon-saturated solution of **1** and **2** and diisopropylamine (DIPA), in toluene at 0°C. [2] In this study, we also examined the compatibility and effectiveness against selected normal and cancer cell lines of metal tris(acetonates). Cytotoxicity evaluations against normal (RBCs, CD-1079sk) and cancerous (MCF-7, HeLa and SKOV-3) cell lines were performed using spectrophotometric based methods (hemolysis assay and MTTT assay).



Scheme 1. *Photochemical reaction of $CpFe(CO)_2I$ with β-diketones*

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P14
Engineering Selective Palladium-Binding Proteins for Catalytic Transformations

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Palladium catalysts play a central role in organic synthesis yet controlling their reactivity in aqueous or biological settings remains a formidable challenge. [1] Building on our group's experience with other metalloenzymes, [2] we have developed a strategy for selectively introducing Pd(II) into engineered protein scaffolds via two distinct cysteine-based conjugation chemistries: maleimide "click" reactions and bromoalkyl nucleophilic substitutions. We systematically compared the selectivity of Pd binding in each approach, employing fluorescence spectroscopy, UV–vis, circular dichroism, LC–MS, and X-ray crystallography to confirm successful palladium coordination under various assembly conditions.
Preliminary catalytic assays, monitored by fluorescence and HPLC, reveal how Pd-protein hybrids, as well as Pd complexes alone or in one-pot mixtures with proteins, behave in different conditions. Notably, certain "failed" catalytic reactions offered insights into the interplay between palladium ions, protein scaffolds, and buffer components, informing subsequent protein redesigns to enhance catalytic efficiency. This iterative process of design, testing, and redesign paves the way for next-generation Pd catalysts with improved selectivity and performance, leveraging the strengths of engineered proteins in tandem with versatile palladium chemistry.

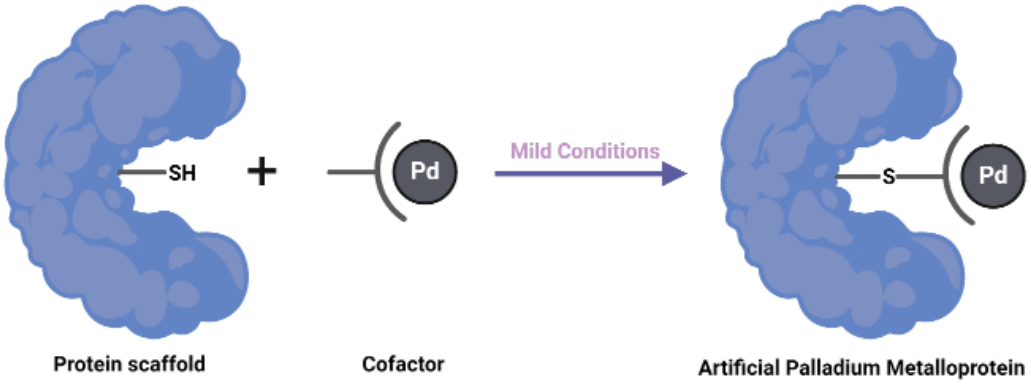

Figure 1. Assembly of an Artificial Palladium Metalloprotein from a Protein Scaffold and Pd Cofactor

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P15

Supremacy of Imidazophenanthroline-Based Iridium (III) Cyclometalated Complexes as Photo-induced Cancer Therapeutics

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Iridium (III) cyclometalated compounds based on imidazophenanthroline ligands are gaining abundant attention as next-generation therapeutics for photo-induced cancer therapy owing to their remarkable photophysical attributes and biological adaptability. When stimulated by light, these complexes effectively produce reactive oxygen species (ROS), especially singlet oxygen ($^1O_2$), which affect cellular organelles, induce oxidative stress, and trigger several programmed cell death pathways in cancer cells. Their customisable emission profiles, great photostability, and strong visible-range absorption allow for fine control over activation while limiting off-target effects. Furthermore, the inert nature of imidazophenanthroline ligands promotes selective localisation in tumour microenvironments and enhances cellular accumulations. Mechanistically, energy transfer to molecular oxygen and subsequent production of ROS are rendered feasible by light-triggered excitation of the iridium centre, promoting intersystem crossover to a long-lived triplet state. This approach lessens systemic toxicity and overcomes drug resistance, thus providing a potent substitute for conventional drugs. Overall, these complexes offer a strong platform to establish target-specific photodynamic cancer therapies. [1,2]

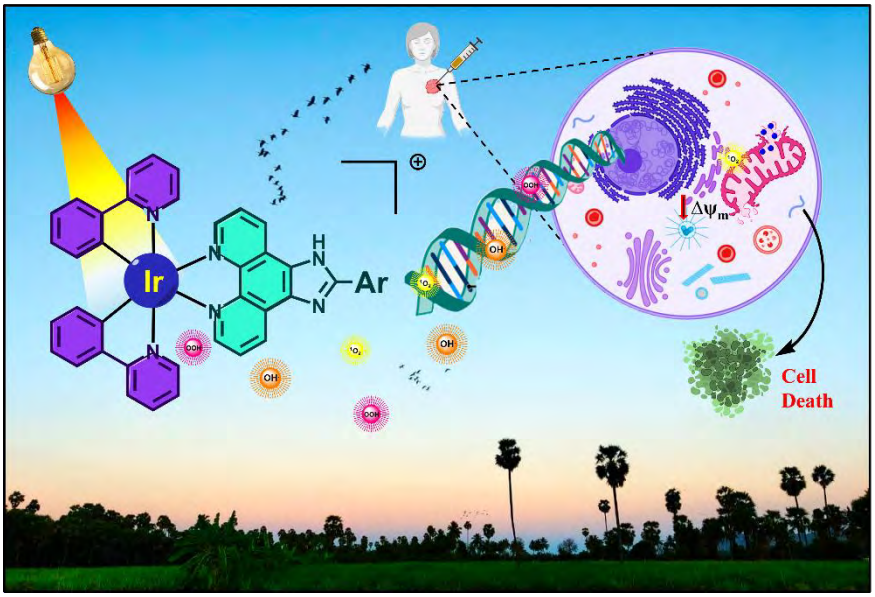

Figure: A Mechanistic Approach of PDT for Destruction of Cancer Cells

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P16

Novel pyridyl-benzimidazol cyclometalated iridium(III) complexes as potential photosensitizers for PDT

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Cisplatin, carboplatin and oxaliplatin are complexes with interesting therapeutic properties. Unfortunately, platin-based compounds present numerous drawbacks such as low selectivity, severe side effects, or high systemic toxicity. Therefore, other novel metal-based compounds have been studied.[1] Specifically, iridium(III) complexes are shown as good candidates for photosensitizers (PS) in photodynamic therapy (PDT), a non-invasive therapeutic treatment against cancer. PDT is based on the combined action between a PS and light to generate reactive oxygen species (ROS), which presents cytotoxic properties.[2]

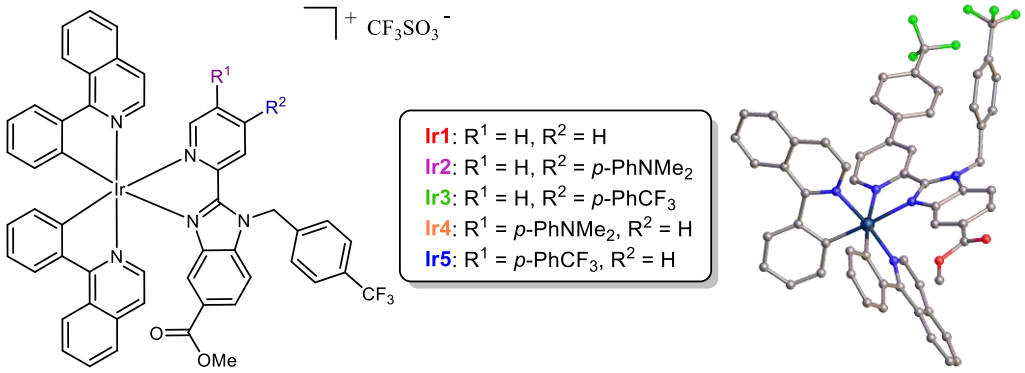

Figure 1. Structure of the New Ir(III) Complexes

Hence, we have synthetized five new Ir(III) complexes with stoichiometry $[Ir(C^N)_2(N^N)]CF_3SO_3$ (Figure 1), where C^N is 1-phenylisoquinoline (piq), and N^N is ligand derived from the pyridyl-benzimidazole framework, with different substituents on the pyridyl ring, that could be good candidates as PSs in PDT. The stability in DMSO and culture medium (RPMI:DMSO 95:5) of the new complexes was tested. Moreover, their photostability upon blue light irradiation (λ = 465 nm, W = 4 mW/cm^2) was studied, proving stable in all conditions. Furthermore, the ability of the complexes to photo-oxidate the NADH coenzyme, besides their potential to photogenerate ROS ($^1O_2$ and/or •OH), in cell-free media, was evaluated. Finally, preliminary biological studies were performed in cancer cells lines exhibiting selective phototoxicity.

Acknowledgements

The research was supported by Ministerio de Ciencia e Innovación (project PID2021-122850NB-I00), M.G. personally thanks Ministerio de Ciencia e Innovación for predoctoral grant (PRE2022-102902).

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P17
Hormonal Attraction: Estradiol Boosts Uptake of Au(I) NHC Complexes in MCF-7 Cells

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Studies indicate that nearly all cancer patients (97.4 %) experience side effects during chemotherapy,[1] while 0.6 % die due to complications directly caused by chemotherapy.[2] The development of new anti-cancer agents is of great importance to minimize side effects and effectively target cancerous cells. Gold complexes, especially Au(I) N-heterocyclic carbene (NHC) complexes, have shown remarkable activity against breast cancer cell lines (MCF-7).[3-4] MCF-7 cells are hormone receptor-positive, exhibiting estrogen receptors. Using estrogens as vectors can potentially increase cellular uptake and increase selectivity for MCF-7 cells.[5] Utilizing the CuAAC reaction, we back-bone functionalized a potent triazole-based Au(I)bis-NHC_{trz} complex (iodide(3-(6-azidohexyl)-1,4-dimesityl-1H-1,2,3l4-triazol-5-yl)(1,4-dimesityl-3-methyl-1H-1,2,3l4-triazol-5-yl)gold(I) iodide) with estradiol. The addition of estradiol does not reduce Au(I)bis-NHC_{trz} complexes' activity as an anti-cancer agent but enhances the cellular uptake of the compound in MCF-7 cells. These results show the great potential of backbone modification of NHC_{trz} via CuAAC reactions.

