Biphenyl-gold(III) scaffold: a new field of investigations for anticancer drug candidates

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Organometallic gold(III) complexes have attracted a large attention as potential anticancer agents in the last decades. The main advantage of organometallic complexes is their high redox stability in physiological media due to the presence of Au-C bounds. In this respect, bis-cyclometalated $[(C\text{^}N\text{^}C)AuL]^+$ and $[(C\text{^}N\text{^}N\text{^}C)Au]^+$ complexes have demontrated great potential.[1,2] However, their main limitations are the large number of coordination site occupied by the pincer ligands leaving only one or no coordination sites for available for other ligands. Moreover, the amount of substitution tolerated on the pincer ligands are quite narrow meaning the possibility of variation of these scaffolds are quite limited. To enlarge the the scope of structures that can be tested and potentially explore new modes of actions while preserving the high redox stability of bis-cyclometalated complexes, a reorganization of their coordination sphere appeared as a promising potential. Using a biphenyl ligand giving two Au-C bounds would preserve the high redox stability of bis-cyclometalated complexes while offering two coordination sites available for various ligands to optimize the anticancer properties of the complexes. Our results on the synthesis and anticancer activity of biphenyl-Au(III) complexes presenting N- and P-donor ligands as anticancer agents will be presented.[3]

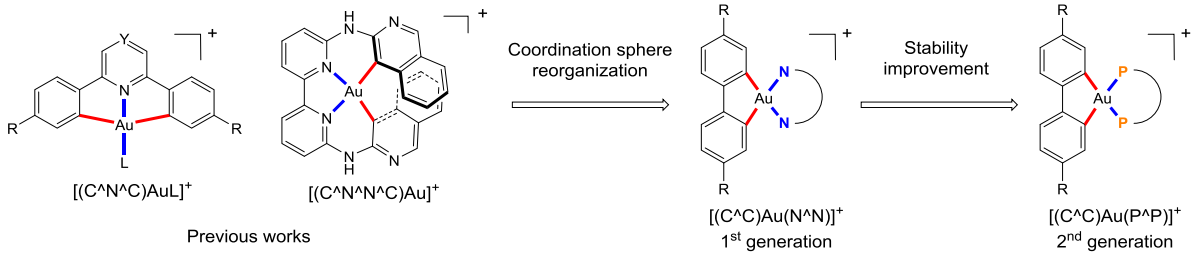

Figure 1: Structures of the $[(C\text{^}C)Au(N\text{^}N)]^+$ and $[(C\text{^}C)Au(P\text{^}P)]^+$ complexes and the related $[(C\text{^}N\text{^}C)AuL]^+$ and $[(C\text{^}N\text{^}N\text{^}C)Au]^+$ complexes.

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Diiron bis-cyclopentadienyl complexes as versatile organometallic scaffolds to develop new anticancer drugs

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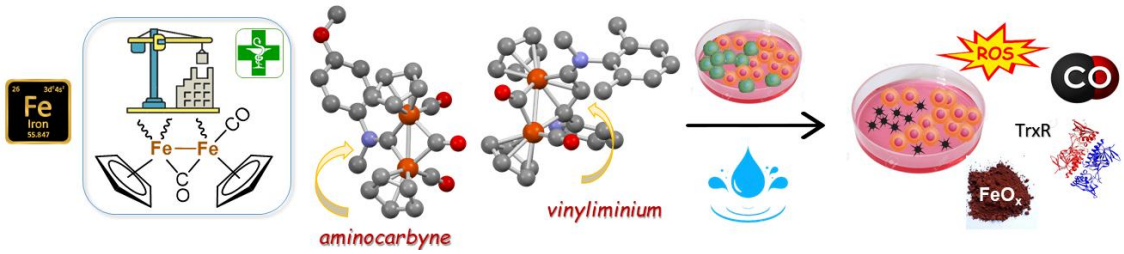
The development of **iron-based drugs** represents an intriguing perspective, looking at the replacement of precious metals (*e.g.* Au, Pt, Ru) with an earth-abundant, bioavailable and less toxic element. In this regard, the peculiar reactivity of the easily available **[$Fe_2Cp_2(CO)_4$]**, traced over the last 35 years, gives access to an arsenal of compounds holding a significant potential in terms of anticancer drug development. Herein, we report our recent biological studies on cationic complexes based on the [$Fe_2Cp_2(CO)_x$] core and containing a bridging C_1 ***aminocarbyne***[1] or C_3 ***vinyliminium***[2] ligand. The best performing compounds are highly cytotoxic *in vitro* on various human cancer cell lines, including 3D models, with a considerable selectivity with respect to normal (non-cancerous) cells. The complexes presumably act at various cellular levels via a multimodal mechanism (*i.e.* ROS production, carbon monoxide release, enzyme inhibition). Besides, these two classes of compounds possess favourable properties in the pharmacological setting, such as simple and high-yielding preparation up to gram scale, mM solubility in water, amphiphilicity (Log $P_{octanol/water}$), inertness in aqueous solution and cell culture medium. The possibility to modify the nature of terminal and bridging ligands, taking advantage of the cooperative effects provided by the [FeFe] scaffold, allows the synthesis of novel types of compounds that will be object of future studies.



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Electron Transfer Studies of DNA with Metal-Mediated Base Pairs

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DNA as a biological supramolecule is forming an antiparallel double helix in nature. It is stabilized by hydrogen bonding between canonical bases as well as by π-stacking interactions. Its great potential as precursor for many different types of nanodevices is due to its high stability, self-assembly properties, molecular recognition and optimized hybridization.[1]

A site-specific replacement of the canonical nucleobases with artificial ones can enable a controlled incorporation of different transition metal ions into the duplex. The resulting oligonucleotides can be used in applications such as charge transfer systems, DNA nanowires or as precursors for DNA-templated nanoclusters.[2,3]

Based on the recent report of diaminonaphthalene-based electron donor systems, we have optimized conditions to maximize the charge transfer through the DNA strand.[4] Furthermore, we were able to build metal-mediated base pairs to modify properties of these systems.[2]

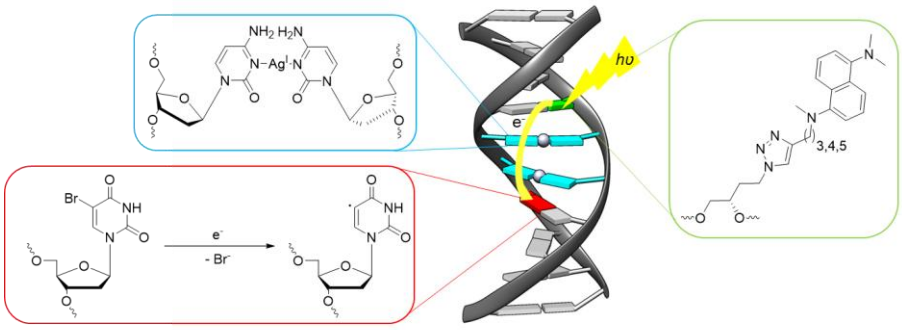

Figure 1. Schematic presentation of the electron transfer process through DNA with a silver(I)-mediated base pair**,** three diaminonaphthalene based units used as electron donor and a bromouracil unit used as electron acceptor.[2]

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Solution equilibrium behaviour of half-sandwich Rh and Ru complexes: an overview

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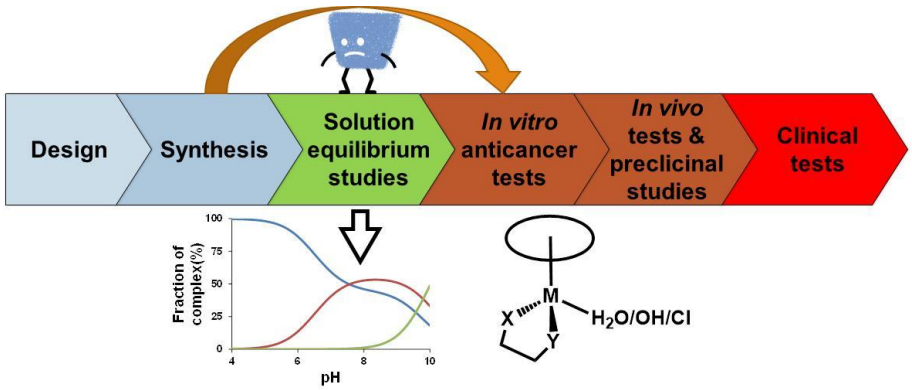
Several promising complexes of ruthenium were developed for cancer treatment and three of them entered into clinical trials.[1] The next-generation drug candidates have half-sandwich structure, which has desirable properties like stabilization of Ru(II), providing ideal lipophilic/hydrophilic character and easily tunable properties by changing the ligands.[2] The half-sandwich Rh(III) complexes are also of interest.[3] Although, a plethora of publications introduces newly synthesized complexes day-by-day and shows their *in vitro* cytotoxic effect, the deeper understanding of their solution stabilities and processes remains unclear. For the rational design, it is important to find the key structural factors which can determine the dominant forms under physiological conditions.



In this work, we collected the results about the solution equilibrium studies on a series of half-sandwich complexes from the last 10 years. The solution stability of Rh(III)(arenyl) and Ru(II)(arene) complexes with different bidentate ligands and the dominant species at physiological conditions (pH = 7.4) are compared. Changing the arene ligand, the metal center and the bidentate ligand has a significant impact on the complex stability, on the chloride ion affinity and on the pK_a of the aqua complex, based on the previously described data. Models will be introduced which can predict the solution behavior of this type of complexes.

Acknowledgements: This work was supported by the National Research, Development and Innovation Office (FK 124240, TKP-2021-EGA-32) and the Eötvös Lóránd Research Network (LP2019-6/2019).

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Comparative solution study on the interactions of Cu(II), Fe(II/III) and Ni(II) with imidazole-derived thiosemicarbazones: impact of methylation, redox and anticancer activity

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Thiosemicarbazones (TSCs) are versatile ligands as they confer a strong coordination tendency towards a wide variety of metal ions forming complexes with high stability. They possess a broad range of biological activities including *e.g.* antibacterial, antimalarial, antiviral, antioxidant and antitumor activities.[1] Notably, the coordination of TSCs to metal ions has been found beneficial either via enhancing their activity or decreasing the side effects of the ligands.[2]

Herein, we report a comparative study on the complex formation of four novel imidazole-derived thiosemicarbazones with Cu(II), Fe(II), Fe(III) and Ni(II) ions in order to investigate the effect of the mono- and dimethylation on the biological activity and the solution chemical behavior. These studies were performed by pH-potentiometry, electron paramagnetic resonance spectroscopy, and UV-visible spectrophotometry. The cytotoxicity of the ligands and their complexes was tested in four human cancer cell lines: drug-sensitive Colo 205 and doxorubicin-resistant Colo 320 human colonic adenocarcinoma cell lines, breast cancer cell line MCF-7, and cervical cancer cell line HeLa, in addition to normal lung fibroblast cells (MRC-5). Spectroelectrochemical studies and direct reactions with physiological reductants were also conducted on the copper and iron complexes of the title TSCs for the better understanding of the redox properties which are assumed to be related to their biological activity.

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Fe(II) metallohelices stabilize DNA G-quadruplexes and down-regulate expression of G-quadruplex regulated oncogenes

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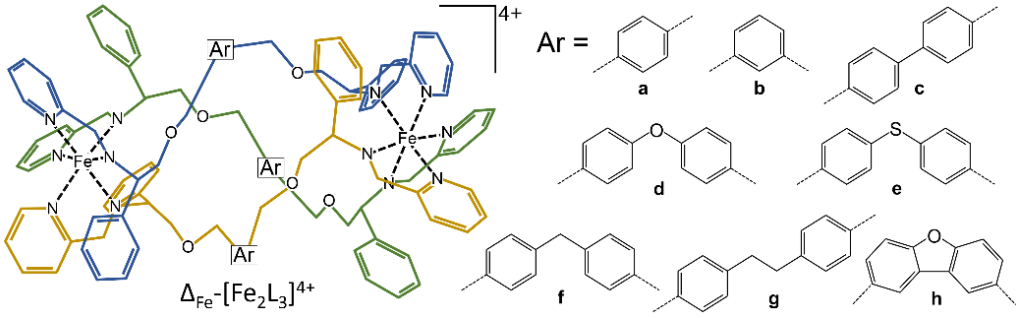
DNA G-quadruplexes (G4s) were identified within the promoter regions of many proto-oncogenes. Thus, G4s represent attractive targets for cancer therapy and the design and development of new drugs as G4 binders is a very active field of medicinal chemistry. Typical G4 binders contain planar aromatic chromophores for π-π stacking with G-tetrads, positively charged side chains for binding to loops and grooves of the G4, and steric bulk to prevent intercalation between DNA base pairs. Reports of nonplanar molecules interacting with G4s are rare, although in contrast many natural proteins have been identified that interact with G4s, commonly via α-helical recognition units. In this context we note that certain metallo-supramolecular helical assemblies, which have similar size, shape, charge, and amphipathic architectures to short cationic α-helical peptides have been shown also to interact. Enantioselective stabilization of human telomeric G4 and inhibitory effect on telomerase was demonstrated for a chiral Fe(II) based metallohelical complex **5a**. This compound, developed in one of our laboratories, was the prototype for several classes of self-assembling, optically pure, water-stable metallohelices based on helical arrays of fully-encapsulated Fe ions connected by different linking bridges.[1]



Here, we employed methods of molecular biophysics and biology to investigate the interaction of the chiral metallohelices[2] with a series of four DNA G4s (*hTelo*, *c-myc*, *c-kit1*, *c-kit2*) that are formed by the human telomeric sequence (*hTelo*) and in the promoter regions of *c-MYC* and *c-KIT* proto-oncogenes. The results show[3] that the investigated metallohelices preferentially bind to G4 over double-stranded DNA and stabilize G4 structures. Notably, both enantiomers of metallohelix **5b** were found to be effective inhibitors of primer elongation catalyzed by *Taq* DNA polymerase by stabilizing G4 structures formed in the template strands containing *c-myc* and *c-kit2* G4-forming sequences. Moreover, both enantiomers of **5b** down-regulated the expression of *c-MYC* and *c-KIT* oncogenes in human embryonic kidney cells at mRNA and protein levels. As metallohelices also bind other alternative nucleic acid structures, they hold promise as potential multi-targeted drugs.