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P18

Multidisciplinary preclinical investigations on ferrocenyl, ruthenocenyl and benzyl derivatives of thiabendazole as new drug candidates against soil transmitted helminth infections

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Soil-transmitted helminth (STH) infections are a class of neglected tropical diseases (NTDs), caused by three different parasitic nematode species that reside in the gastrointestinal tract. The World Health Organization (WHO) guidelines to reduce morbidity involve preventive chemotherapy by mass drug administration (MDA) campaigns based on benzimidazole drugs, increasing the risk of anthelmintic drug resistance. With only few treatment options available, there is a high need for new and improved anthelmintic drugs. In this study we report the synthesis, characterization, and biological evaluation of four novel (organometallic) derivatives (**1**-**4**) of the broad-spectrum anthelmintic drug thiabendazole. After being found non-toxic on three cell lines, the compounds were evaluated *in vitro* on different life stages of five nematode and one trematode species, as well as *in vivo* on a mouse model. While thiabendazole and the organometallic derivatives showed only low to moderate activity *in vitro*, we observed considerable worm burden reductions *in vivo*.

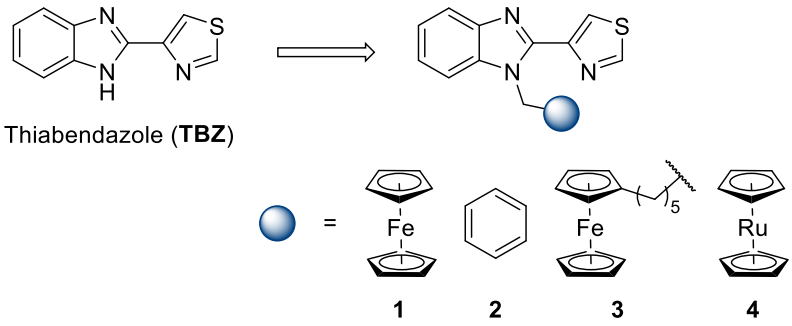

Figure Chemical structures of thiabendazole (TBZ) and the synthesized analogues **1**-**4**

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P19

Development of phosphorescent iridium(III) complexes for imaging liver injury

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Due to the worldwide prevalence of drinking culture in recent years, the incidence of alcohol-related hepatitis has increased globally. On the other hand, the outbreak of coronavirus and drug abuse are also important factors leading to liver damage. Oxidative stress in mitochondria and cells is closely related to liver injury, during which plenty of reactive oxygen species are produced, especially hypochlorous acid (HClO) and peroxynitrite($ONOO^-$). Therefore, if the fluctuation of mitochondrial HClO and $ONOO^-$ levels can be accurately detected in real time, it will be of great significance to reveal their role in physiological and pathological processes and the early diagnosis of liver injury. The transition metal iridium (III) complex has become a new type of mitochondrial targeting bioimaging probes because of its advantages such as large Stokes shift, high quantum yield, easy color modulation, high light stability, and mitochondrial targeting potential. Based on fusion of existing recognition strategies, we developed a luminescent iridium(III) complex **1** with an *N*-alkyhydrazone to detect HClO and a luminescent iridium(III) complex **2** with an *N*-morpholinoarylimine to detect $ONOO^-$. The complexes also significantly diminishing background luminescence through the photoinduced electron transfer (PeT) effect. Specifically, the complex **1** demonstrates high specificity, rapid response time, and high stability. Furthermore, it offers a visual detection capability and is capable of sensing both exogenous and endogenous HClO in liver injury model cells and three-dimensional spheroids, underscoring its potential utility in the diagnosis of liver injury. The complex **2** boasts high specificity, a high response multiple, a low background signal, and an optical detection mode, enabling it to track both endogenous and exogenous $ONOO^-$ in living cells. More importantly, the probe can visualize the generation mechanism of mitochondrial $ONOO^-$ and assess the therapeutic effect of certain inhibitor in liver cells, showcasing its potential for probing the pathogenesis of liver injury and diagnosing liver injury in the clinic.

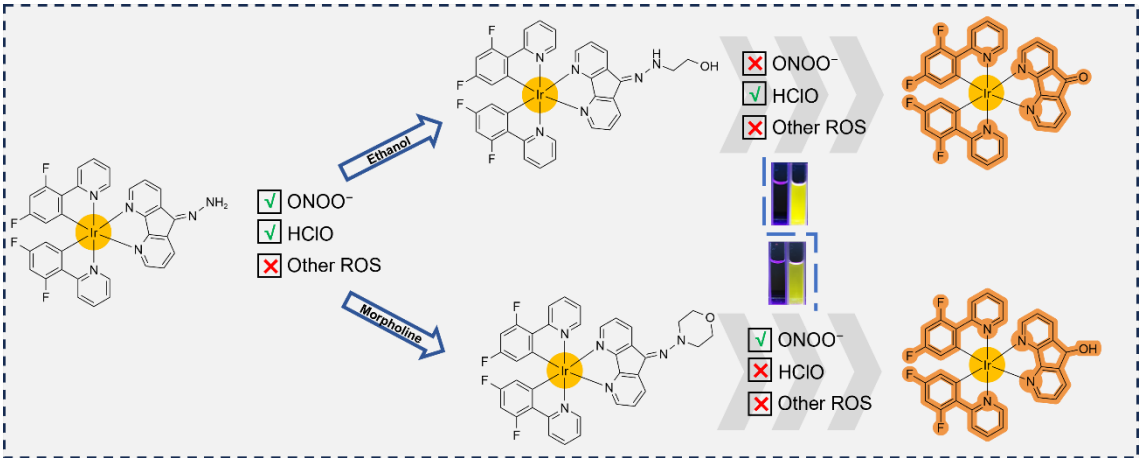

Figure Schematic illustration of improved iridium(III) complexes imaging of mitochondrial HClO or $ONOO^-$

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P20
Synthesis, activity and speciation of anticancer gold(III) complexes displaying original reactivity

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Although chemotherapeutic management of cancers has seen many advances in the last years, the need for molecules displaying new modes of action and new reactivities is still relevant. Biphenyl gold(III) complexes with (N^N),[1] (P^P)[2] and N-heterocyclic carbene (NHC)[3] ligands have emerged in the last years as particularly promising. In this context, I investigated the synthesis of a new family of 8 neutral biphenyl Gold(III) N-heterocyclic Carbene (**BGC**) complexes of general formula [(C^C)Au(NHC^het)Cl] where het is a pyridine-type heterocycle and (C^C) the 4,4'-ditertbutylbiphenyl ligand. These complexes were further converted to the cationic complexes [(C^C)Au(NHC^het)]PF_6 through chloride abstraction, leading to the formation of a 6-membered metallacycle by coordination of the pyridine. Extensive *in vitro* reactivity and speciation studies carried out by ^{1}H NMR on the neutral and cationic forms in various biologically meaningful media, including cell culture medium, showed the irreversible and quantitative conversion of the cationic complexes into their neutral pendants upon addition of as low as 1 equiv. chloride. *In cellulo* X-ray Absorption Spectroscopy (XAS) further confirmed the speciation of a representative of **BGC** complexes in cryo-fixed HeLa cells. **BGC** complexes proved antiproliferative in the low micromolar range against a panel of cancer cell models, each neutral complex being as cytotoxic as its cationic pendant. Perinuclear accumulation of gold in cryo-fixed HeLa cells was demonstrated by Synchrotron Radiation X-ray Fluorescence (SR-XRF) nanoimaging. Fluorescence videomicroscopy experiments showed evidence of the activation of caspases 3/7, a characteristic event occurring during apoptosis, and preliminary studies suggested that this apoptotic cell death may partially arise from mitochondrial depolarization.

Acknowledgements:
This work was financially supported by ITMO Cancer of Aviesan within the framework of the 2021-2030 Cancer Control strategy, on funds administered by Inserm.

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P21

Synthesis of fluorinated ferrocene building blocks for the derivatization of biologically relevant scaffolds

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The use of fluorine in medicinal chemistry has become a common way to tune the properties of a drug as various effects can be expected through the incorporation of fluorine in drug candidates.[1] The interface between fluorine chemistry and medicinal chemistry is thus well-developed. However, grey areas remain on biologically relevant organometallic scaffolds that have gained tremendous interest in medicinal chemistry, such as ferrocenes.[2] The fluorination chemistry of ferrocene has progressed to develop fluorine-containing metallocene chemistry.[3-5] Several examples of fluorinated metallocenes were synthesized for biological purpose, such as trifluoromethylthio-,[6] trifluoromethyl-,[7,8] hexafluoroacetone-[9] substituted metallocenes. Despite this diversity of fluorinated metallocenes, some fluorination patterns remain underexplored. Herein, we present our work on synthesizing fluorinated ferrocene building blocks, which could be further incorporated into drug candidates using usual synthetic strategies.[10]

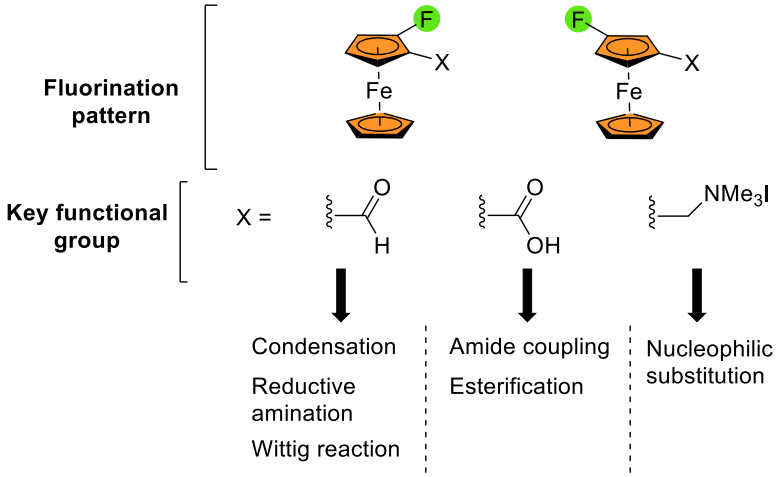

Figure Examples of fluorinated building blocks and the possibilities of reactions for incorporation in drug scaffolds.

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P22

New Three-Legged Piano Stool Complexes based on Ru(II), Rh(III) and Ir(III): Synthesis and Antitumor Evaluations

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In recent years, cancer has become one of the leading causes of morbidity and mortality worldwide. According to the World Health Organization (WHO) and the American Cancer Society (ACS), approximately 10 million deaths were recorded in 2022 due to this disease. In this context, our group has actively developed organometallic compounds as potential biological agents against diseases such as cancer. With the aim of contributing to the discovery of new antitumor agents, this work presents the synthesis, structural characterization, and biological evaluation of Ru(II), Rh(III), and Ir(III) complexes [1-3].

The new three-legged piano stool coordination entities have been synthesized through the reaction of the imine ligand [(η^5-C_5H_4-CH=N-(4)-C_2N_3-(3,5)-C_5H_5N)-FeCp] with the corresponding metal dimers [Ru(η^6-*p*-cimeno)$Cl_2]_2$, [Ru(η^6-benceno)$Cl_2]_2$, [Ir(η^5-Cp*)$Cl_2]_2$, [Rh(η^5-Cp*)$Cl_2]_2$. The resulting coordination compounds are cationic, evidencing the neutral bidentate behavior of the ligand. All complexes were characterized using conventional spectroscopic techniques (FT-IR, ^{1}H and ^{13}C NMR), and by X-ray diffraction. Finally, the biological evaluation of their antitumor activity is underway against the MCF-7 human breast cancer cell line.

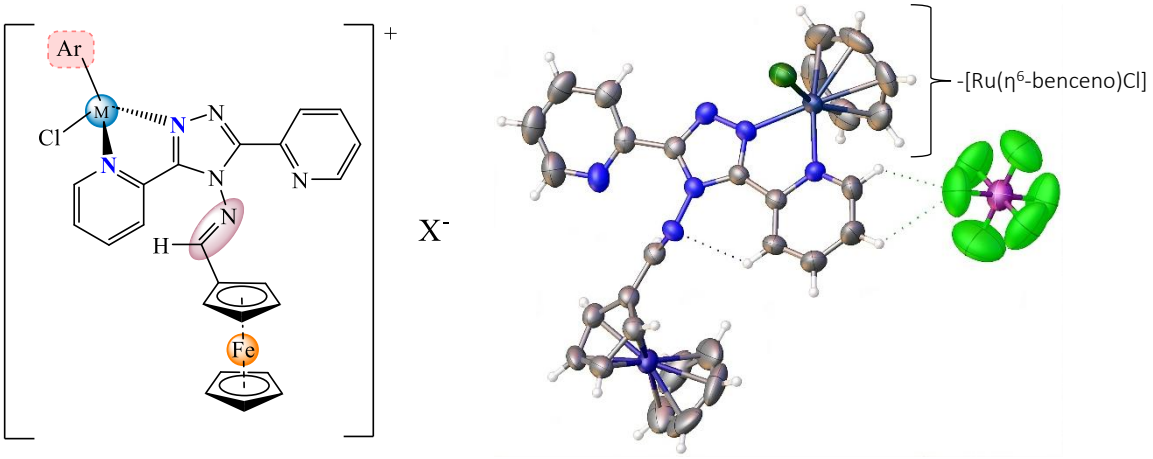

Figure 1. Structures of a) compounds obtained (X^- = PF_6^- or BPh_4^-), and b) ORTEP representation of compound **1a**.

Acknowledgments: The authors acknowledge financial support from FONDECYT Project No. 1230296.

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P23

Re(I) and Re(III) Half-Sandwich Complexes: From Synthesis to Biological Assessment

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Following the discovery of cisplatin, organometallic half-sandwich complexes of Rh(III), Ir(III), Ru(II) and Os(II) have attracted attention due to their strong potency against cancer cells.[1] In particular, we are focused on the organometallic tethered half-sandwich structure of general formula $[M(\eta^5{:}\kappa^1\text{-Cp*Z}/\ \eta^6\text{-areneZ})XY]^{n+}$, to explore new chemical reactivities inside cells. Metal mediated chemistry is enabled by the vacancy created through the labile ligand Z, which is purposely the only metal bond in our structure susceptible to cleavage in aqueous media. [2,3]

By extensive SAR analysis on Rh(III), Ir(III), Ru(II) and Os(II) half-sandwich tethered complexes, we have built a library of over 400 compounds with tunable metal-Z reactivity based on careful metal and ligand selection. We are now building on the knowledge have acquired to Re(Cp*R) half-sandwich complexes.

In alignment with the d^6 electronic configuration presented by the above mentioned metals, we began exploring Re(I) half-sandwich complexes, $[Re^{I}(\eta^5\text{-}C_5Me_4R)(CO)_3]$, yet their inert tricarbonyl core limited the coordination of several bidentate ligands and functionalities. To overcome this challenge, we have expanded to Re(III), which successfully allows us to introduce a variety of ligands and to synthesise for the first time new families of four-legged piano-stool compounds with general formulae: $[Re^{III}(\eta^5{:}\kappa^1\text{-}C_5Me_4R)X(CO)_2]^+$, $[Re^{III}(\eta^5\text{-}C_5Me_4R)X_2(CO)_2]$, $[Re^{III}(\eta^5{:}\kappa^1\text{-}C_5Me_4R)X_2(CO)]$ and $[Re^{III}(\eta^5{:}\kappa^1\text{-}C_5Me_4R)(en)(CO)]^{2+}$ (X= Cl, I; Figure 1).

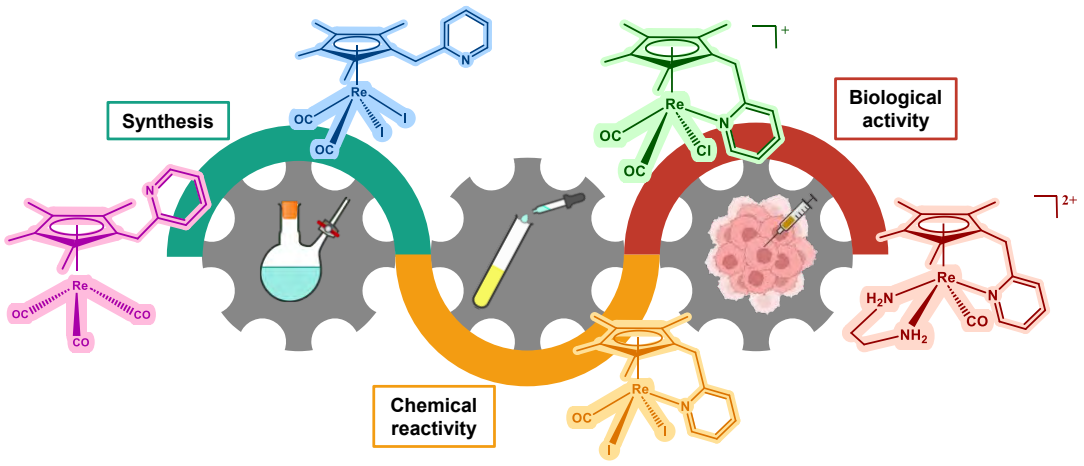

Figure 1. Re(I) and Re(III) complexes presented I this work.

Investigations into the reactivity in DMSO and the aqueous speciation of the new compounds corroborated the higher reactivity of Re(III) vs Re(I) towards substitution reactions. Additionally, biological studies demonstrated that Re(III) complexes exhibit greater cytotoxicity than their Re(I) counterparts, highlighting Re(III) as promising candidate for further research.

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P24

Reactions of Cobalt Porphyrin Nitrite with Oxophilic Substrates. Role of Sulfur Bound Hydrogen in Nitrite Reduction.

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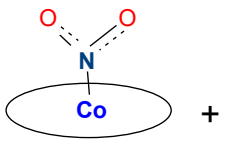
The endogenous reduction of nitrite (NO_2^-) to nitric oxide (NO) is drawing increasing attention as a protective mechanism against hypoxic injury in mammalian physiology and as an alternative source of NO, which is involved in in physiological regulation of blood flow, cell signalling and vasodilation [1]. Thus, chemical mechanisms for this transformation, which are mediated by metallo proteins and model compounds are of considerable interest. While thiol mediated reduction of nitrite at heme-model iron porphyrins has received significant attention [2], comparatively little is known about analogous reactions at other biologically relevant metal centers. Recently we have reported that reaction of cobalt porphyrin nitrite with H_2S/thiol results in formation of cobalt nitrosyl along with the formation of disulfide and H_2O via proposed proton-assisted O-atom transfer mechanism [3].

Here we present the reactions of the model porphyrin nitrite Co(TTP)(NO_2) (TTP = meso-tetratolylporphyrinato dianion) in sublimated solid films with oxophilic substrates such as phosphine, sulfide and different thiols at various temperatures from 77 K to room temperature using in situ infrared and optical spectroscopy. The eventual products of this reaction in all cases are determined. The possible mechanisms of the reactions that accounts for all spectroscopic observations with the use ^{15}N and ^{18}O labeled and natural abundance NO_2 are proposed.



Co(Por)(NO_2)

$PR_3 \longrightarrow Co(Por)(PR_3)_2^+ + NO_2^-$

$SR_2 \longrightarrow Co(Por)(SR_2)(NO_2)$

$HSR \longrightarrow Co(Por)(NO) + RSSR + H_2O$

$HS(R)(OH) \longrightarrow Co(Por)(NO) + (HO)RSSR(OH) + H_2O$

Acknowledgements: The financial support from SCS of the Republic of Armenia (Project 21AG-1D040) is gratefully acknowledged.

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P25
In-vitro Evaluation of Silver-NHC-Complexes against Coronavirus OC43

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Organometallic complexes are widely recognized for their anticancer and antibacterial properties.[1] However, there are only few reports investigating possible applications in antiviral therapy. Since the emergence of SARS-CoV-2, efforts to study antiviral activity of organometallic compounds have revealed multiple targets in the viral life-cycle, such as papain-like protease (PL^{pro}) and the spike protein.[2, 3]
Recent publications by Gil Moles et al. highlight the potential of *N*-heterocyclic carbene (NHC)-silver-complexes as antiviral agents showing a potent uncompetitive inhibition of PL^{pro}.[3]
In-vitro screening for antiviral activity against SARS-CoV-2 is currently a challenging topic as it requires a biosafety-level (BSL)-3 environment. A more accessible approach is using human beta-coronavirus OC43 (HCoV OC43) as a surrogate, which can be maintained in a BSL-2 level laboratory.[4]
An in-cell ELISA protocol (Figure 1) using rhabdomyosarcoma (RD) cells and HCoV-OC43 as a host cell-virus system was developed for preliminary screening of compounds of interest. To evaluate the method, twelve silver-NHC complexes were successfully synthesized and characterized by NMR, MS and elemental analysis. The complexes were evaluated for their toxicity against RD host cells, antiviral activity as well as their time-of-addition-dependent effect on virus replication and show activity in the low micromolar range.