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Novel Planar Pt(II) Cyclometallated Cytotoxic Complexes with G-Quadraplex Stabilisation and Luminescent Properties

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There is a clear and increasing need for efficient cancer treatments but current options for cancer patients are not optimal, with low success rates for many types of cancers, particularly those in the later stages of the disease. Herein is described the development of a series of novel quadruplex DNA (QDNA) targeting cyclometallated square-planar metal complexes (CMCs).The cyclometallated ligand benzo(h)quinolone coordinates through C1, forming an organo-metallic bond that results in deprotonation of the carbon, making it a effective σ-donor whilst the polypyridyl group is a good π-acceptor creating a strong ligand field (Figure 1). This increase in the energy gap between the unoccupied and occupied orbitals caused by the σ-bond results in fluorescence. The fluorescence of the complexes may allow them to be tracked within cells, which would reveal the intercellular target of the complex, enabling the elucidation of the mechanism of action in future studies. Melting experiments using quadraplex DNA (QNDA) demonstrate that interactions with the complexes, increase the melting temperature by up to 19˚C. This QDNA stabilisation was determined in two of the major G-quadruplex structures formed in the human c-MYC promoter gene (c-MYC) and a human telomeric repeat sequence (H-Telo). CMCs were found to stabilise H-telo more strongly than c-MYC, and the CMCs with the highest cytotoxic effect had a low to moderate correlation between H-telo binding capacity and cytotoxicity (R2 values up to 10 times that of c-MYC). Melting experiments further revealed the stabilisation effect was altered depending on whether the CMC was introduced before or after the formation of the QDNA. All CMCs GI50 values are comparable or better than cisplatin in human cancer cell lines HT29, U87, MCF-7, H460, A431, Du145, BE2-C, SJ-G2, MIA, and ADDP. Complexes 6, 7 and 9 were significantly more cytotoxic than cisplatin in all cell lines tested and had good to moderate selectively indices, 1.7 - 4.5 in MCF10A/MCF-7. Emission quantum yields were determined (0.015 to 0.064) and emission occurred outside cellular autofluorescence, meaning CMC fluorescence is ideal for in vitro analysis.

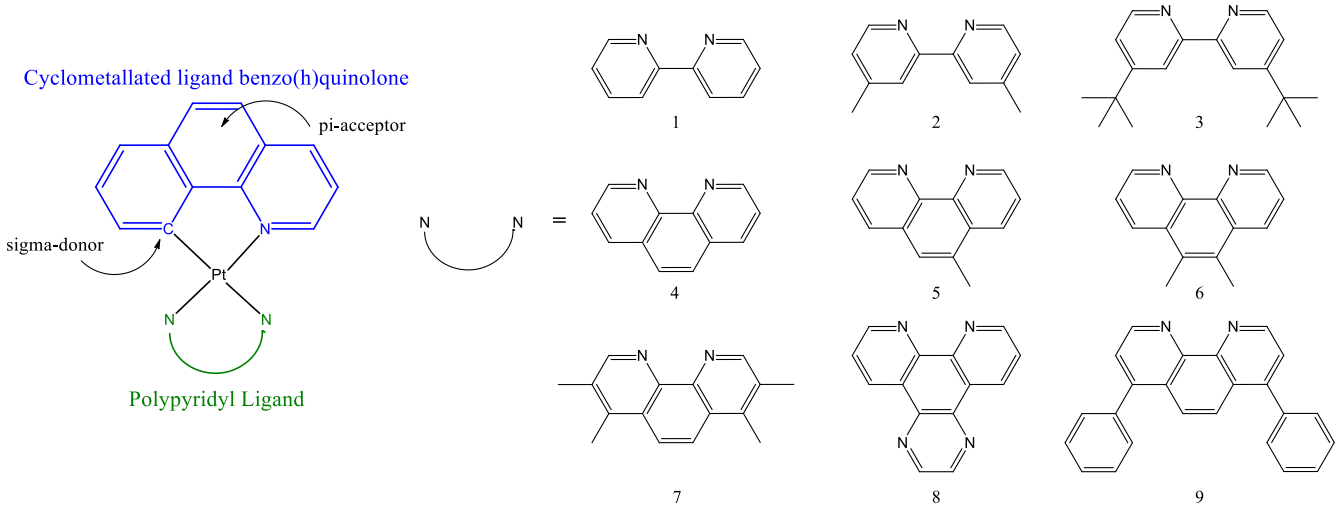

Figure 1: Structure of all CMCs numbered one through nine.

Activable 19F MR Imaging nanoprobes for the in vivo detection of biomarkers

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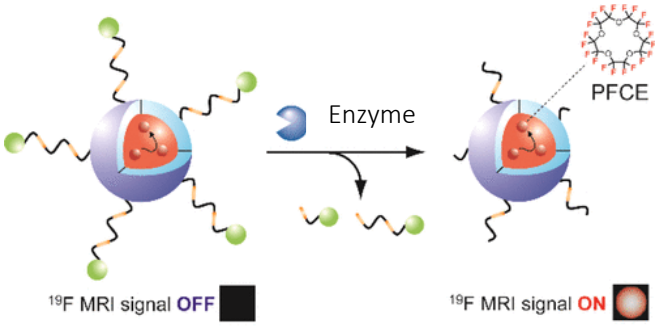
Converting MRI from a classical imaging modality into a molecular one is a technical as well as a scientific challenge that continues to require tremendous efforts [1]. A chemical solution in the form of a molecular probe able to respond to a biomolecular analyte with a sufficient signal gap could redefine our current paradigm concerning *Imaging* and *Diagnosis*. Until now, academic proposal of probe designs based on paramagnetic ions such as Gd(III), Mn(II) or Fe(III) do not yet show enough sensitivity enhancement for efficient *in vivo* detection of bio-analytes of interest [2]. In fact, obtaining a sufficient signal to background noise ratio encounter a fundamental limit due to the intrinsic relaxivity they generate in their initial state, prior to their encounter with the analyte. On the contrary, ^{19}F-MRI have shown promising results for the democratization of molecular MRI as a routine experiment and has attracted the interest of researchers thanks to the NMR sensitivity of ^{19}F atoms close from the one of hydrogen and its negligible endogenous background signals, which render it superior for monitoring specific biological events in living animals. Thus, several ^{19}F-MRI single molecular probes have been reported [3], but the low sensitivity of ^{19}F-MRI render difficult the detection of biomarkers *in vivo* considering their sub-nanomolar concentration on site. One solution is to increase the number of ^{19}F atoms onto one probe, but is unfortunately limited to its molecular size, disponible space, chemical feasibility, while keeping a low hydrophobicity for good biocompatibility. An alternative approach is the design of bigger objects, such as nanostructures, composed of large amounts of ^{19}F atoms-bearing molecules, as smart platforms that allow a stimuli-induced response [4]. Our group is pioneer in the design of PFC containing silica nanoparticles based nanoprobe responsive to biomarkers. Recently, we reported new systems with improved targeting and multicolor imaging capacity [9,10].



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Development of dual-action Pt(IV)-Imatinib and Nilotinib pro-drug conjugates targeting colorectal cancer

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Side-effects due to the lack of selectivity toward cancer tissues is one of the major drawbacks to Platinum(II) anticancer agents (i.e. *cis*platin, oxaliplatin). Nevertheless, despite these severe side-effects, platinum-based compounds remain one of the first worldwide choice to treat a variety of tumours. Tyrosine Kinases (TK) are promising targets in oncology and play a major role in cell regulation pathways. For example, overexpression of Platelet Derived Growth Factor Receptor (PDGFR) is associated with angiogenesis and metastasis in colorectal cancer[1]. Colorectal cancer itself is the third most common cancer worldwide with the second highest mortality rate[2] and shows high resistance with respect to cisplatin treatment. Here-in we describe the successful synthesis of Pt(IV)-prodrugs tethering in axial position TK inhibitors (i.e. Imatinib/Nilotinib hybrid conjugates) with the aim to target colorectal cancers (Figure 1). While Imatinib and Nilotinib are successful BCR-ABL inhibitors, they also show potent PDGFR inhibition[3]. The synthetic challenges/successes encountered, different strategies used to successfully link Imatinib/Nilotinib in axial position of Pt(IV) and preliminary biological data will be discussed.

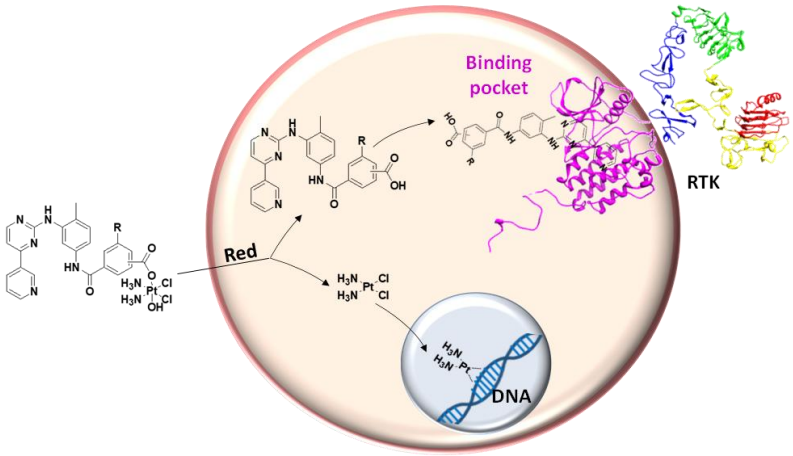

Figure 1. Mechanism of action of the Pt(IV)-Imatinib/Nilotinib Pro-drug.

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Asymmetric bidentate ligand complexes of $[Mo_2O_2(\mu\text{-}S)_2(S_2)]^{2+}$ as a potential cyanide antagonist: Mechanistic approach.

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A public health issue who has been studied throughout decades is cyanide poisoning[1,2]. These efforts are related to understanding aspects of toxicity, and its quick conversion into a less harmful product. Molybdenum complexes have been explored as a catalytic antagonist in this conversion. The complex, $(DMF)_3Mo_2O_2(\mu\text{-}S)_2(S_2)$, was used in the conversion of cyanide as parallel ligand exchange[3] of the DMF and a sulfur abstraction reaction take place, forming thiocyanate[4,5] (Figure 1). New complexes using bidentate ligands such as oxamate and oxalate were synthesized with the formulas; $K[(oxamate)Mo_2O_2(\mu\text{-}S)_2(S_2)]$ and $K_2[(oxalate)Mo_2O_2(\mu\text{-}S)_2(S_2)]$ respectively. Their properties were compared with complexes with proposed mechanism for sulfur abstraction reaction, forming thiocyanate[6].

The proposed mechanism under current study is initiated by sulfur abstraction from the complex; a conclusion that is strongly supported by results. A next generation design of new complexes brings close attention to the charge of the bidentate ligand and chelate ring size effect, which may elucidate further details of the reaction mechanism.

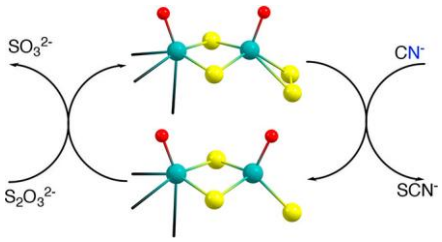

Figure 1. Proposed catalytic cycle for the thiocyante formation[5]

Financial support by Icelandic Centre of Research grant nr 195726 is gratefully acknowledged.

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Click-Pt(IV)-carbohydrates pro-drugs for treatment of osteosarcoma

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The selectivity of cancer cells has always been a major drawback for chemotherapeutic agents and in particular for cisplatin, one of the most important anticancer drugs for the treatment of several kinds of tumours. One strategy to overcome this challenge is to modify the coordination sphere of the metallic centre with specific targeting vectors whose receptors are overexpressed on the tumour's cell membrane, such as monosaccharides. [1] Here we report the strategic synthesis of four novel glyco-modified Pt[IV] pro-drugs, based on a cisplatin scaffold (Figure 1), and their biological activity against osteosarcoma (OS), a malignant tumour which is common in adolescents and young adults. [2] The carbohydrate moiety (glucose and galactose) and the Pt scaffold are linked using the Copper-catalysed Azide Alkyne Cycloaddition (CuAAC) reaction, which has become the flagship of click chemistry due to its versatility and mild conditions.[3] Cytotoxicity and drug uptake on three different OS cell lines, as well as on OS Cancer Stem Cells (CSCs) are discussed.[4]

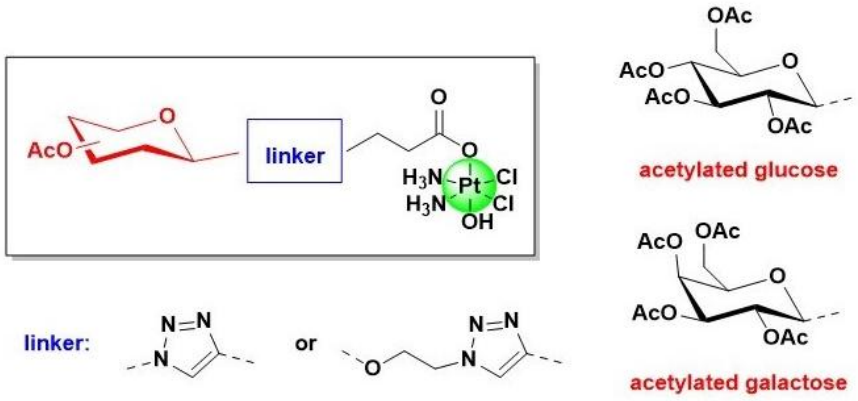

Figure 1. General structure of the novel Pt(IV) complexes based on cisplatin scaffold and functionalised with acetylated glucose and galactose.