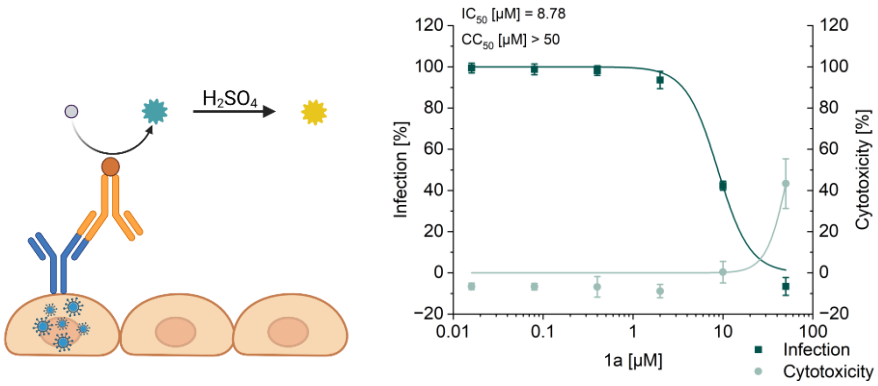

Figure 1: Schematic representation of the in-cell ELISA assay and the results for compound 1a.

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P26

Accelerating Antibiotic Discovery with Iridium(III) Complexes via Automation and Machine Learning

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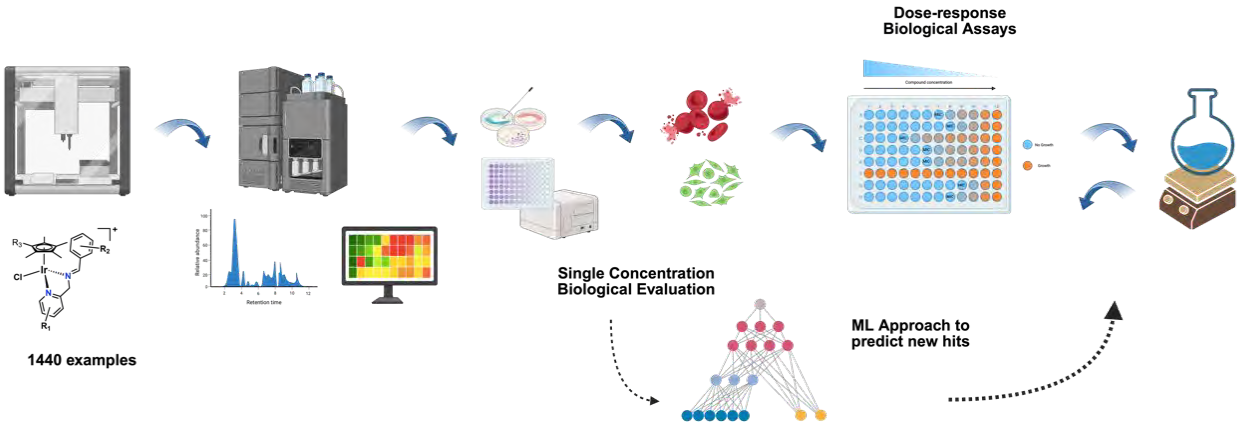
Antimicrobial resistance (AMR) is a major global health threat, linked to 4.95 million deaths in 2019, including 1.27 million directly caused by resistant infections. Projections indicate that by 2050, AMR could become the leading cause of mortality, with an estimated 10 million deaths annually.[1,2] These statistics highlight the pressing need for innovative strategies to address this growing threat to public health. While the conventional drug pipeline of antibiotics, based on organic chemistry, has shown insufficient development, *exploring novel chemical spaces and unconventional approaches in antibacterial drug discovery is emphasized as an urgent need.*[3] Among these, metal-based complexes have recently gained attention as potential antibacterials. However, current methodologies remain limited in their ability to screen large compound libraries or systematically evaluate structure–activity relationships. *Previously in our group, we have utilised Schiff-base chemistry to synthesize large antibacterial compounds library.*[4] In this study, we expanded this approach by synthesizing a diverse library of 1440 piano-stool iridium complexes with high efficiency. The synthesised library was screened against bacteria strains and HEK293T (Human Embryonic Kidney cells) cell lines at single concentration to determine hit compounds (high antibacterial activity, low cytotoxicity). While the selected compounds are resynthesized to confirm activity, the data from the combinatorial library will be used to train machine learning models to predict more efficient complexes. Once lead compounds are identified, their antibacterial mode of action and potential for resistance induction will be investigated.



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P27

Exploring a New Class of Organometallic 1,2,3-Triazoles: Rational Design, Characterization and Evaluation as Potential Anticancer Agents

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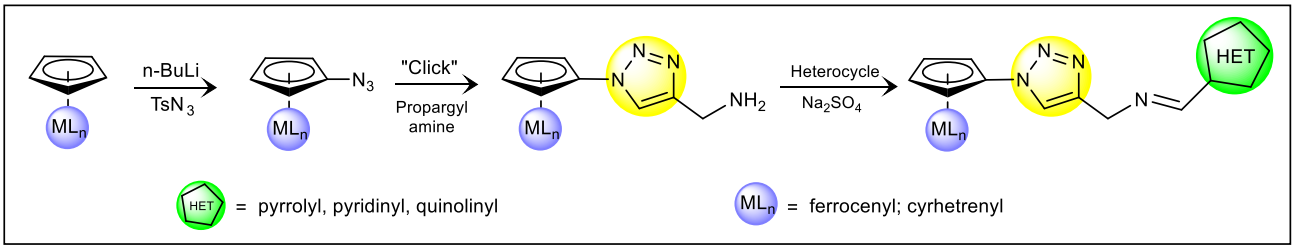
Historically, Medicinal Chemistry has focused on developing compounds capable of addressing a wide range of diseases. In this context, heterocycles such as 1,2,3-triazoles have emerged as privileged scaffolds due to their structural versatility in the design of bioactive molecules and their efficient synthesis through Click Chemistry reactions **[1]**. Despite the extensive exploration of organic 1,2,3-triazoles, their organometallic counterparts remain largely underexplored. Notably, recent studies have revealed promising anticancer properties for ferrocenyl-containing triazoles, suggesting a valuable therapeutic potential **[2]**.

Considering these findings, this work presents the design, synthesis, and characterization of a new series of 1,2,3-triazoles featuring a ferrocenyl and cyrhetrenyl organometallic moieties as well as bioactive organic heterocycle moieties connected by imine entity (**Scheme 1**). This study contributes to the expanding frontier of bioorganometallic chemistry by providing novel hybrid compounds with potential biomedical relevance.



Scheme 1. Synthesis of novel organometallic 1,2,3-triazole compounds.

All compounds were isolated and purified using classical experimental methodologies. Structural characterization was carried out through standard spectroscopic techniques, including FT-IR, ^{1}H and ^{13}C NMR, and single-crystal X-ray diffraction. Currently, their biological evaluation as potential anticancer agents is underway, aiming to further elucidate their therapeutic relevance within the context of bioorganometallic drug discovery.

Acknowledgements
We gratefully acknowledge funding from the FONDECYT project #1230296, which made this research possible.

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P28
Synthesis and assessment of biological effects of rhenium(I) pyrithione complex

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Rhenium(I) tricarbonyl complexes have been trending topic in recent years. Due to their stability and spectroscopic properties, they are of particular interest as they show promising biological and catalytic activity. In addition, their spectroscopic properties can also be utilised for diagnostic applications [1,2].
Pyrithione (pth) is a naturally occurring compound that has been known and researched for almost 75 years [3]. It forms $M(pth)_2$ or $M(pth)_3$ complexes with most metals in the periodic table. Some of them have limited use due to their poor solubility. Complexes with different ligands in combination with pth, as in the case of [ruthenium(II)(η^6-*p*-cymene)(pyrithionato)(chlorido)] complex, are better soluble and exert excellent activity in biological systems [4].
Over the last couple of years, our research group has prepared various pth analogues. We have extensively investigated pyrithiones and their complexes with various metals for their anticancer, antibacterial and antiviral activity [4,5]. The promising results prompted us to investigate rhenium complexes with pth, as this topic is virtually unexplored. We focussed on the preparation of *fac*-tricarbonylrhenium(I) complexes with pth. The synthesis proved to be challenging and we unexpectedly identified several different products. After finally isolating a stable complex, we investigated its stability and equilibria in aqueous media as well as the interaction with human serum albumin. In addition, we investigated its cytotoxicity, antibacterial and antiviral activity and inhibition of cysteine cathepsins. We also performed *in silico* studies to explore possible interactions of the complex with cathepsin B [4].

Acknowledgement
We are grateful for the financial support of the Slovenian Research and Innovation Agency (ARIS): a Junior Researcher Grant to Uroš Rapuš and grants P1-0175, P4-0127, J3-3071 and P1-0208. The authors also acknowledge the support of the Centre for Research Infrastructure at the Faculty of Chemistry and Chemical Technology, which is part of the Network of Research and Infrastructural Centres UL (MRIC UL) and is also financially supported by ARIS; Infrastructure programme No. I0-0022) for the use of the Supernova diffractometer. This research is also based upon work from COST Action EURESTOP, CA21145, supported by European Cooperation in Science and Technology. Project no. TKP2021-EGA-32 has been implemented with the support provided by the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-EGA funding scheme.

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P29

Novel cyclometalated Ir(III) complexes with tridentate ligands as potential phototherapeutic agents

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Millions of people around the world are affected by cancer. There are different treatments to combat it, with photodynamic therapy (PDT) being one of the most promising. Among the photosensitizers used, iridium(III) complexes have gained recognition, thanks to their photophysical and photochemical characteristics, such as: large Stokes shift, long phosphorescence lifetimes, enhanced (photo)stability, and high singlet oxygen quantum yields. Previous studies have shown that Ir(III) complexes based on terpyridine ligands can eliminate chirality, reducing unwanted side effects. [1,2] This has served as a precedent for the design of a new family of Ir(III) complexes with tridentate ligands.

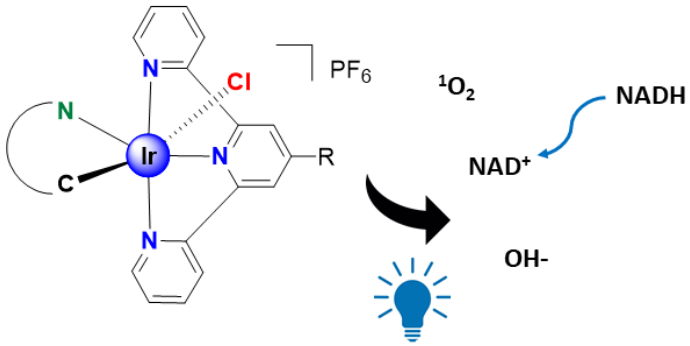

Figure 1: Chemical structure of the new Ir(III) complexes, and their ability to generate some reactive oxygen species.

This work introduces a novel series of eight Ir(III) complexes with general formula $[Ir(N^N^N)(C^N)Cl]PF_6$ (**Figure 1**). They have been structurally characterized by NMR spectroscopy, HPLC-MS, X-ray diffraction (for complex **Ir3**), and elemental analysis (C, H, N and S). Additionally, their stability in DMSO, RPMI cell media and after irradiation with blue light has been studied, as well as their ability to photo-oxidize the NADH coenzyme and generate reactive oxygen species such as singlet oxygen ($^1O_2$) and hydroxyl radicals ($OH^{\bullet}$).

Acknowledgments

This work has been financially supported by the Spanish Ministry of Science and Innovation as well as the National Research Agency (MCI/AEI/10.13039/501100011033), FEDER funds (project PID2021-122850NB-100) and Fundación Séneca (project 21989/PI/22). I. Romero thanks to Fundación Séneca for her predoctoral grant (21854/FPI/22). M. J. Piernas thanks the Spanish Ministry of Science and Innovation, and the European Union (NextGeneration EU/PRTR) for her Juan de la Cierva Fellowship (IJC2020-045287- I/MCIN/AEI/10.13039/501100011033).

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P30

Isolation and mechanistic aspects of cytotoxic intermediates formed in-situ upon ROS scavenging by hydroxycinnamic acid-terpyridine conjugates

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The development of active therapeutic agents to treat highly metastatic cancer, like triple negative breast cancer (TNBC), while minimizing damage to healthy cells is of utmost importance.1 Cancer cells, especially TNBC cells, generally possess higher levels of reactive oxygen species than normal cells, and this can serve as a possible therapeutic target. Hence, antioxidant-inspired therapeutics are quite applicable to treat this sort of highly metastatic cancer. In this regard, due to potential antioxidant properties and structure–activity relationships, ester and amide derivatives of hydroxycinnamic acid and hydroxybenzoic acids are reported to gain much higher radical scavenging ability than their naked acidic analogs, which are capable of inhibiting TNBC cell growth, without much effect on normal cells.2. Moreover, it was also found that an antitumor metabolite is formed in situ from a hydroxycinnamic acid derivative upon ROS scavenging.3

Herein, we present a set of antitumor metabolites of hydroxybenzoic acid and hydroxycinnamic acid derivatives and their cytotoxicity towards TNBC cells. The in-situ formation of those metabolites in the presence of ROS has been confirmed by mass spectroscopy. Further, these metabolites have been isolated in ex-situ medium by reacting the synthesized cytotoxic compounds with (Diacetoxyiodo)benzene (PIDA) in aqueous acetonitrile medium. The cytotoxicity of these active species has been studied towards various cancer cell lines, including TNBC. These results demonstrate the therapeutic advantages of an in situ-formed, oxidative stress-related metabolite that might be of particular importance for designing new strategies for antioxidant-based drug discovery.

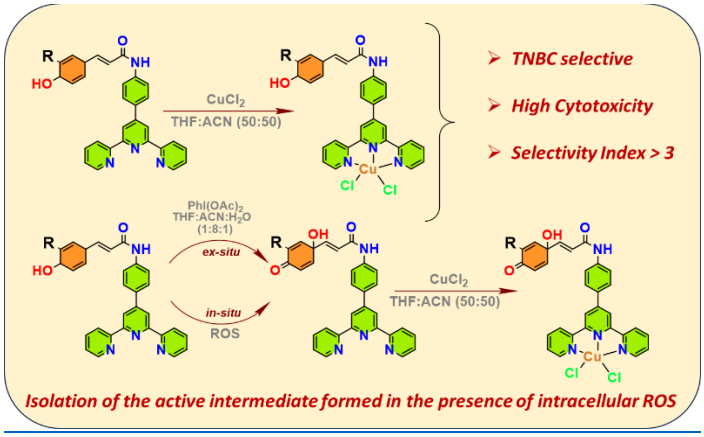

Figure: Cytotoxicity of hydroxycinnamic acid-terpyridine conjugates and ex-situ isolation of their antitumor metabolites

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P31

Design of pH-Sensitive Ruthenium-Peptide Conjugates for Targeted Therapy of Metastatic Breast Cancer

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Metastatic breast cancer (MBC) is a highly aggressive subtype of cancer that accounts for 15-20% of all breast cancer cases. There is still no clinical cure for MBC, and available treatments have limited effectiveness and often cause severe side effects due to their lack of selectivity [1]. To overcome these limitations, our group is currently developing novel ruthenium smart metallodrug delivery systems (SMDS) capable of targeting both primary tumors and metastases of breast cancer (Figure 1) [2]. SMDS comprise a peptide that recognizes with high affinity the fibroblast growth factor receptor (FGFR), often overexpressed by MBC cells, linked to a cytotoxic Ru(II)-(η^5-C_5H_5) complex through an entity sensitive to the slightly acidic tumor microenvironment. These systems allow accumulation, site- and time-specific release of the active species into the tumor. One of these SMDS, containing a hydrazone as a pH-sensitive linker, showed high and selective antiproliferative activity against FGFR(+) BC cells, allied to the controlled release of the cytotoxic ruthenium complex in its active form [2]. In this work, we explored the use of hydrazones and oximes as pH-responsive linkers to conjugate Ru(η^5-C_5H_5) complexes to the FGFR-targeting peptides, through the Cp or bipyridine ligand. The synthesis and characterization of the new pH-responsive Ru SMDS and the drug release at pH values that mimic the tumor microenvironment and bloodstream will be presented. The 3-dimensional conformation of the free and conjugated peptide was determined by NMR. The cytotoxic activity of these systems was evaluated in four breast cancer cell lines with different levels of FGFR expression at pH values that mimic the tumor microenvironment and bloodstream.

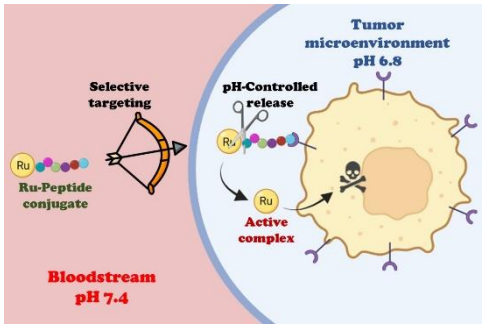

Figure 1 Proposed mechanism of action of the ruthenium-peptide conjugates.

Acknowledgements

We thank the Fundação para a Ciência e Tecnologia (FCT), I.P./MCTES for the financial support through the projects UIDB/00100/2020 (CQE, DOI 10.54499/UIDB/00100/2020), LA/P/0056/2020 (IMS, DOI 10.54499/LA/P/0056/2020) and UID/Multi/04349/2019 (C2TN). MS thanks FCT for his doctoral grant (UI/BD/154814/2023). TSM also thanks FCT POPH and FSE-European Social Funds for the Individual Call to Scientific Employment Stimulus 2022.00028.CEECIND/CP1722/CT0005 project (DOI 10.54499/2022.00028.CEECIND/CP1722/CT0005).

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P32

Quinolines as copper ionophores: from molecular mechanisms to nanocrystal-based delivery for cancer therapy

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Copper (Cu) plays a crucial role in the etiology and progression of cancer, making it a target for arresting cancer development. Conventional anticancer therapies often suffer from severe off-target effects due to their impact on critical cellular processes shared by all rapidly proliferating cells. Future therapeutic goals should increase selectivity, reduce side effects, overcome cell resistance, and target cancer stem cells. Some metal-binding compounds have shown promise in this direction [1].

Various classes of copper ionophores, such as dithiocarbamates, bis(thiosemicarbazone) ligands, and 8-hydroxyquinolines (8-HQs), have been studied and found to exhibit a modest degree of intrinsic selectivity in promoting cuproptosis in cancer cells over normal cells [2]. Cuproptosis is defined as Cu-dependent cytotoxicity (with a unique mechanism) leading to cell death. In particular, quinoline derivatives have been widely investigated for their metal-chelating ability and biological properties, exhibiting notable anticancer activity in the form of transition metal complexes. Nevertheless, their precise mechanisms of action have not been thoroughly elucidated.

In this research, we investigated 8-aminoquinoline (8AQ), 8-nitroquinoline (8NQ), and 5-aminomethyl-8-hydroxyquinoline (5-AMHQ) in combination with Cu^{2+} against hepatic, lung, prostate and colon cancer cell models. Among the three metal complexes, 5-AMHQ demonstrated the highest cytotoxicity in *in vitro* tests. We further explored the mechanism of toxicity of 5-AMHQ. Quantification of total cellular thiol groups, glutathione levels and its oxidation state in treated cancer cells revealed a decrease in cellular thiols and an increase in glutathione oxidation, indicating redox imbalance.

Given that mitochondria are the cell's "powerhouse" and crucial reactive oxygen species (ROS) producers, we analyzed respiratory chain function and ROS production in treated cancer models. Our results showed that 5-AMHQ in combination with copper influenced mitochondrial oxygen consumption and increased ROS levels, consistent with the observed oxidative stress induction.

To enhance the targeting of copper ions to cancer cells and improve cell penetration efficiency, we functionalized cellulose nanocrystals (CNCs) with 5-AMHQ. CNCs are being studied as nanocarriers for drug delivery. Upon CNC functionalization, we analyzed cytotoxicity in the same cancer cell models and found improved activity.