Acknowledgements

EM is grateful to Maynooth University for sponsoring his PhD with a Graduate Teaching Fellowship. EM, SP, MM and DM strongly acknowledge NANO4TARMED consortium H2020-WIDESPREAD-2020-5 project number 952063.

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Anticancer rhenium di- and tricarbonyl complexes and synthesis of new α-diimine rhenium dicarbonyl complexes

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In our effort to discover novel selective and non-toxic agents effective against CRC, we synthesized a series of rhenium(I) tricarbonyl-based complexes with increased lipophilicity. Two of these novel compounds were discovered to possess remarkable anticancer, anti-angiogenic and antimetastatic activity in vivo (zebrafish-human HCT-116 xenograft model), being effective at very low doses (1-3 μM). At doses as high as 250 μM the complexes did not provoke toxicity issues encountered in clinical anticancer drugs (cardio-, hepato-, and myelotoxicity). In vivo assays showed that the two compounds exceed the anti-tumor and anti-angiogenic activity of clinical drugs cisplatin and sunitinib malate, and display a large therapeutic window.[1]

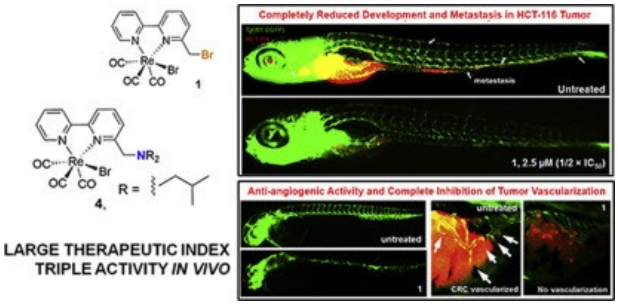

Figure 1. Rhenium tricarbonyl complexes showed great anticancer properties.

In another study, we reported a rhenium(II) dicarbonyl complex, which displayed better cytotoxicity against MCF-7 breast cancer cells than cisplatin.[2] We investigated later new synthetic routes to aerobically stable and substitutionally labile α-diimine rhenium(I) dicarbonyl complexes. The molecules were prepared in high yield from the *cis–cis–trans*-$[Re(CO)_2(^tBu_2bpy)Br_2]^-$ anion (where $^tBu_2bpy$ is 4,4′-di-*tert*-butyl-2,2′-bipyridine), which could be isolated from the one electron reduction of the corresponding 17-electron complex. Ligand substitution of Re(I) complexes proceeded via pentacoordinate intermediates capable of Berry pseudorotation. In addition to the *cis–cis–trans*-complexes, *cis–cis–cis*- (all *cis*) isomers were also formed. $[Re(CO)_2(^tBu_2bpy)Br(L)]$ complexes may be considered as synthons for the preparation of a variety of new stable diamagnetic dicarbonyl rhenium *cis*-$[Re(CO)_2]^+$ complexes, offering a convenient entry in the chemistry of the core.[3]

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Binding of half-sandwich organorhodium(III) and organoruthenium(II) complexes towards human serum albumin: kinetics, affinity, binding mode

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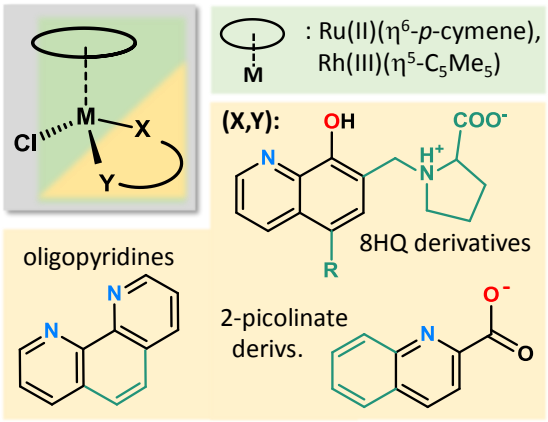
Ru(II)(η^6-arene) and Rh(III)(η^5-C_5Me_5) half-sandwich complexes are extensively studied as potential anticancer agents, and recently numerous organometallic compounds were synthesized and tested *in vitro* against human cancer cells.



Our studies focus on mainly Ru(II)(η^6-*p*-cymene) and Rh(III)(η^5-C_5Me_5) complexes formed with bidentate (O,N) and (N,N) donor bearing ligands (see figure). 8-hydroxyquinoline (8HQ) derivatives are extensively studied due to their broad range of pharmacological properties.[1] Among the studied complexes Ru(II)(η^6-*p*-cymene) and Rh(III)(η^5-C_5Me_5) complexes of 8-hydroxyquinoline derivatives and Rh(III)(η^5-C_5Me_5)(1,10-phenantroline) showed remarkable *in vitro* cytotoxic effect in various cancer cell lines (*e.g.* in MES-SA, MES-SA/Dx5, MCF-7 and Colo320 cells).[2]

Binding to transport proteins *e.g.* to human serum albumin (HSA) is suggested to have an important effect on the distribution, metabolism and excretion of a metal complex. Besides, albumin binding can be advantageous due to the enhanced permeability and retention effect in solid tumor tissues, resulting in the accumulation of protein bound drugs close to the cancer cells.

Herein we provide a comprehensive picture on the kinetic aspects, binding strength, binding mode and location of HSA binding of these complexes. Studies with amino acid side chain models and low molecular mass constituents of blood are presented as well. Correlations were found between albumin binding and thermodynamic stability, lipophilicity or kinetic lability of the metal complexes.

Acknowledgements: This work was supported by the National Research, Development and Innovation Office of Hungary (FK 124240, TKP-2021-EGA-32), the Eötvös Lóránd Research Network (LP2019-6/2019).

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Diimine Re(I) tricarbonyl complexes: toward novel highly potent and non-toxic antimicrobial agents

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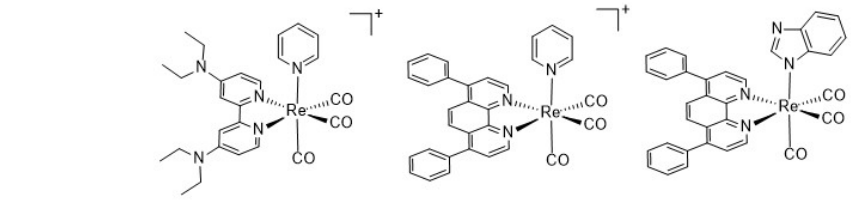
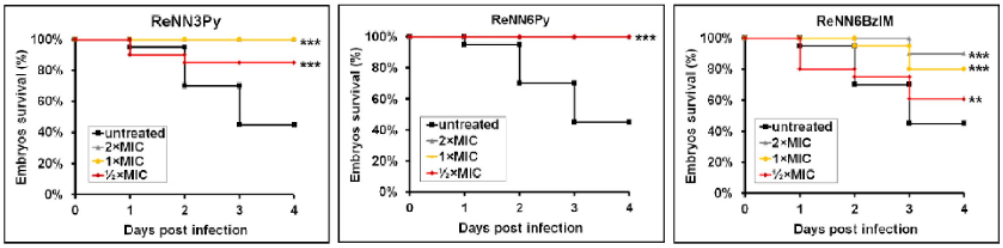
The current increase of antimicrobial resistance (AMR) poses a serious need for new classes of therapeutic compounds. For this purpose, our group has been interested in organometallic antimicrobial agents and more precisely in rhenium(I) tricarbonyl (RTC) molecules, which have been known for possessing promising therapeutic properties against a variety of bacteria and fungi.[1,2] Our work features the synthesis of various RTC complexes bearing a diimine moiety as bidentate ligand and a pyridine or imidazole derivative as monodentate ligand. The biological activity of these compounds is tested against several strains of bacterial and fungal pathogens.[3,4]



	ReNN3Py	ReNN6Py	ReNN6BzIm
MIC agianst MRSA	0.8 µM	0.4 µM	6.2 µM



The already obtained results suggest great potential, as some RTC species exhibit excellent activity against methicillin-resistant *Staphylococcus aureus* (MRSA), *Candida albicans* or MRSA-*C. albicans* co-infection with a minimum inhibitory concentration (MIC) in the nanomolar range. Furthermore, *in vivo* tests using zebrafish as model organism show no toxicity toward the embryos, increasing the infected fish rate survival up to 100 %.

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Metal-based glycoconjugates for the targeted anticancer chemotherapy

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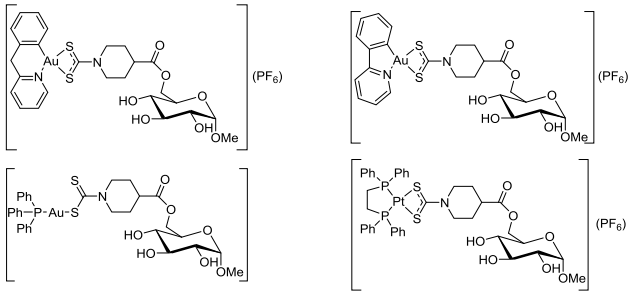
Glucose enters the cell by facilitated diffusion through the glucose transporters (GLUTs) and, subsequently, undergoes a series of biochemical steps to produce energy. In order to sustain their abnormal proliferation rates,cancer cells overexpress GLUTs to facilitate glucose internalization, thus satisfying their greater demand for energy. Remarkably, aerobic glycolysis was proved to be the major glucose metabolic pathway in tumor sites (the so-called"Warburg effect").[1]Therefore, conjugation of chemotherapeutic agents (including metallodrugs) to glucose-like substrates shows potential in a view to achieving tumor-specific intracellular drug transfer and delivery by taking advantage of the increased demand of glucose and the overexpression of GLUTs in cancer cells.[2]

In thiscontext, we here report on the development of someplatinum(II)- and gold(I/III)-dithiocarbamatoglycoconjugates (see figure below) obtained by exploiting an elegant and efficient synthetic route recentlydeveloped by our group.[3]Such metal-glycoconjugates would combine the antitumor properties and the favourable toxicological profile of the metal-dithiocarbamato non-glycosylated analogues,[4]along with improved tumor selectivity and cellular uptake provided by the glucose-containing ligand coordinated to the metal center, through the exploitation of the glucose-mediated cellular internalization facilitated by overexpressed GLUTs.



Acknowledgements. Financial support by NUI Galway (*Millennium Fund Minor Project 2013* to LR) and the Irish Research Council (*Postgraduate Scholarship GOIPG/2018/38* to IT)is gratefully acknowledged.

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Solution chemistry studies of the interaction of COTI-2 and its derivatives with endogenous metal ions

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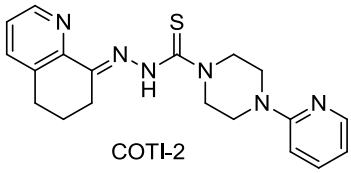
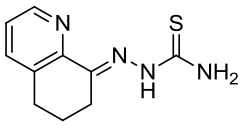
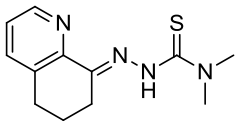
Thiosemicarbazones and their metal complexes have a wide variety of structures and pharmacological effects, and their best-known representative is 3-aminopyridine-2-carbaldehyde thiosemicarbazone (triapine), which is undergoing phase III clinical testing.[1] Triapine is accompanied by a number of side effects (vomiting, methaemoglobinaemia), and these problems have prompted the development of additional derivatives, including a number of promising compounds such as COTI-2 showing much higher cytotoxicity than triapine.[2,3] COTI-2 is currently evaluated in phase I clinical trial for the treatment of gynecological and other solid cancers. This compound contains {N,N,S} chelating moieties and complexation with endogenous metal ions might have a role in its mechanism of action, although its coordination chemistry has not been investigated so far.



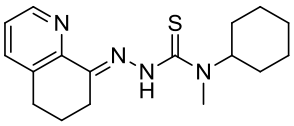
COTI-2



COTI-NH_2



COTI-NMe_2



COTI-Nchexyl

Herein, the complex formation of COTI-2 and its two novel terminal N-disubstituted analogues (COTI-NMe_2 and COTI-Nchexyl) and their non-substituted version (COTI-NH_2) with iron(II), iron(III), copper(II) and zinc(II) ions was characterized in solution by UV-visible, electron paramagnetic resonance spectroscopy and X-ray crystallography, Aim was to reveal the influence of the various substituents on the structure, stability and redox activity of their complexes, in addition to their anticancer properties, the mode of action and cellular accumulation.

Acknowledgments: NRDI (Hungary) FK 124240, 2019-2.1.11-TÉT-2019-00003; bilateral OeAD project HU 02/2020, and the Austrian Science Fund (FWF) grant P31923.

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HPLC-based analytical studies on a promising ruthenium anticancer agent in aqueous solutions

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In recent years ruthenium complexes have gained a huge interest in anticancer drug research.[1] They are considered a potential alternative as anticancer agents to the well-established Cisplatin since they are likely to have different modes of action.[2] Despite the intense research their active form and targets remain largely unknown.[3] This is partly due to the limited options for analytical monitoring of newly synthesized complexes and their decomposition products and metabolites. However, analytical studies are highly relevant as they not only provide insights into stability and possible targets of a drug candidate, but can also help to conclude on structure-activity-relationships.

Therefore, an HPLC method was developed to investigate the aqueous solution chemistry of a ruthenium complex (see Figure 1), which had shown in vitro antiproliferative activity with an IC_{50} value in the low micromolar range.[4]

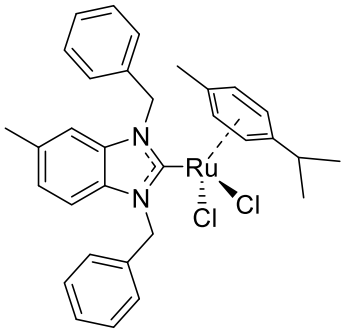

Figure 1: Structure of the investigated ruthenium complex.