In conclusion, our study shows the promising anticancer potential of 5-AMHQ in combination with copper, highlighting its ability to induce oxidative stress and mitochondrial dysfunction in cancer cells. Furthermore, the successful functionalization of cellulose nanocrystals with 5-AMHQ offers an innovative approach to enhance targeted drug delivery, paving the way for more effective and selective cancer treatments.

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P33
Platinum(II)-modified DNA oligonucleotides as phosphorescent dioxygen sensors

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Site-specific incorporation of transition metal ions into DNA is of high interest, as it can equip the nucleic acid with metal-based properties.[1] However, applications with potential biological relevance are still absent, most likely because of the scarcity of suitable metal ions in the intracellular microenvironment and the lability of many coordinate bonds. To tackle this challenge, we developed an organometallic platinum(II) complex with robust phosphorescence. It is composed of a tridentate C^N^N ligand and an ancillary monodentate ligand. The phosphorescence is essentially independent of the identity of the ancillary ligand.[2]
Most recently, we were able to covalently link the phosphorescent platinum(II) complex to a series of DNA oligonucleotides.[3] Interestingly, when two platinum complexes were introduced into the oligonucleotide in adjacent positions, the phosphorescence lifetimes turned out to be strongly dioxygen-dependent, which makes the respective oligonucleotide an excellent candidate for $^3O_2$-sensing applications.[3] To facilitate the click reaction, an azide-functionalized propylene side chain was attached to the platinum(II) complex, allowing the incorporation of the complex into the oligonucleotide. Our current research focuses on shortening the linker of the complexes, allowing a more precise prediction of their localization in the DNA. Therefore, platinum(II) complexes containing an azide-functionalized ethylene and methylene linker, respectively, were synthesized. This presentation will report on the characteristics of the corresponding platinated oligonucleotides and present an evaluation of the linker's influence on thermal stability and photophysical properties. Moreover, it will include experimental data on the possible application of the oligonucleotides as sensors for $^3O_2$ in aqueous solution.

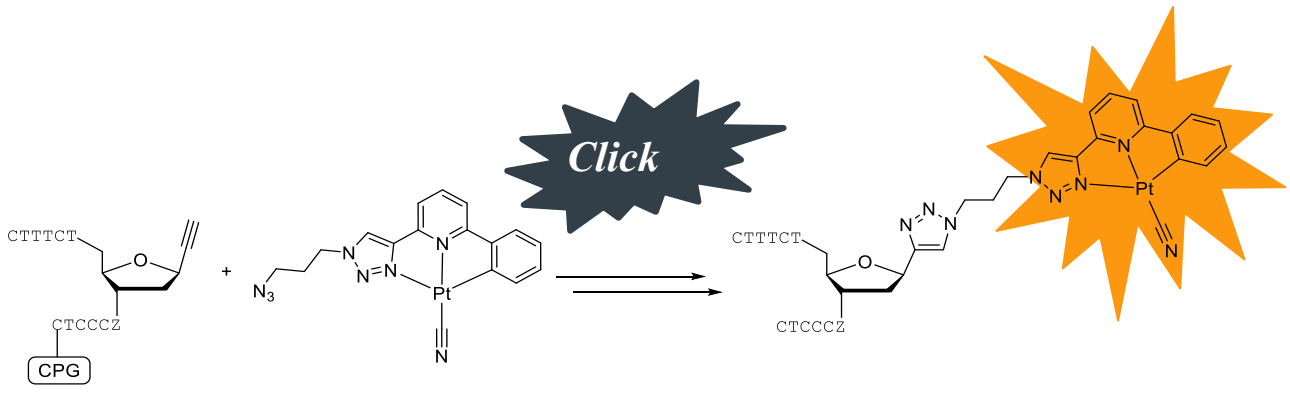

Figure: General scheme of the incorporation of platinum(II) complexes into the oligonucleotide sequence.

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P34

In Pursuit of the Golden Bullet: Bifunctional Gold(I) NHC Complexes for Targeted Cancer Therapy

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Developing selective chemotherapeutic agents remains a key goal in cancer treatment, driven by persistent challenges such as drug resistance and the systemic toxicity observed in conventional therapies.[1],[2] Drug conjugates - comprising a cytotoxic payload, a linker, and a targeting vector - offer a powerful strategy to overcome these limitations by delivering the cytotoxic agents directly to the tumor cells while minimizing off-target effects.[3] In this context, gold(I) *N*-heterocyclic carbene (NHC) complexes have emerged as promising warhead candidates owing to their proposed DNA-independent mechanism of action, structural tunability, and potent antiproliferative properties.[4],[5]

Previously, our group developed highly antiproliferative gold(I) bis-1,2,3-triazolylidene complexes featuring mesityl (Mes) wingtips and two azide groups for bioorthogonal modification.[6] However, the identical reactivity of both azide groups is limiting selective conjugation in drug conjugate design. To address this challenge, we enhanced post-functionalization possibilities by designing heteroleptic gold(I) NHC complexes with orthogonal functional groups, enabling targeted, sequential (bio)conjugation. This approach allows independent modifications of the ligand backbone, offering versatile conjugation strategies and expanding the potential of these complexes for targeted cancer therapies.

As a proof of concept, our current work focuses on functionalizing the highly cytotoxic heteroleptic complex *AuAzAm* (IC_{50} < 100 nM in A2780, MCF-7, MDA-MB-231 cancer cell lines) with simple targeting vectors (e.g., vitamins) and imaging agents (e.g., DOTA, FITC). These efforts aim to establish a new generation of bifunctional gold(I) bis-NHC complexes designed for targeted therapy and theragnostic applications. Our results highlight the promise of bifunctional gold(I) complexes as versatile organometallic platforms for next-generation targeted cancer therapies.

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P35

Mannose conjugated palladium complexes: synthesis, characterization and anticancer activity

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The development of anticancer drugs that target specifically tumor sites is of outmost importance in cancer chemotherapy and this research line is currently in significative expansion. Cancer tissues require larger amounts of glucose than non-cancerous ones, having high rates of aerobic glycolysis. This is known as Warburg effect, and it's recognized as a hallmark of cancer [1]. The conjugation of biomolecules such as monosaccharides to drugs could improve their selectivity towards cancer cells exploiting the effect of specific enzymes overexpressed in cancer tissues (*e.g.* α-mannosidase), facilitating the release of the cytotoxic payload on the tumor site [2]. Based on the promising recent results on cancer therapy obtained with organopalladium compounds [3] and the limited number of works dealing with Pd-mesoionic carbene (MIC) complexes, we report in this contribution the synthesis of some novel organopalladium complexes conjugated to mannose through a 1,2,3-triazol-5-ylidene moiety (**Figure 1**) and the evaluation of their antiproliferative activity against tumoral and non-tumoral cell lines. Bio-conjugated 1,2,3-triazol-5-ylidene precursors were synthesized exploiting the Copper(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC). Then, complexes were obtained by reacting the triazolium salt with a palladium precursor, adopting the "weak base route". This reaction, whose mechanism consists in a concerted deprotonation/metalation of the triazolium salt, proceeds in air and in mild conditions using inexpensive and mild bases such as K_2CO_3. To the best of our knowledge, this is the first extension of this type of process to the synthesis of palladium MIC complexes. Moreover, we were also able to isolate the allyl palladate intermediates.

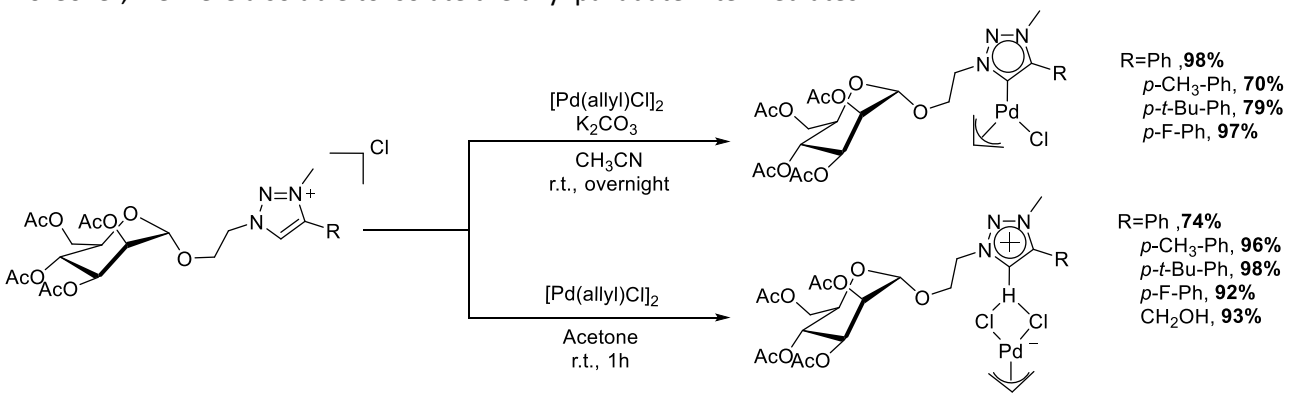

Figure 1. Synthesis of mannose conjugated palladium MIC complexes and allyl palladates.

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P36

Dual-Target Gold(I) NHCs: Optimizing the NHC Ligand Structure to Disrupt Energy & Hormone Pathways in Breast Cancer Cells

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Gold(I) complexes, such as auranofin, have historically been explored for their therapeutic potential, notably in rheumatoid arthritis, but their cytotoxic effects on cancer cells have sparked new interest in gold-based anticancer agents.[1–3] Building on these findings, our research focuses on novel gold(I) *N*-heterocyclic carbene (NHC) complexes designed for enhanced selectivity and potency against breast cancer cells.

What sets our lead compound apart is its remarkable selectivity: it exhibits pronounced cytotoxicity towards estrogen receptor alpha (ERα)-positive MCF-7 breast cancer cells, while sparing triple-negative MDA-MB-231 cells *in vitro*. Mechanistic studies suggest a dual mode of action. First, molecular docking and binding assays reveal that the complex is able to target ERα, occupying the estradiol binding pocket and potentially disrupting receptor signaling. Secondly, the compound induces a rapid depolarization of the mitochondrial membrane potential, resulting in a marked impairment of cellular energy metabolism.

To unravel the structure–activity relationships (SAR) underlying the unique selectivity, we benchmarked our gold complex against a diverse set of structural modifications and analogous silver compounds. Comparative studies highlight how subtle changes in metal center and ligand architecture dramatically influence cytotoxicity and selectivity details that are visualized and discussed in depth on our poster.

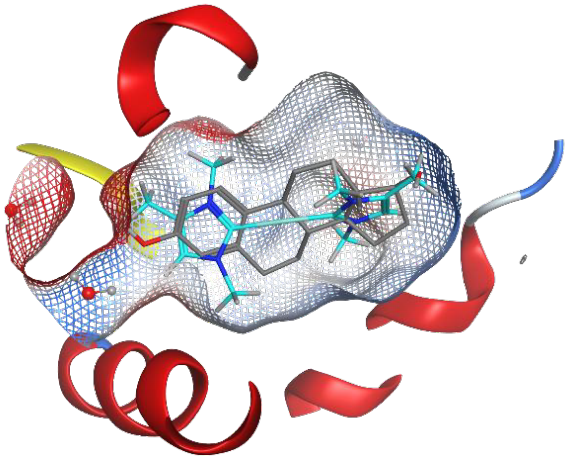

Figure Estradiol inside the binding pocket of ERα in comparison to the investigated gold NHC compound (blue).

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P37

Triazolylmethylquinoxaline and Bipyrimidine-Based Cyclometalated Binuclear Ir(III) Complex: Unlocking New Potential in Photoinduced Cancer Therapy

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Photo-induced chemotherapy provides the most promising approach for selective cancer treatment among current modalities. Cyclometalated Iridium (III) complexes, with their outstanding photophysical and photochemical properties, are regarded as highly effective candidates for photo-responsive cancer therapy. These complexes were strategically designed to enhance anticancer efficacy by incorporating key features: (a) intrinsic biological activity, (b) responsiveness to the tumor microenvironment (hypoxia, high GSH, low pH), (c) extended π-conjugation for improved fluorescence in bioimaging, (d) hydrophobic groups to boost membrane permeability and cellular uptake, and (e) strong DNA-binding capability. The proposed strategy entails developing photoactive binuclear cyclometallated Iridium (III) complexes based on triazolyl methyl quinoxaline and bipyrimidine ligand, which generate reactive oxygen species (ROS) upon light exposure. Mechanistically, these electropositive binuclear complexes are selectively transported to the cancer cell membrane *via* serum albumin, where they induce GSH depletion through ROS generation under light exposure. This process leads to significant disruption of mitochondrial membrane potential (MMP), DNA photocleavage, and subsequent apoptosis[1,2].

Keywords: Photodynamic therapy, Cyclometalated Iridium (III) complexes, ROS generation, GSH depletion, Apoptosis.

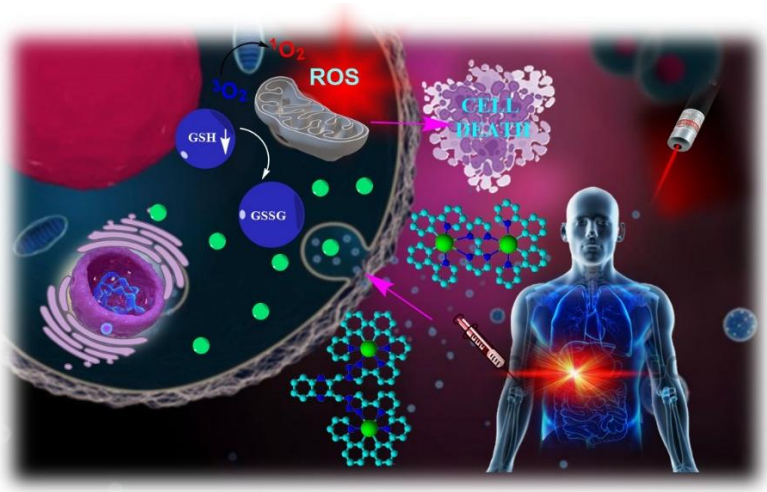

Figure: Mechanism of drug action in PDT for targeted cancer cell destruction.

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P38

Triphenylphosphine Gold(I) PROTACs as Potential Degraders of Thioredoxin and Thioredoxin Reductase

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Proteolysis Targeting Chimeras (PROTACs) are currently 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] Recent publications showed that this concept can also be transferred to metal-containing molecules. Thioredoxin Reductase (TrxR) and Thioredoxin (Trx) were successfully degraded with a Cereblon (CRBN) recruiting Pt-PROTAC in MM.1S and JJN-3 cells.[3]

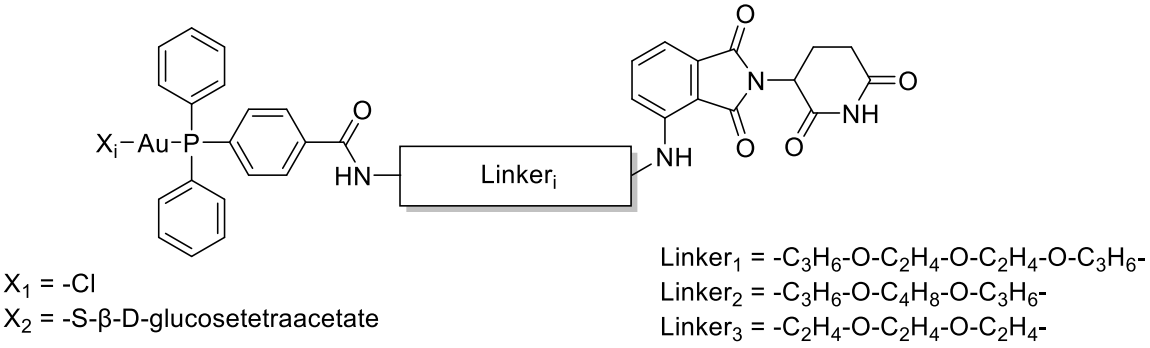

Figure 1. Synthesized triphenylphosphine gold(I) PROTACs

To combine this promising approach with our expertise with gold(I)-based TrxR inhibitors, an auranofin-inspired series of CRBN-directed triphenylphosphine (TPP) gold(I) PROTAC molecules was successfully synthesized using a pomalidomide-derivative as the E3 ligase binding moiety[4] and TPP gold(I) complexes as TrxR binding warheads (Fig. 1).[5] The attachment point of the pomalidomide linker conjugate to the gold complex, the linker and the second ligand of the TPP gold(I) complex were varied. Antiproliferative effects of the new compounds were evaluated in A549 lung carcinoma cells and MM.1S multiple myeloma cells and compared with the parent compounds. To investigate degradation effects on TrxR and Trx, a western blot method was developed. Newest results will be presented on the poster.

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P39
Anticancer Gold(III) Porphyrin Targets HSP60 for Combating Nasopharyngeal Carcinoma

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Cancer remains one of the leading causes of mortality worldwide. Although targeted therapies have improved the survival rates for patients with certain cancers, such as lung and breast cancers, many malignancies still lack effective targeted treatment options. This unmet clinical need highlights the importance of developing novel therapeutics that can achieve selective biomolecular targeting to advance cancer treatment paradigms and enhance the clinical outcomes.

Metal-based anticancer agents offer unique therapeutic potential due to their distinct structural scaffolds, facilitating non-covalent interactions with proteins involved in cancer cell proliferation and metastasis. This feature is often unattainable with conventional organic-based drugs. Gold(III) tetraphenylporphyrin (Gold-1a) is one of such antitumor complexes that has been previously identified as an inhibitor of heat shock protein 60 (HSP60) with low micromolar binding affinity.[1] HSP60, a mitochondrial chaperone implicated in protein folding and assembly, playing a key role in modulating cancer progression and apoptosis, has emerged as a pivotal therapeutic target for a wide range of cancers. As evidenced by the bioinformatic analysis using The Cancer Genome Atlas (TCGA) database, the overexpression of HSP60 in solid tumors compared to normal tissues further reinforces its clinical relevance in cancer therapy. In this study, Gold-1a demonstrated potent anticancer activity, significantly reducing the viability of HSP60-overexpressed Epstein-Barr virus (EBV)-positive nasopharyngeal carcinoma (NPC) cells and patient-derived organoids of stage III NPC at low micromolar concentrations. Moreover, Gold-1a effectively suppressed the tumor growth in a human NPC xenograft model. The interaction between Gold-1a and HSP60 was validated through thermal proteome profiling and cellular thermal shift assays, confirming the target engagement *in cellulo.* Computational study further elucidated the specific non-covalent binding mode of Gold-1a within the binding site of HSP60. Taken together, these findings position gold(III) porphyrin as a promising lead compound that targets HSP60 in human NPC, with compelling preclinical efficacy that warrants further development for clinical translation.

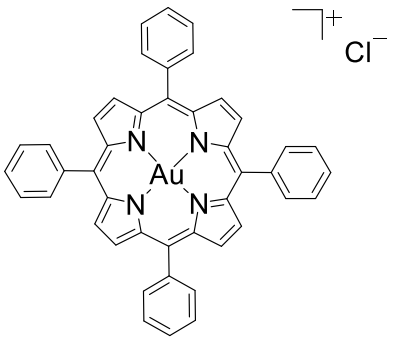

Figure 1. Chemical structure of Gold-1a.

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P40
High-Throughput Discovery of Antimicrobial Ruthenium(II) Polypyridyl Complexes

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Antimicrobial resistance (AMR) accounts for >1 million deaths annually and is projected to cause > 5 million deaths by 2030. [1] Despite this looming threat, the antibiotic development pipeline remains stagnant, with most new candidates being derivatives of existing drugs. [2] This highlights not only the urgent need for novel scaffolds but also for more efficient discovery strategies. Metallodrugs, though well-established in oncology, remain relatively underexplored for their use as antimicrobial agents. Among these, ruthenium(II) polypyridyl complexes, known for their structural diversity and potent biological activity, are emerging as a promising class of metalloantibiotics.[3]

To accelerate efficient exploration of the chemical space and the discovery of effective ruthenium(II) polypyridyl-based antibiotics, we leverage automated combinatorial synthesis and high-throughput biological screening. By carefully selecting ligand chemistries, we have synthesized three distinct libraries of complexes, which are directly screened for antibacterial activity and mammalian cell cytotoxicity at a fixed concentration. This approach enables the rapid identification of compounds with potent antibacterial activity and minimal toxicity to mammalian cells. Hit compounds are subsequently re-synthesized on a larger scale, fully characterized, and subjected to more detailed biological evaluation.