The complex and its potential metabolites were successfully separated on a RP-column containing a mixed phase of phenyl and C18 chains and were quantified by DAD detection. The resulting peaks were partly identified by MS. Furthermore, model substances such as N-acetylcysteine and 9-ethylguanine were added to investigate the binding behavior and reactivity in aqueous solutions.

The complex is highly reactive, with its stability strongly dependent on pH, chloride concentration, and temperature of the medium. Concerning the binding profile, a high reactivity towards thiol groups was confirmed. Both proteins and DNA come into consideration as targets, since substances consisting of amino acids as well as 9-ethylguanine were bound by the ruthenium complex.

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Silver nanocluster stabilized by double-stranded DNA bearing 1*H*-imidazo[4,5-*f*][1,10]phenanthroline

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Metal nanoclusters consist of a small number of metal atoms, usually not more than 100. The small size of such components leads to the collapse of the band structure and results in the formation of discrete energy levels similar to the ones found in molecules.[1] As a result, such clusters have chemical and optical properties similar to those of molecules, making them suitable for applications in the fields of biosensing or catalysis.[2]

In this work the synthesis and characterization of DNA-templated silver nanoclusters (AgNCs) starting from silver-mediated base pairs formed by the artificial nucleobase 1*H*-imidazo[4,5-*f*][1,10]phenanthroline (ImPhen) is presented.[3] The subsequent reduction of the silver(I) ions by treatment with $NaBH_4$ yields the desired nanoclusters, which are characterized by CD, UV and fluorescence spectroscopy.

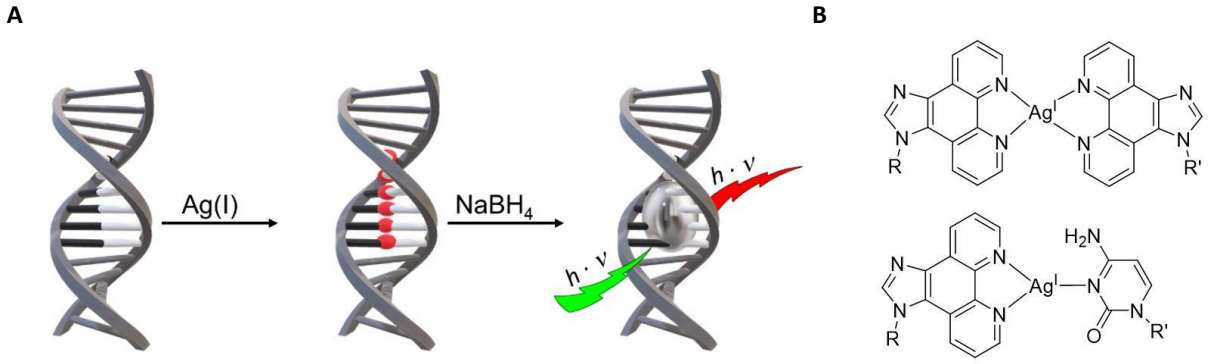

Figure 1: A: Synthesis of DNA-stabilized AgNCs starting from a double helix with six base mismatches (black / white bars), each of which can bind one silver ion (red balls). **B:** Proposed structures of the silver(I)-coordinating base pairs ImPhen–Ag(I)–ImPhen (top) and ImPhen–Ag(I)–cytosine (bottom) formed prior to their reduction by $NaBH_4$.

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Tracking CXCR4 with a small synthetic organic vector: chelator conjugation, ^{64}Cu radiolabeling and *in vivo* targeted-PET imaging

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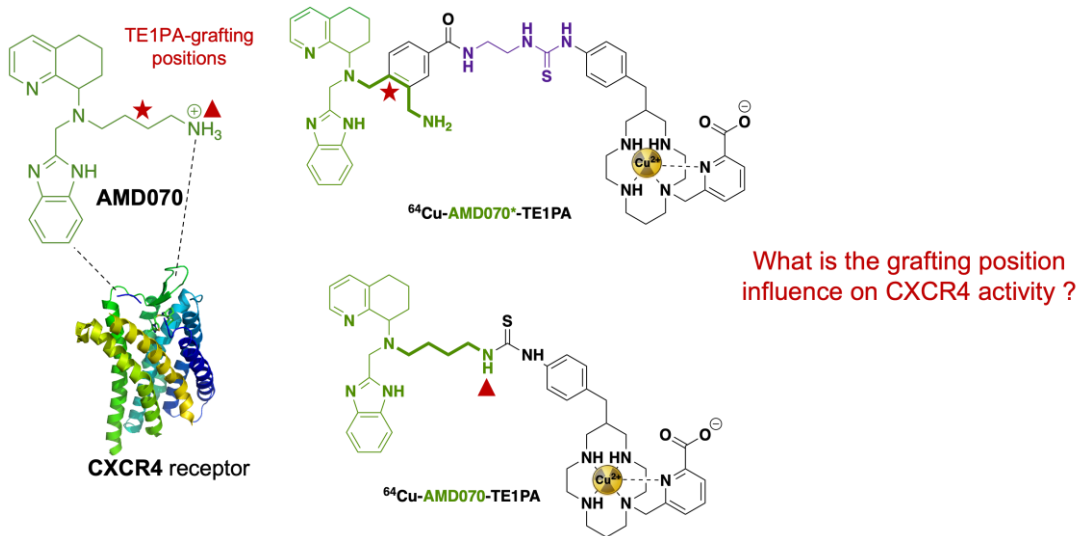
Current hot challenges in targeted PET-imaging of cancer are the quest for novel biomarkers to track, and the design of corresponding radiopharmaceuticals, labeled with relevant radionuclides. In this context, CXCR4 receptor has recently emerged as a highly promising marker because of its overexpression in 23 types of human cancers. Considering this critical function, several CXCR4 antagonists have been identified, such as antibodies and peptide derivatives allowing targeted imaging of cancers.[1] We propose to go a step further by targeting CXCR4 with synthetic organic vectors, that allow easier preparation and faster pharmacokinetics of corresponding radioconjugates. These will be grafted with TE1PA, an excellent ^{64}Cu bifunctionnal chelator designed by our group, that outperformed DOTA or NOTA in ^{64}Cu PET imaging of tumors in murine models.[2] AMD070 is a small organic CXCR4 antagonist,[3] that will first be conjugated to TE1PA *via* its free amine moiety. As this function has a role in interactions with CXCR4, the AMD070* analogue has also been selected to provide a different conjugation site while preserving a primary amine with the same chain length. Overall, two novel purely synthetic organic vectors coupled with TE1PA were synthesized. The ^{64}Cu-radiolabeling and purification of the corresponding radiopharmaceuticals were fully optimized through fast and simple procedure. *In vitro* studies are under progress to evaluate the effect of this grafting strategy on CXCR4 targeting.



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Silver(I) halido NHC complexes: structural studies and comparative antibacterial activity

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Silver and its compounds have a long and remarkable history of application as antibacterial agents, since they inhibit bacterial growth at low concentration with only small toxic effects in human cells. Currently, silver nitrate and silver sulphadiazine are widely used for desinfection of wounds[1]. The exact mechanism of antibacterial activity of silver is not defined, however, it is strongly related to the rate of silver ions released and covalent inhibition of polynucleotides RNA, DNA and bacterial enzymes such as thioredoxin reductase (TrxR) [2].

Since the concentration and the rate of silver ion release are crucial for antibacterial activity, a proper scaffold should be applied. In this regard, N-heterocyclic carbenes (NHC) are a suitable choice due to significant stabilization of metal ion and ease of lipophilicity adjustment.

Over the last 20 years, a variety of silver NHC complexes has been tested against Gram-negative and Gram-positive bacteria[2]. Among them, silver halide NHCs prevail as stable and easy to prepare. One of the features of silver halide NHC complexes is the ability to exist in two forms: neutral monocarbene with halide coordinated to silver ion and ionic biscarbene with a dihalidoargentate anion. Depending on the NHC scaffold and polarity of media, the equilibrium between two forms may be shifted, which can lead to significant changes of the biological activity. Although studies of the equilibrium were recently performed[3], almost no attention was paid to coexistence of two different forms in biological studies. Moreover, the influence of different halide atom on this equilibrium and biological activity of complexes is almost unknown.

Herein, a thorough structural and antibacterial study of 16 Ag(I) NHC complexes is reported. Using NMR spectroscopy and conductometry performed for 1 mM solutions in DMSO, an equilibrium between neutral and ionic structures with predominance of the monocarbene form was revealed. Using broth microdilution assay performed on *E.coli*, MIC values of the compounds were calculated (figure 1b). According to the results of the assay, iodido complexes have better antibacterial activity (MIC = 10.97-21.24 μM) than chloride and bromide compounds (MIC = 21.85-116.38 μM).

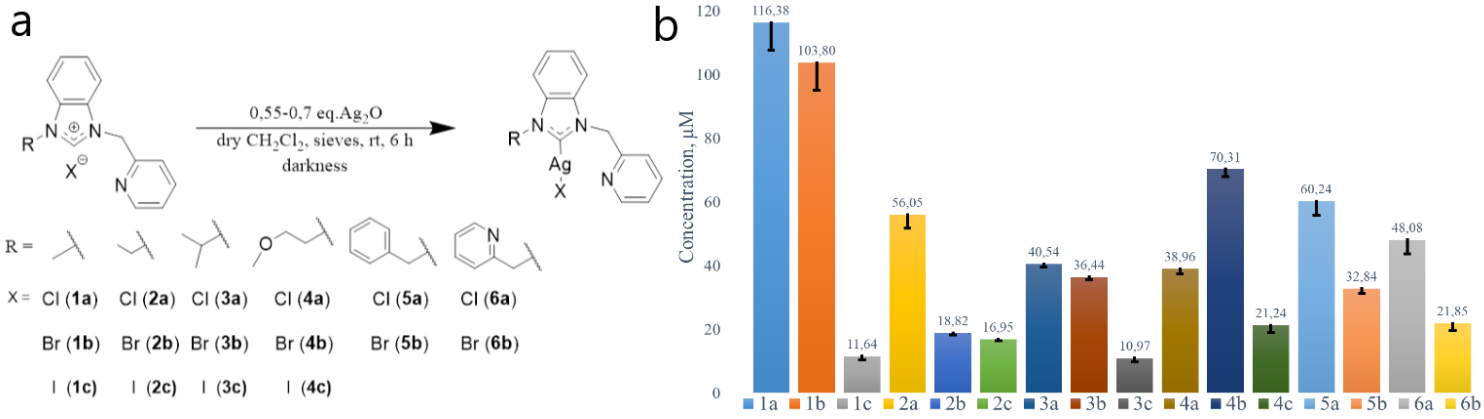

Figure 1. a) Synthetic procedure of Ag(I) NHC complexes; b) MIC values of silver complexes for *E.coli*

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BODIPY-Ruthenium(II) Bis-Terpyridine Dyads for Bioimaging and Dual Type-I, Type-II Photodynamic Therapy

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Photoactive ruthenium complexes have gained considerable interests as new generation photosensitizers for phototherapeutic applications in recent years. However, these photosensitizers are commonly based on ruthenium-polypyridyl scaffolds that possess a perceived limitation of inadequate absorption in the visible region and short triplet state lifetime. A plausible solution to address this limitation is to attach a light-harvesting organic chromophore to Ru(II)–polypyridyl scaffolds to construct a dyad. A series of multichromophoric ruthenium(II) complexes of formulation [Ru(tpy-BODIPY)(tpy-R)]Cl_2 (**1**−**4**), containing BODIPY (boron-dipyrromethene) linked to Ru(II)-$(tpy)_2$ were designed, prepared, characterized and their utility as photodetection agent and photosensitizes for PDT (photodynamic therapy) was investigated. Complex **1** as its PF_6 salt (**1a**) was structurally characterized by a single-crystal X-ray diffraction study. It has a distorted-octahedral RuN_6 core with a Ru(II)-bis-terpyridine unit that is covalently linked to one photoactive BODIPY unit. The bichromophoric molecules feature enriched photophysical properties like strong visible light absorption ($10^{-4} \times \varepsilon \approx 3.7-7.8\ M^{-1}\ cm^{-1}$) and high singlet oxygen quantum yield (Φ_Δ = 0.57 to 0.75 in DMSO) that are highly desirable for an excellent photosensitizer. Luminescence-based studies using Singlet Oxygen Sensor Green (SOSG) revealed singlet oxygen generation by complex **4** in an aqueous buffer and under in vitro conditions on photoirradiation. DNA (pUC19) photocleavage and in vitro DCFDA assays using ROS scavengers/stabilizers revealed generation of singlet oxygen and superoxide anion radical by respective type-II and type-I photosensitization process. Cancer targeting biotin-appended complex **4** showed high photocytotoxicity with a remarkable phototherapeutic index (PI) of >1400 in HeLa cancer cells with a low light dose activation (400−700 nm, 2.2 J cm^{-2}). The complexes displayed reduced activity in noncancerous HPL1D cells. The luminescence of the complexes was utilized in bioimaging, thus making them suitable as next-generation theranostic PDT agents. The findings presented here offers a new direction in the emerging chemistry of metal-based phototherapeutic agent.

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Novel Re (I) tricarbonyl complexes of thiazolhidrazinylidene-chroman-2,4-diones

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Rhenium complexes, mostly explored for their anti-tumor properties, were recently shown to possess promising antibacterial properties. A new strategy for designing metal complexes entails using ligands that already have biological activities. In medicinal chemistry, several derivatives of the coumarin core have already shown a wide spectrum of physiological and pharmacological activities. Based on that, a previous study in our group evaluated a series of arylcoumarin of *fac*-[Re(I)$(CO)_3$] complexes for their antimicrobial activities.[1] Some of these species showed remarkable antimicrobial activity against methicillin-resistant *S. aureus* (MRSA) with MIC values *in vivo* as low as 350 ng/mL (Fig 1, left). This encouraged us to explore the synthesis of new complexes of coumarin. In particular, derivatives of thiazolhidrazinylidene-chroman-2,4-diones and their corresponding bidentate and monodentate *fac*-[Re(I)$(CO)_3$] complexes were prepared (Fig 1, right).