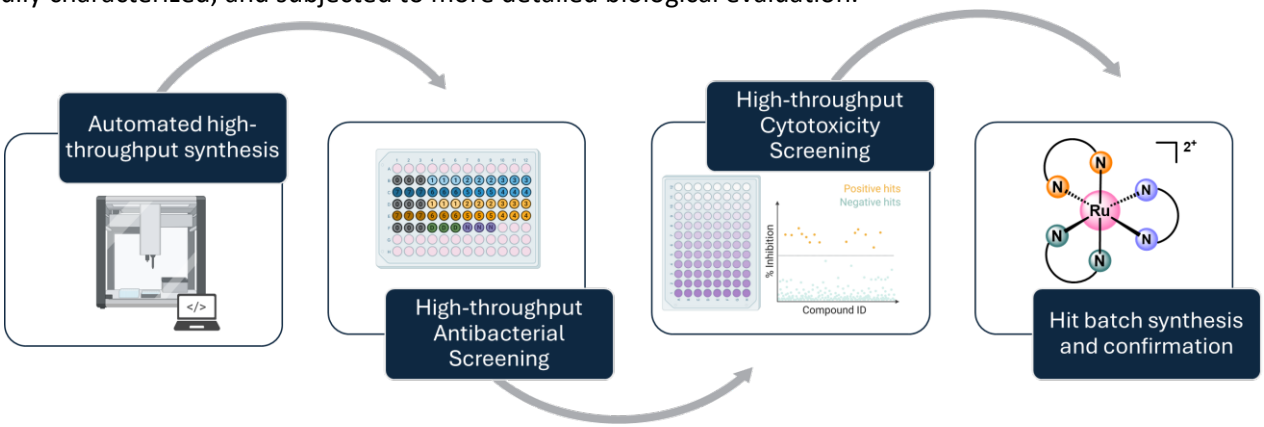

Figure 2. Overview of the workflow used in this work.

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P41
Stability and Interaction with Biomolecules of (NHC)Gold(I)-thiolate and -thiocarboxylate Complexes

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During the last decade, several types of organometallic compounds have gained attention in medicinal chemistry as promising anticancer agents. Among them, gold(I) *N*-heterocyclic carbene (NHC) complexes have a high potential in terms of antiproliferative effects.[1]

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

Recent results indicate similar σ-donor capabilities and thus improved stability based on ^{13}C NMR chemical shifts of thiocaboxylate (SOR), NHC and alkyne ligands.[2] Complexes of the latter two have already demonstrated high stability in the form of gold(I) biscarbene and gold(I) alkyne complexes.[1,3]

Therefore, gold(I)(NHC) complexes with thiocarboxylate and thiolate ligands [(NHC)Au(SR)] were synthesised for detailed analytical studies by HPLC-MS to investigate their chemical stability and potential interaction with thiol-containing amino acid derivatives, such as *N*-acetylcysteine (NAC) and glutathione (GSH).

A reversed phase-based chromatographic method was developed to separate the complexes from their ligands and to monitor possible interactions between the [(NHC)Au(SR)] complexes and the thiol moiety of NAC and GSH. Each compound was dissolved in dimethyl sulfoxide and incubated in either water or phosphate-buffered saline (PBS) with one of the thiol containing molecules.

Initial analytical tests indicated different stabilities depending on the media and biomolecule used. The latest results of this ongoing project will be presented on the poster.

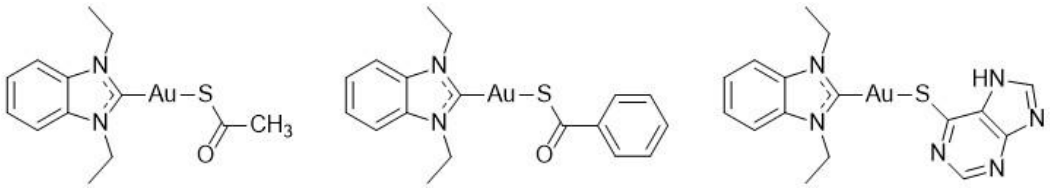

Figure: Synthesised and investigated gold(I) complexes.

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P42

Synthesis, Characterization, and Biological Evaluation of Fe (III)-NHC Complexes for Photodynamic Therapy and Chemotherapy

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Photodynamic therapy (PDT) has emerged as a promising alternative to traditional cancer treatments due to its reduced side effects, selective destruction of tumor tissues with minimal damage to healthy cells, and its ability to stimulate the immune response.[1] In recent years, the development of photosensitizers based on first-row transition metals has gained attention as a more sustainable alternative to those relying on heavy metals, owing to their greater natural abundance and lower cost. Among them, iron complexes stand out as particularly attractive candidates due to iron's Earth-abundant nature, low toxicity, and excellent biocompatibility. Although the application of iron complexes has historically been limited by ultrafast excited-state deactivation and poor photostability, recent advances in ligand design have enabled the stabilization of charge-transfer states and significantly improved their photophysical properties.[2,3]

Herein, we report the synthesis and characterization of a series of Fe(III) N-heterocyclic carbene (NHC) complexes (**Fig. 1**) and provide a comprehensive evaluation of their potential as both anticancer agents and photosensitizers. Some of these complexes exhibit enhanced cytotoxicity against cancer cells compared to cisplatin. ICP-MS analyses revealed that increased hydrophilicity correlates with reduced cellular uptake, which in turn decreases cytotoxicity. This class of molecules displays promising bioactivity and tunability, positioning them as potential candidates for future chemotherapeutic development.

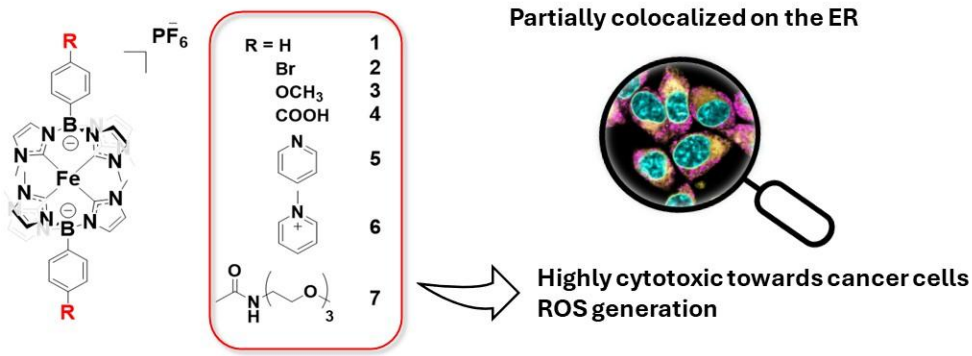

Fig. 1. Schematic representation of developed Fe(III)-NHC complexes.

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PLENARY LECTURES

KEYNOTE LECTURES

INVITED LECTURES

SHORT LECTURES

SL24	A nanoencapsulated Ir(III)-phthalocyanine photosensitizer for hypoxia-tolerant photodynamic therapy	Ashoo Pezhman
SL25	A Trojan Horse Approach for Overcoming Antibiotic Resistance using Nature's Most Beautiful Cofactor	Brasch Nicola
SL26	Ferrocene Correlates with Ferroptosis: Multiple Approaches to Explore Ferrocene-appended GPX4 Inhibitors as Anticancer Agents	Wang Yong
SL27	Stimuli-responsive Prodrug Activation in Mitochondria for Improved Chemotherapy	Paira Priyankar
SL28	Theranostic clinical study with 188 Re P2045 in lung cancer expressing SSTR and well differentiated Neuroendocrine tumours	Adams Christopher
SL29	Synthesis and Investigation of Monometallic and Heterobimetallic Re(I)/Au(I) Complexes for Cell Imaging Applications	Scholtyssek Oliver Christoph
SL30	Modulation of Redox potential in Ferrocene-peptide conjugates with potential antitumor activity	Santi Saverio
SL31	Luminescent organometallic iridium(III) complexes as affinity-based probes for imaging subcellular biomolecule biomarkers	Wang Wanhe
SL32	Unveiling the in vitro/in vivo potential of Co(III)-cp complexes	Morais Tânia
SL33	Gold Acyclic Diaminocarbene Complexes: A Promising Class of Multitarget Anticancer Agents	Gil Moles Maria
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SL35	Chemistry and Bioactivity of Ferrocenyl Quinone Methides	Mcglinchey Michael
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SL39	BiFcT a new ferrocene-based ferroptosis inducer to cancer cells	Kowalski Konrad
SL40	Preparation, stability, photochemistry and anticancer study of photoactivatable Pt(IV) prodrugs bearing axial alkoxido Ligands	Zhigang Wang

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P02	Designing Cold Plasma Cleavable RGD-Metal Peptide Bioconjugates for Targeted Tumor Therapy	Afzal Fahd
P03	Multi-targeting Ir(III) Catalysts for the Treatment of Ovarian Cancer	Alsaif Sitah
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P05	Expanding the Horizons of Organometallic Redox Intracellular Chemistry To Half-Sandwich Cobalt(III) Complexes	Annunziata Alfonso
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P09	Exploring the synthesis and cytotoxicity of Pd(I) dimers bearing phosphine and isocyanide ligands	Botter Eleonora
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P13	Photochemical reaction of CpFe(CO)2I with β-diketones and biological activity of the resulting products.	Doroszko Cyprian
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P20	Synthesis, activity and speciation of anticancer gold(III) complexes displaying original reactivity	Lacoma Tom
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P22	New Three-Legged Piano Stool Complexes based on Ru(II), Rh(III) and Ir (III): Synthesis and Antitumorales Evaluations.	Macaya-De La Hoz Juan Carlos
P23	Re(I) and Re(III) Half-Sandwich Complexes: From Synthesis to Biological Assessment	Martín Hoyas Alejandro
P24	Reactions of Cobalt Porphyrin Nitrite with Oxophilic Substrates. Role of Sulfur Bound Hydrogen in Nitrite Reduction.	Martirosyan Garik
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P27	Exploring a New Class of Organometallic 1,2,3-Triazoles: Rational Design, Characterization and Evaluation as Potential Anticancer Agents	Peña Méndez Luis Ignacio
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P31	Design of pH-Sensitive Ruthenium-Peptide Conjugates for Targeted Therapy of Metastatic Breast Cancer	Sá Marco
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P36	Dual-Target Gold(I) NHCs: Optimizing the NHC Ligand Structure to Disrupt Energy & Hormone Pathways in Breast Cancer Cells.	Türck Sebastian
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P40	High-Throughput Discovery of Antimicrobial Ruthenium(II) Polypyridyl Complexes	Welsh Athi
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