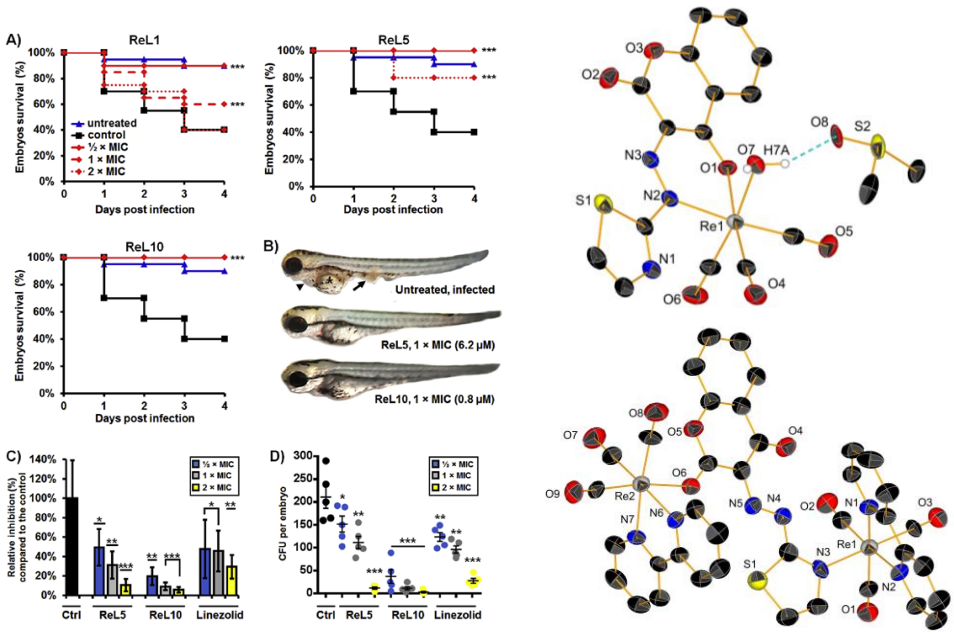

Fig.1 Left. Effect of arylcoumarin *fac-[Re(I)$(CO)_3$] complexes in efficiently rescuing zebrafish embryos of the lethal MRSA-infection. Right. New bidentate and monodentate fac-[Re(I)$(CO)_3$] thiazolhidrazinylidene-chroman-2,4-dione species prepared in this study.*

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Novel Pt(IV) complexes conjugated with biologically active molecules as anticancer prodrugs

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According to WHO, cancer is still one of the major responsible for death worldwide. Despite the efforts to find new therapies with higher efficiency and selectivity and fewer side effects, traditional anticancer drugs are still the first choice in the clinical treatment of this disease. In this frame, DNA-damaging drugs, such as Cisplatin and its derivatives (namely Carboplatin and Oxaliplatin) are still widely used in clinical protocols. However, these drugs possess several drawbacks, ranging from their low bioavailability, the insurgence of acquired resistance and oto- and nephrotoxicity which dramatically lower the patients' quality of life. To tackle these problems, one possible approach is based on the use of Pt(IV) prodrug complexes. Indeed, Pt(IV) complexes are kinetically more inert than their Pt(II) counterparts, and thus less prone towards off-target reactivity.[1] These complexes act as prodrugs that can be activated inside the cancer cells through reduction, thus releasing the Pt(II) drug and the two axial ligands.[2] The Pt(II) species are responsible for the cytotoxicity but the introduction of bioactive axial ligands might further improve the pharmacological properties of these molecules.[3] In this context, mitochondria-targeting agents are particularly attractive candidates to fill this position.

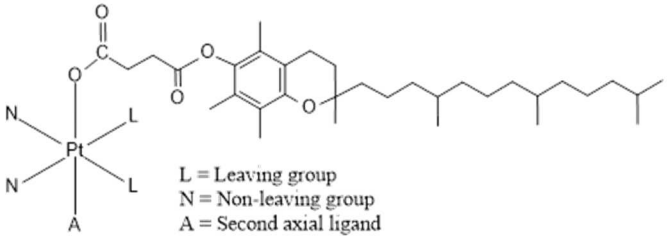

Figure 1. General structure of a Pt(IV) complex functionalized with α-TOS in the axial position.

Indeed, we selected the α-tocopherol succinate (α-TOS), an analogue of Vitamin E, which was proved to be cytotoxic in many different cancer cell lines by targeting the aforementioned organelles.[4] Its mechanism of action involves the inhibition of some anti-apoptotic proteins, which ultimately results in the trigger of mitochondria-mediated apoptosis.[4] In this frame, we propose new Pt(IV) complexes bearing α-TOS as axial ligand able both to damage the DNA (thanks to the Pt-containing moiety) and to disrupt the mitochondrial function (thanks to α-TOS).

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Magnetogenic Fe(II)-based molecular probes for Magnetic Resonance Imaging

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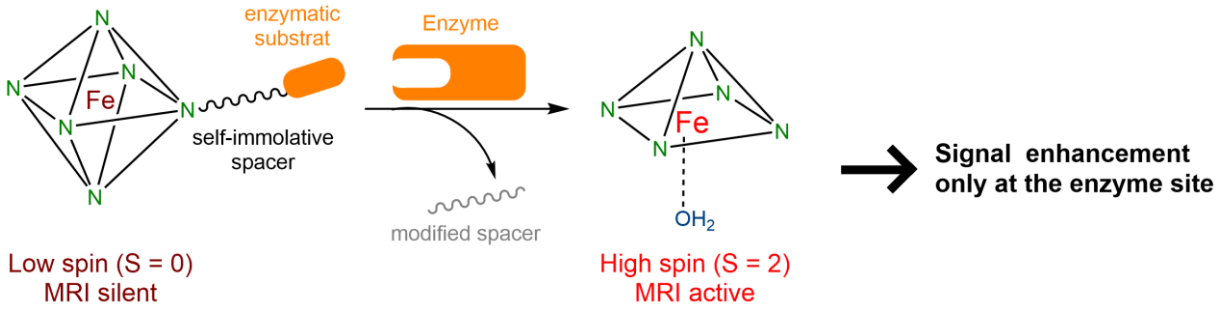
Magnetic Resonance Imaging (MRI) relies on the translation of changes in relaxation time of water's hydrogen nuclei into grey-scale variations on the final image. It is nowadays widely used for diagnosis, especially because it does not require harmful ionizing radiation and is not hampered by any limits of penetration into deep tissue. However, MRI suffers from intrinsically low sensitivity. To enhance it, paramagnetic molecules are used as contrast agents: they interact with water molecules and influence the relaxation time. In order to identify biomarkers, it is possible to use magnetogenic molecular probes, which react specifically with a target, thus modifying the local contrast on MRI. To overcome the sensitivity limit, we chose to aim at enzymes because their catalytic activity can be exploited for signal amplification. To this end, our team works on Fe(II) based probes that change their spin state[1] when they are converted by an enzyme. As a proof of concept, DPTACN based Fe(II) complexes responding to nitroreductase activity (Off/ON) showed promising results.[2-4] However, the spin-state change occurred only at acidic pH. With the aim of finding a system operating at physiological pH (7.3), structural variations of the ligand are explored. This communication will present some of the recent developments of our team, including the modulation of electronic effects, change of the coordinating moieties or even the replacement by a macrocyclic ligand with a molecular cage.[5]



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Metallohelix vectors for efficient gene delivery via cationic DNA nanoparticles

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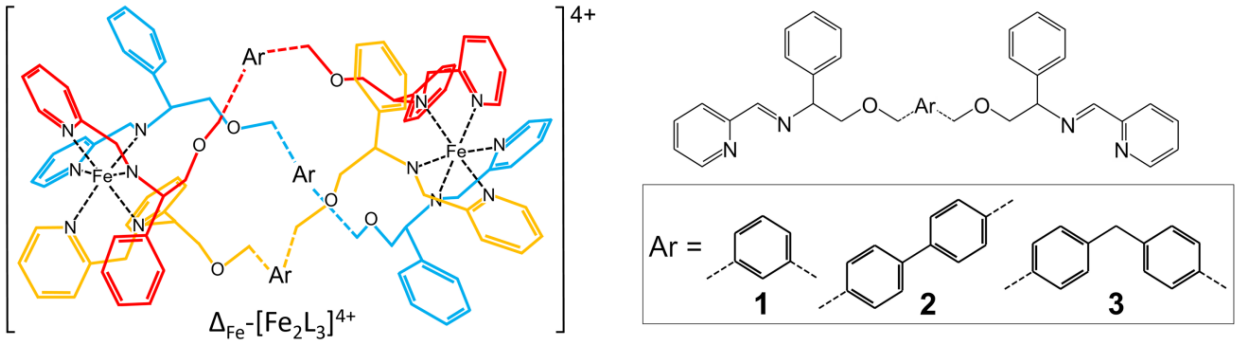
The design of efficient and safe gene delivery vehicles remains a major challenge for the application of gene therapy. Of the many reported gene delivery systems, metal complexes with high affinity for nucleic acids are emerging as an attractive option. As potential DNA condensing agents, metal complexes offer several advantages. They exhibit a high positive charge density required for the neutralization of the negatively charged DNA backbone, which is essential for DNA condensation to occur. Ligands in coordination complexes can be functionalized for specific targeting, cellular uptake or accumulation. Recent studies showed that some Fe metallohelices exhibited a high affinity to DNA and were able to condense DNA molecules more efficiently than conventional condensing agents such as polymines.[1] That encouraged us to investigate the potency of three selected pairs of Fe(II) metallohelices Δ_{Fe}- and Λ_{Fe}- $[Fe_2L_3]^{4+}$ as nonviral DNA delivery vectors.



We have discovered that certain metallohelices – optically pure, self-assembling tripple-stranded arrays of fully encapsulated Fe act as nonviral DNA delivery vectors capable of mediating efficient gene transfection.[2] They induce formation of globular DNA particles which protect the DNA from degradation by various restriction endonucleases, are of suitable size and electrostatic potential for efficient membrane transport and are successfully processed by cells. The activity is highly structure-dependent – compact nad shorter metallohelix enantiomers are far less efficient than less compact and longer enantiomers.

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Dipyridophenazine iridium(III) complex as a phototoxic cancer stem cell selective, mitochondria targeting agent

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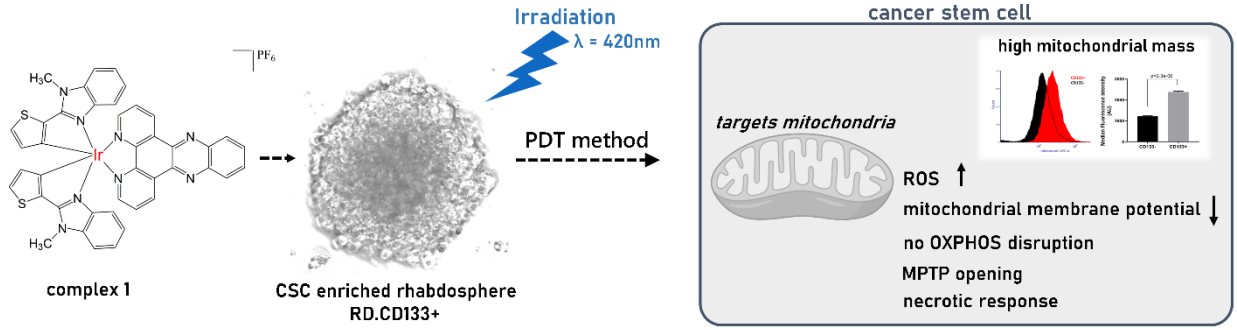
Transition metal complexes are suitable candidates for antitumor photoactivatable therapy. This type of chemotherapy offers an exciting approach to effectively treat cancer with enhanced effectivity and minimization of side effects. Photosensitizers excited by light exert their therapeutic effect by producing cytotoxic radicals which interact with biomolecules.
In this work, the mechanism underlying the anticancer activity of a newly synthesized[1] photoactivatable Ir(III) compound of the type $[Ir(C^N)_2(dppz)][PF_6]$ where C^N = 1-methyl-2-(2'-thienyl)benzimidazole (complex **1**) was investigated.



Complex **1** photoactivated by visible light (λ = 420 nm) shows potent activity against highly aggressive and poorly treatable Rhabdomyosarcoma (RD) cells, the most frequent soft tissue sarcomas of children. This remarkable activity of **1** was observed not only in RD cells cultured in 2D monolayers but, more importantly, also in 3D spheroids, which resemble in many aspects solid tumors and serve as a promising model to mimic the *in vivo* situation. Importantly, photoactivated **1** kills not only differentiated RD cells but also even more effectively mitochondria-rich cancer stem cells (CSCs) of RD. One of the factors responsible for the activity of irradiated **1** in RD CSCs is its ability to produce ROS in these cells more effectively than in differentiated RD cells. Moreover, photoactivated **1** caused in RD differentiated cells and CSCs a significant decrease of mitochondrial membrane potential and promotes opening mitochondrial permeability transition pores in these cells, a mechanism that has never been demonstrated for any other metal-based anticancer complex. The results of this work give evidence that **1** has a potential for further evaluation using *in vivo* models as a promising chemotherapeutic agent for photodynamic therapy of hardly treatable human Rhabdomyosarcoma, particularly for its activity in both stem and differentiated cancer cells.

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ANTICANCER FLAVIN-BASED METAL COMPLEXES AND THEIR REACTIVITY TOWARDS BIOMOLECULES

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Over the past decades, the need of dealing with the side effects associated with Pt(II) chemotherapy agents has attracted considerable attention on the use of Pt(IV) derivatives that display high hydrolytic stability.[1] Moreover, the interest in this class of compounds has triggered the development of numerous prodrug activation approaches.[2]

In this context, our group reported a new strategy for the biorthogonal photoactivation of Pt(IV) prodrugs in which flavins and flavoproteins acted as photoredox catalysts for the reduction of Pt(IV) precursors into clinically-approved Pt(II) anticancer drugs upon irradiation with visible light and in the presence of different electron donors.[2-5] In these catalytic reactions, the metal complex unconventionally acts as the substrate and the flavin plays the role of the catalyst, showing biorthogonal selectivity, that is they could take place in biological environments upon application of low light doses.

In this contribution, I will describe the design and synthesis of new flavin-based metal complexes as new redox active prodrugs for photochemotherapy. I will discuss the behavior of these new agents in the presence of different bioreductants, under physiologically relevant conditions, and finally report on their antiproliferative properties *in vitro*.

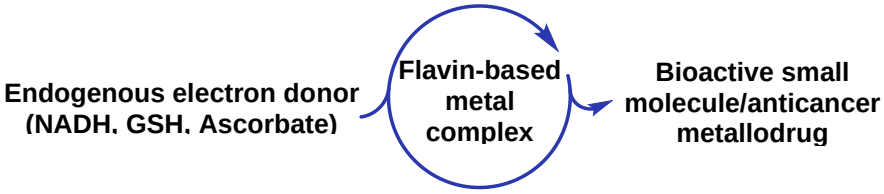

Figure 1. Bioorthogonal photoactivation of flavin-based metal complexes.

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Shining a Light on Bacteria : Lanthanide-based Glycoconjugate Molecular Sensors for Lectins

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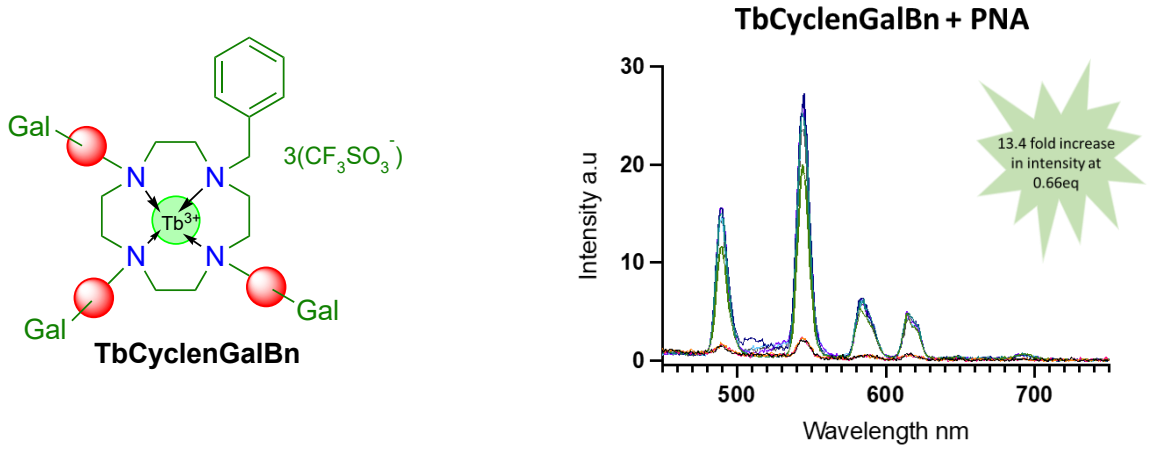
Lanthanide probes offer several advantages for sensing applications, including their characteristic and time-resolved emission spectra, which can be easily distinguished from background fluorescence of biological samples.[1] Many pathogenic bacteria such as *Pseudomonas aeruginosa* and *Escherichia coli* produce carbohydrate-binding proteins (lectins), which present viable targets for detection of these organisms, as well as for new therapies. Diagnostic methods for bacterial infections typically take several days, relying on cell culture, leading to delays in targeted treatment. New rapid detection methods would aid in the fight against antimicrobial resistance. The aim of this project is to use the selective nature of carbohydrate-lectin interactions to develop new visually responsive glycoconjugate probes, which would be suitable for diagnosis of infections, such as by *P. aeruginosa*, a bacterium classified as a Priority 1 pathogen by the WHO, with urgent need for new antibiotic treatments and diagnostics due to the ongoing problem of antimicrobial resistance.[2] LecA and LecB are lectins on the surface of *P. aeruginosa* with high affinity for galactoside and fucoside glycans respectively.[3] Many approaches have been developed to inhibit the binding of these lectins to human tissue cells by the development of inhibitory glycoconjugates with varying degrees of success.[4a-e] We report several multivalent glycoconjugate lanthanide complexes, based on different scaffolds and presentation modes, which demonstrate enhanced emission in the presence of relevant lectins. Integration of these probes into “smart” materials has potential for application in the medical devices industry. This strategy could be expanded to other bacteria in the future.

Figure 1. Structure of a lanthanide glycoconjugate on a cyclen scaffold and its sensing activity of PNA, a galactose-specific lectin.



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Glucoconjugates of halido Au(I) NHC complexes: synthesis, reactivity, and anticancer properties

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Gold(I) NHC complexes (NHC= N-heterocyclic carbene) are promising anticancer metallodrug candidates.[1] Over the last decades, several research groups investigated the chemical and biological properties of Au(I) NHC complexes. This class of metal complexes preferentially binds to proteins, in particular the mitochondrial enzyme thioredoxin reductase (TrxR), that is considered the most likely target.[2] TrxR inhibition ability was found to be dependent on the nature of the ancillary ligand (L) in linear [Au(NHC)L] complexes.[3]

The conjugation of metal complexes to biomolecules is a strategy adopted to improve the pharmacological properties of the resulting metallodrugs. Carbohydrate-containing complexes display enhanced biocompatibility, water solubility and selectivity, due to the increased uptake of sugars in cancer cells, with respect to healthy ones (Warburg Effect).[4] Recently, we successfully applied glycoconjugation to organometallic platinum complexes with NHC ligands.[5] In this work the concept was extended to gold(I) NHC complexes, by designing and studying new neutral halido complexes (**Au1-Au3** in Fig. 1). The carbene ligand is decorated with a glucoside fragment via a triazole linker. Chlorido, bromido and iodido derivatives were synthesized and characterized, to evaluate the impact of the ancillary ligand, by studying the in-solution stability, the reactivity with model proteins and the biological activity of the complexes.

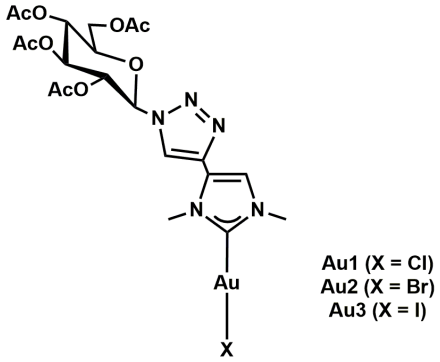

Fig. 1. Au(I) NHC halido complexes studied in this work

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Metallodrug screening against SARS-CoV-2 target proteins: Inhibitors of Spike/ACE2 interaction and papain-like protease

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The global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to an unprecedent global crisis health and is requiring major efforts for development of antiviral therapeutics and vaccines. The antiviral effects of metal-based drugs have occasionally been reported, nevertheless, this area of application has not been studied as intensively compared to the development of metallodrugs against cancer among others[1].

The development of effective antiviral therapies against COVID-19 requires an understanding of the viral replication cycle. We have been analysing the potential ability of different metallodrugs to inhibit two different pathways of the viral cycle: 1) the entry of the coronavirus into the host cell (interaction of ACE2 with the spike protein), 2) the viral replication (e.g. the activity of the papain-like protease PL^{pro}). For this purpose, we conducted a preliminary study with different gold complexes where promising results were obtained. The complexes displayed very promising activity against SARS-CoV-2 PL^{pro} activity and moderately inhibited the spike / ACE2 interaction. In view of these promising results, we decided to extend this study to other metals. We screened over 100 structurally diverse compounds, including: Au, Ru, Fe, Rh, Pt, Ag, Pd, Ti, Re, Mn, Hg complexes and 11 polyoxometalates (POMs). The metallodrug profiling afforded strong inhibitors of the S/ACE2 interaction and in particular of the PL^{pro} enzymatic activity. Several complexes were selected for antiviral assays in SARS-CoV-2 infected cells and the most promising results were obtained with three gold compounds, one silver-NHC, one POM and titanocene dichloride, which showed antiviral activity starting at low micromolar concentrations or strongly blocked viral replication at a high dosage. Taken together, the results of this preliminary study provide the basis for the design of antiviral metallodrugs against SARS-CoV-2 in future studies.

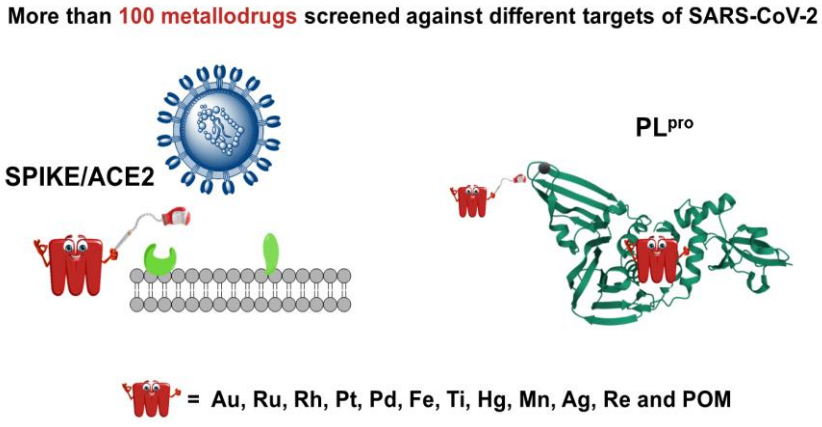

Figure 1: Biological targets evaluated against different metallodrugs

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Site-Specific Modification of DNA with Heavy Metal Ions

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Using solid-phase DNA synthesis it is possible to design oligonucleotides with chosen nucleobase sequences that contain artificial nucleosides. By introducing metal ions to a complementary pair of these oligonucleotides, metal-mediated base pairs can be formed. Even though most published metal-mediated base pairs are integrated in antiparallel-stranded B-DNA, examples of other DNA topologies can be found in literature as well.[1] Applications of such metal-modified DNA include for example the expansion of the genetic code, the generation of metal nanoclusters and the utilization as sensors for metal ions.[2]

So far, a large number of published artificial nucleobases is structurally related to canonical bases with nitrogen donor atoms for metal-binding.[3] Their alignment into the base stack and coordination of metal ions, especially Ag^{I} and Hg^{II}, has proven to be feasible. The terminal incorporation of a ligand into an oligonucleotide duplex could facilitate coordination environments other than square-planar, in principle allowing the use of more flexible ligands.

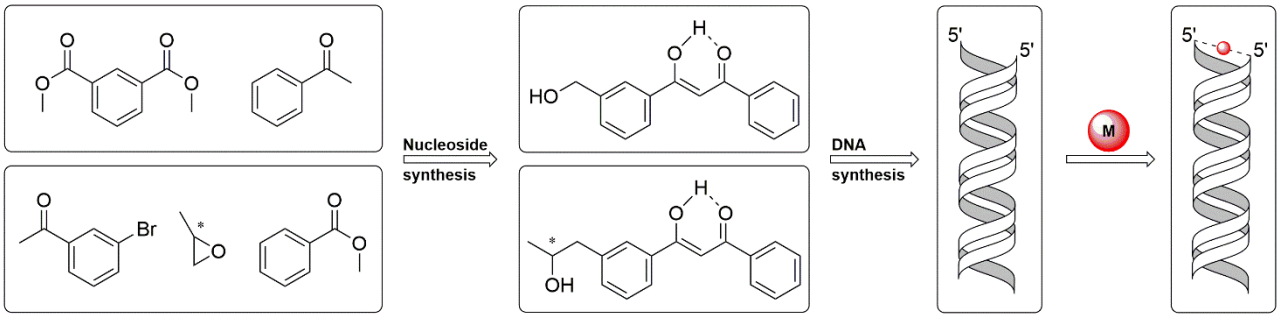

Figure 1. Schematic representation of the synthesis of β-diketonate-based nucleobase surrogates and their introduction into parallel-stranded DNA to form terminal metal-mediated base pairs.

To study the metal-binding properties and effects of an artificial nucleobase that significantly differs from the canonical bases on double-stranded DNA, we developed β-diketonate-based ligands. Here we present the results of our studies towards the site-specific incorporation of various metal ions into modified DNA comprising such ligands.

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New gold(I)-NHC-1-thio-beta-D-glucose tetraacetate complexes for a targeted anticancer strategy

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In recent decades, the repurposing of Auranofin (AF) as an anticancer agent has triggered growing interest in gold-based complexes as promising candidates in the search for new anti-cancer therapeutic strategies.[1] Gold complexes can activate apoptosis response in cancer cells, mainly through inhibiting mitochondrial thioredoxin reductase (TrxR), a flavoenzyme involved in maintaining cellular redox homeostasis and often overexpressed in several cancer cell lines. Indeed, TrxR's key role in apoptotic evasion and deregulation of mitochondrial metabolism makes it an attractive druggable target for new anticancer metallodrugs.[2] The mitochondrial-mediated apoptosis induction presents several advantages, including the potential overcoming of resistance that can occur after treatment with conventional platinum-based drugs. Regarding gold-based complexes, N-heterocyclic carbenes (NHCs) ligands offer many advantages: their nature of strong sigma donors provides increased stability to the metal complexes in physiological-like conditions.[3] Also, their convenient synthetic flexibility allows a straightforward modification of substituents on the carbenic core, to obtain diversified panels. In cancer cells, the increased aerobic glycolysis, explained by the Warburg effect, requires a higher glucose uptake and consequent overexpression of glucose transporters (GLUT) to sustain the rapid cell proliferation and elevate energy usage. A well-established targeting strategy is the conjugation of the metal complex to biomimetic glucose substrates, such as the thiosugar moiety in AF, to increase the metal-complex uptake in tumor cells by exploiting GLUT-mediated transport.[4] The preferential entry of the complex into tumor cells can potentially lead to increased selectivity and cytotoxicity, with reduced side effects. With this idea in mind, we synthesized and characterized four new gold-based N-heterocyclic carbene complexes (Figure 1), two of which were functionalized with 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranose. Moreover, the four gold (I) complexes share some other functional elements, such as the anthracenyl residue as a fluorescent label, and eventually a linker for subsequent conjugation to other carrier molecules. UV-Vis, fluorescence, and ESI-MS experiments were performed to evaluate the interaction of the four gold complexes with macromolecules such as DNA, RNA, human serum albumin (HSA) and a synthetic dodecapeptide mimetic for the TrxR active site. Preliminary tests on A2780 cell lines showed cytotoxic activity for all four Au(I)-complexes, especially for the sugar-conjugated ones, that show IC_{50} values falling in the low micromolar range. Further biological tests on cellular uptake and cellular localization by confocal microscopy are currently in progress.

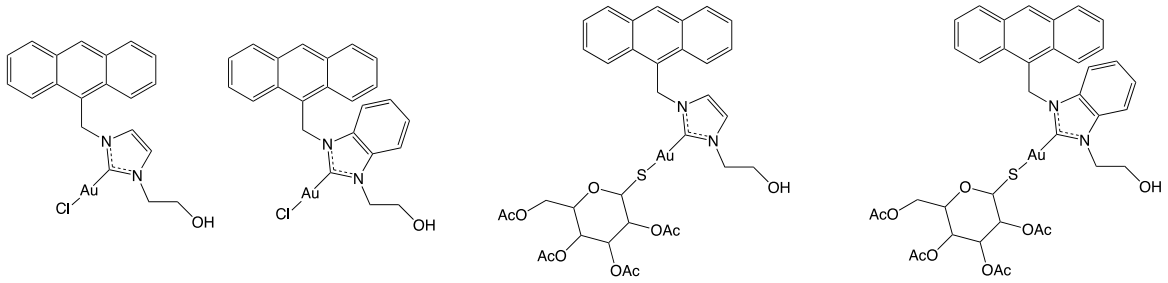

Figure 1: Structure of the four new gold-based NHC complexes

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Fine-tuning the Photochemistry of Sulfur-based Linkages with Ru(II) Polypyridyl Photocages for Optimal PACT Application

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In recent years photoactivated chemotherapy (PACT) has shown tremendous potential in alleviating the side effects of traditional cancer chemotherapy.[1] Due to their tunable and intense light absorption in the visible region and exciting favorable photochemistry, Ru(II) polypyridyl complexes are extensively explored as PACT agents. It has been shown that sulfur-based monodentate ligands are photoreleased from Ru-photocages effectively with highest quantum yields.[2] However, the nature of sulfur linkages *i.e.* Ru(II)-sulfoxides or Ru(II)-thioether based systems more effective for PACT remain unexplored.

To delve into the core of the intricate Ru(II)-S bond photophysics, we synthesized two Ru(II) polypyridyls having Ru-S bonds: $[Ru(ttp)(phen)(DAS)](PF_6)_2$ (**RuDAS**) and $[Ru(ttp)(phen)(DMSO)](PF_6)_2$(**RuDMSO**) [ttp=*p*-tolyl-terpyridine, phen=1,10-phenanthroline, **DAS**=diallyl sulfide, DMSO =dimethyl sulfoxide]. DAS is a highly potent bioactive ligand and shows multitude of therapeutic effects.[3] Solution state identity of the complexes were thoroughly examined by ^{1}H-NMR, ESI-MS and structurally characterized by X-ray crystallography. Here we used DMSO for sulfoxide linkage, while DAS an anticancer phytochemical from garlic to make thioether-based systems with Ru(II). The photosolvolysis studies with white LED in CH_3CN indicate a much faster release of the DAS ligand from the Ru(II) core than the release of DMSO. The photolysis was monitored by UV-vis, ^{1}H-NMR studies. The exact speciations of the photoproducts were studied using ESI-MS and X-ray crystallography. Both the complexes were converted to their nitrate salts, which imparted significant water-solubility and allowed us to study the photoreactivity in water. Upon photorelease of the monodentate ligands, the complexes could bind to 5'-GMP, a truncated version of DNA.

In conclusion, although both the S-linked Ru(II) compounds show comparable dark stability, however, markedly faster photorelease of DAS confirms thioether-based Ru(II)-polypyridyls portray better options for photocaging of prodrugs and photochemotherapy applications.

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Rhenium (I) complexes with enantiopure pinene-bipyridine ligands

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Rhenium coordination chemistry allows the development of various supramolecular architectures based on tricarbonyl complexes, whose biomedical applications as anticancer and antibiotic drugs are currently being investigated with high interest. Dicarbonyl rhenium complexes, still relatively rare in the literature, already demonstrated promising bioactivity on their side.[1]

The rhenium dicarbonyl coordination compounds offer larger coordination options compared to the tricarbonyl ones because of their additional "uncarbonylated" site. The possibility of attaching two pinene-bipyridine ligands to a dicarbonyl rhenium core has been recently demonstrated in our lab.[2] This opens new options towards rhenium multinuclear chain structures, combining dicarbonyl central units with tricarbonyl chain ends.

The use of chiral ligands like pinene-polypyridine derivatives which are able to predetermine the chirality at the metal centers is an important step. In fact, numerous studies demonstrated that chirality is a key point in many biological processes, particularly in the molecular recognition phenomena, playing an essential role in the development of new drugs.[3]

Here we will present a series of rhenium complexes containing pinene bipyridine type ligands (Figure 1), their characterization and *in vitro* biological effects.

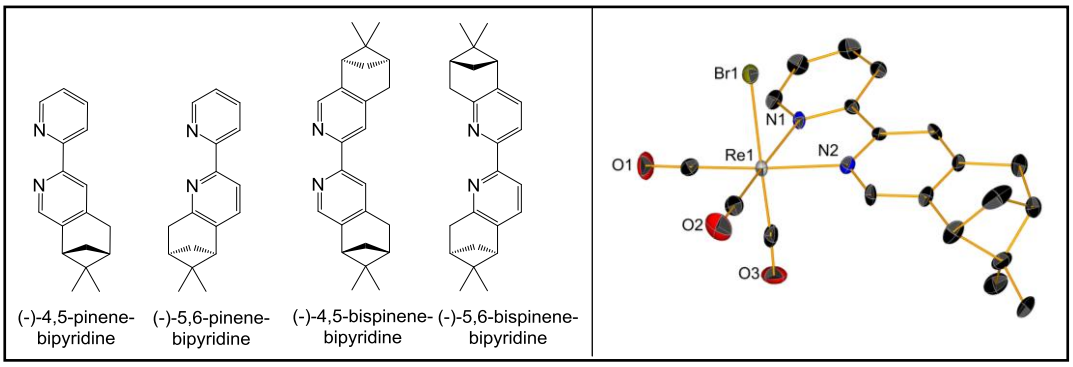

Figure 1. Chiral pinene-bipyridine ligands and an example of rhenium (I) tricarbonyl complexe [$ReBr(CO)_3$(4,5-pinenebipyridine)].

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New strategies in the development of hydrogels for contact lenses that are able to reduce microbial infection risk

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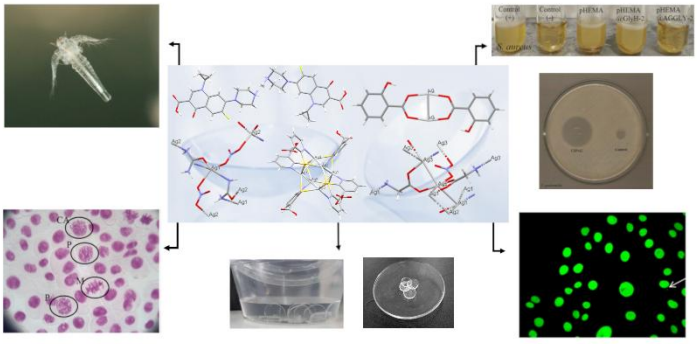
The use of soft contact lenses is a popular method for correcting eye refractive errors [1]. Their poor handling and hygiene practices are the key reasons for their frequent contamination, which can lead to microbial keratitis (MK). The manufacturing of next generation soft contact lenses involves the use of novel active biomaterials which control microbial colonisation and thus the incidence of MK. Silver(I) ions, on the other hand, exhibit a broad spectrum of antimicrobial activity against both Gram-positive and Gram negative bacteria. Therefore, the development of contact lenses combined with silver based antimicrobial agents is a research, technological and financial issue. For this purpose, three strategies have been developed from our group. One involves the use of silver nanoparticles using extracts from natural products as combined reducing and capping agents. The second one involves the use of small molecules which act as antimicrobial agents as well, while the third one, small molecules which are ingredients of natural products.

In the course of our studies on the development of new antimicrobial agents and their non-infectious contact lens the novel biomaterials were synthesized by the dispersion in polymeric poly(2-hydroxyethyl methacrylate) (pHEMA) of AgNPs(natural products) or small bioactive silver(I) complexes. The biomaterials were characterized by XRD, XRF, TG-DTA, DTG/DSC and FT-IR-ATR analytical techniques. The prepared materials were evaluated for their antibacterial activity against the Gram-negative species *P. aeruginosa* and Gram positive ones *S. epidermidis* and *S. aureus* which are abundant in microbial keratitis. The *in vitro* and *in vivo* toxicity of the biomaterials was tested against human corneal epithelial (HCEC) cells, by the micronucleus assay, *Artemia salina* and *Allium cepa* models.



Acknowledgements: This research has been co-financed by the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation, under the call RESEARCH – CREATE – INNOVATE (project code:T1EDK-02990)».

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Exploring the structure-activity relationship of Rhenium(I)-tricarbonyl complexes of 1H-imidazo[4,5-f][1,10]phenanthroline derivatized ligand

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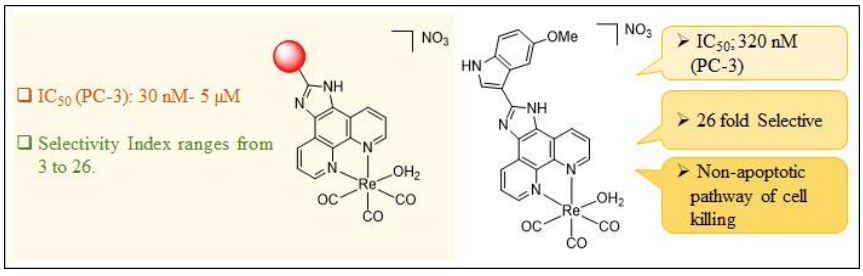
Cancer is one of the leading causes of death worldwide. Recurrence of cancer and growing resistance to chemotherapeutic drugs are the key hurdle to the complete eradication of the disease. Overexpression of cellular thiols and cellular exporter or detoxifying proteins (ATP-binding cassette (ABC) transporters, multidrug resistance proteins (MRPs), etc.) and DNA damage repair pathways are the primary reasons for the resistance.[1] Platinum-based drugs *viz.*, cisplatin, oxaliplatin, carboplatin, are used worldwide to treat different forms of cancer. Regrettably, all these platinum drugs can be detoxified by cellular thiols proteins.[2] Hence, an ongoing search is in progress to find some better alternatives. Ongoing research work on anticancer metal-based alternatives includes mainly ruthenium, iridium, osmium, rhenium, vanadium, and heavily on platinum due to its clinical success.[3] At our ends, we prepared a series of rhenium (I)-carbonyl complexes by altering the 1H-imidazo[4,5-f][1,10]phenanthroline ligand counterpart (Figure) and performed a structure-activity relationship. Low nanomolar to micromolar cytotoxicity against human prostate cancer (PC-3) cells was unveiled for our compounds. Interestingly, all of our compounds showed some degree of selectivity against cancer cells (selectivity index (SI), 3-26) over normal cells. The most selective complex (Figure) exhibited a non-apoptotic cell killing pathway.



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Targeted Alpha Therapy with Actinium-225 Labelled Antibodies

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The emerging potential of radionuclide therapy with alpha (α^+) emitting actinium-225 has stimulated significant interest in developing chemistry to enable the selective delivery of actinium to tumours. Ac-225 ($t_{1/2}$ 9.9 days) decays to the long-lived isotope Bi-209 ($t_{1/2}$ 1.9 x 10^{19} y) *via* the release of a total of four α-particles, and two beta (β^-) particles. The high particle energy and linear energy transfer of α-emission delivers high doses of radioactivity, capable of causing double stranded breaks in DNA, across relatively short distances (40-90 μm). Therefore, there is significant interest in developing bifunctional chelators that form stable complexes with Ac^{3+} which are easily conjugated to antibodies for targeted alpha therapy of cancer. Carbonic anhydrase IX (CAIX) is a metalloenzyme which is overexpressed on the surface on clear cell Renal Cell Carcinoma.[1] The monoclonal antibody Girentuximab selectively binds CAIX with high affinity (Figure 1a) and has the potential to selectively deliver therapeutic radiation to tumours.

A crown ether macrocyclic ligand functionalised with two picolinic acid arms, H_2macropa (Figure 1b) forms stable complexes with actinium (III), the largest trivalent cation in the periodic table.[2,3] In this work a new bifunctional variant with a pendant diethyl squarate ester, H_2macropa-tzPEG$_3$Sq, that allows the conjugation of the macrocycle to antibodies will be presented (Figure 1c). The conjugation of H_2macropa-tzPEG$_3$Sq to Girentuximab (and other cancer targeting antibodies) and radiolabelling with Ac-225 will be discussed. An evaluation of the therapeutic efficacy of [^{225}Ac]Ac-macropa-tzPEG$_3$-Girentixumab in a mouse model of renal cancer will also be presented.

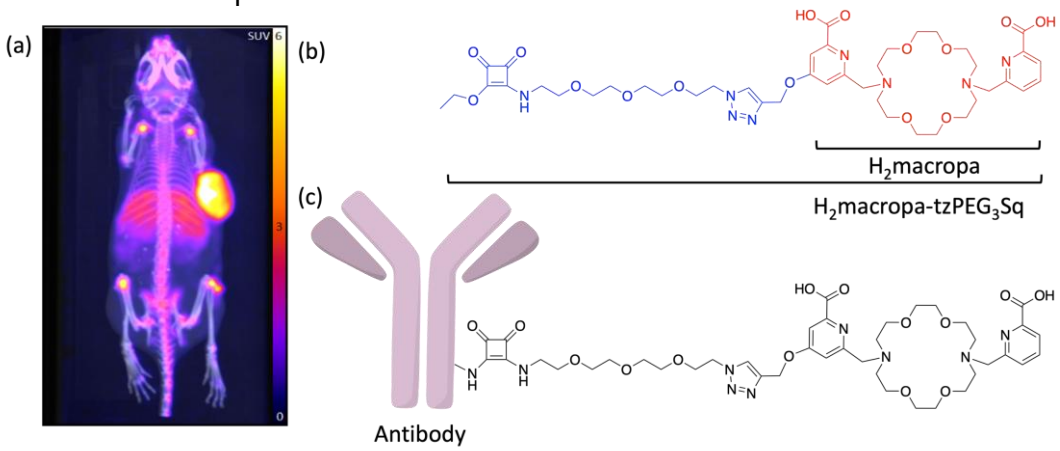

Figure 1. (a) Positron Emission Tomography image of [^{89}Zr]Zr-DFOsq-Girentuximab mice showing CAIX overexpression in a renal tumour model; (b) chemical structure of H_2macropa and H_2macropa-tzPEG$_3$Sq; (c) H_2macropa-tzPEG$_3$Sq conjugated to a monoclonal antibody.

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Redox Active Cobalt(III) Complexes for Photo-induced Delivery of BODIPY, Cellular Imaging and Photodynamic Therapy

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Photodynamic therapy (PDT) is advantageous in cancer treatment as the localized activation of a photosensitizer generates reactive oxygen species (ROS) to damage the diseased cells leaving the photo-unexposed healthy cells unaffected. High lipophilicity and poor bio-distribution of some organic photosensitizers often lower bioavailability and limit their therapeutic applications. A cobalt-based drug delivery system (DDS) was designed to selectively deliver the BODIPY (boron-dipyrromethene) as a photosensitizer upon photoactivation or in the presence of a chemical reducing agent.[1] Cobalt(III) complexes of acetylacetonate-linked BODIPY ligands (**L^1**, acac-BODIPY; **L^2**, acac-diiodo-BODIPY) namely [Co(TPA)(L^1)](ClO$_4$)$_2$ (**1**), [Co(4-COOH-TPA)(L^1)](ClO$_4$)$_2$ (**2**), [Co(TPA)(L^2)]Cl$_2$ (**3**) and [Co(4-COOH-TPA)(L^2)]Cl$_2$ (**4**) were synthesized, characterized and their efficacy as bioimaging and phototherapeutic agents were evaluated (TPA, tris-(2-pyridylmethyl)amine; 4-COOH-TPA, 2-((bis-(2-pyridylmethyl)amino)methyl)isonicotinic acid). **HL^1**, **HL^2**, and complex **1** were structurally characterized by X-ray crystallography. The Co(III)–Co(II) redox responses in these complexes are observed near −0.2 V vs. SCE in DMF-0.1 M TBAP. Complexes **1** and **2** on photoactivation or in the presence of excess reducing agents (glutathione, ascorbic acid, and 3-mercaptopropionic acid) released the acac-BODIPY ligand. The complexes have strong absorbance near 501 nm ($10^{-4} \times \varepsilon \sim 5.2-5.8$ M^{-1} cm^{-1}) and emission bands near 513 nm ($\Phi_F \sim 0.13$, $\lambda_{ex} = 490$ nm) in DMSO. Complexes **3** and **4** have absorption maximum at ~ 530 nm ($10^{-4} \times \varepsilon \sim 1.2-1.8$ M^{-1} cm^{-1}) and have high singlet oxygen generation ability ($\Phi_\Delta \sim 0.79$). Mechanistic pUC19 DNA photocleavage by complex **4** revealed the formation of both singlet oxygen and superoxide anion radicals as ROS. Complex **1** showed selective accumulation in the endoplasmic reticulum (ER) in A-549 cells in confocal fluorescence microscopy. Complex **4** with a diiodo ligand has a high phototherapeutic index (PI >7,000) in HeLa cells ($IC_{50} \sim 0.007$ μM in 400−700 nm visible light, total dose ~5 J cm^{-2}). The ancillary TPA ligand derivatives play important roles on the Co(III)−Co(II) redox potential, the complex solubility, ligand release kinetics, phototherapeutic efficacy, and providing a structure-activity relationship.

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Mn(II) complex of salinomycin – new potential theranostic agent

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Theranostic is a modern field of medicine which combines methods for therapy with the methods for diagnosis[1]. Unlike conventional contrast agents, which provide only imaging of tissues and organs, a theranostic agent allows therapy and visualization of the affected organs at the same time. Salinomycin is a polyether ionophorous antibiotic, isolated from *Streptomyces albus* species. It was found that this antibiotic exerts severe cytotoxicity on cancer stem cells and multidrug-resistant human cancer cell lines[2]. Herein we present characterization of Mn(II) complex of salinomycin by elemental analysis, IR and EPR spectroscopies and demonstrate its potential as a theranostic agent. The spectral studies as well as elemental analysis data confirmed that the coordination compound is of a composition $[Mn(C_{42}H_{69}O_{11})_2(H_2O)_2]$. The metal centre is placed in an octahedral environment. Two salinomycinate monoanions are coordinated to Mn(II) via a deprotonated carboxyl group and a secondary hydroxyl group, located at the opposite ends of the ligand molecule. The axial positions of the octahedron are occupied by two water molecules as their participation in intramolecular hydrogen bonds stabilizes the pseudo-cyclization of salinomycin. The complex shows relaxivity comparable to the relaxivity of Magnevist (clinically approved contrast agent). Furthermore, Mn(II) disalinomycinate exerts cytotoxicity in submicromolar concentrations in the human tumor cell lines A549 (IC_{50}: 0.19 ± 0.11 μM), SW480 (IC_{50}: 0.52 ± 0.22 μM) and CH1 (IC_{50}: 0.17 ± 0.05 μM). These results demonstrate the potential application of the complex as a theranostic agent.

Acknowledgements. The authors acknowledged the financial support from the National Science Fund of Bulgaria (grant: KP-06-Austria-6/6.08.2019) and the Austrian Federal Ministry of Education, Science and Research (BMBWF) (Project No: BG 07/2019).

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Cisplatin−cyclooxygenase inhibitor conjugates, free and immobilised in mesoporous silica SBA-15, prove highly potent against different breast cancer cell lines

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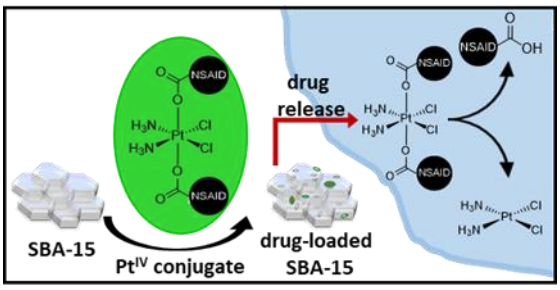
For the development of anticancer drugs with higher activity and reduced toxicity, two approaches were combined: preparation of platinum(IV) complexes exhibiting higher stability compared to their platinum(II) counterparts[1] and loading them into mesoporous silica SBA-15 with the aim to utilise the passive enhanced permeability and retention (EPR) effect of nanoparticles for accumulation in tumour tissues.[2] Three conjugates based on a cisplatin scaffold bearing the anti-inflammatory drugs naproxen, ibuprofen or flurbiprofen in the axial positions (**1**, **2** and **3**, respectively) were synthesised and loaded into SBA-15 to afford the mesoporous silica nanoparticles (MSNs) SBA-15|**1**, SBA-15|**2** and SBA-15|**3**.



Superior antiproliferative activity of both free and immobilised conjugates in a panel of four breast cancer cell lines (MDA-MB-468, HCC1937, MCF-7 and BT-474) with markedly increased cytotoxicity with respect to cisplatin was demonstrated. All compounds exhibit highest activity at submicromolar concentrations against the triple negative cell line MDA-MB-468, with conjugate **1** being the most potent. The most remarkable enhancement of up to 240-fold lower IC_{50} values than cisplatin was, however, observed against the cell lines MCF-7 and BT-474. Mechanistic investigations employing different flow cytometry assays show that all compounds induce apoptotic cell death elevating the levels of both early and late apoptotic cells. Furthermore, autophagy as well as formation of reactive oxygen species (ROS) and nitric oxide (NO) were elevated to a similar or greater extent than with cisplatin.

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Targeting RNA G-quadruplex to combat SARS-CoV-2

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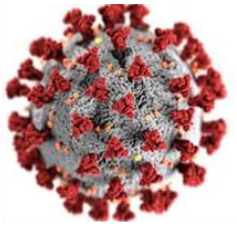
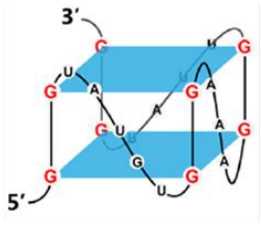
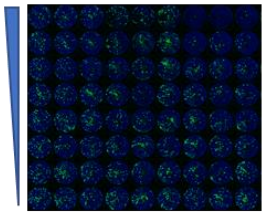
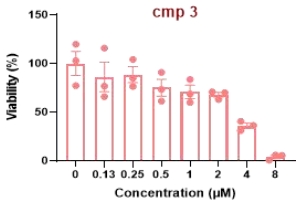
The ongoing pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a serious threat to human health globally with nearly half billion laboratory-confirmed cases, including over 6 million global deaths by the end of March 2022[1]. Understanding the underlying mechanisms of infection and developing novel therapeutic strategies are urgently needed for the prevention and treatment of this disease. G-quadruplexes (G4s) are important noncanonical secondary structures formed within guanine-rich strands of regulatory genomic regions. Viral G4s are normally located in regulatory regions of the genome and implicated in the control of key viral processes[2]. Thus, targeting G-quadruplex sequences in the virus genome by G-quadruplex ligands could be a new approach to conquer virus infection[3].

It has been reported that there are conserved G-quadruplex sequences among SARS-CoV and SARS-CoV-2[4]. In our recent work, we evidence that these sequences could form stable RNA G4 structure *in vitro* and in live cells by various biochemical characterizations, including CD, ^{1}H NMR and fluorescence imaging. We are solving the solution structure of RNA G4 from SARS-CoV-2 and screened for ligands that can stabilize G4. Further test on the antiviral activities showed that these ligands can inhibit the growth of virus with IC_{50} values of these ligands ranging from 2 to 7 μM. This study provides a promising anti-SARS-CoV-2 strategy through targeting G-quadruplexes.









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Gold-based Aza-BODIPY Theranostic

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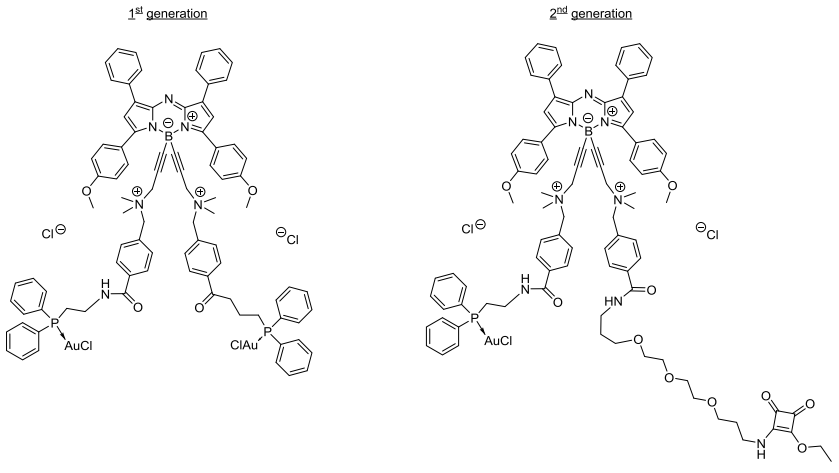
Since the discovery of cisplatin, metal-based compounds have drawn the attention of numerous researchers looking for new and better anticancer drug. However, very often, these complexes induce numerous side-effect, and their mechanism of action is badly understood.

One solution to know how to improve these innovative complexes and to prevent side effects is to understand their mechanism of action. To do so, a convenient strategy is to track the compound trough the organism thanks to an imaging technique: those types of molecules that display both a therapeutic moiety and an imaging probe can be called theranostic. For the probe part of our molecule, our choice turned to the optical imaging that is a versatile, sensitive and non-invasive technique. The main drawback of this technique is its low penetrability of biological tissues that often limits the following of the theranostic agent to *in vitro* studies. However, in a first study[1], we showed that the use of near-infrared emitting fluorophores such as aza-BODIPYs allows such monitoring *in vivo* by optical imaging. As for the therapeutic moiety, our attention has turned toward gold(I)-based complexes. Indeed, we previously observed that gold(I) metal ions does not quench fluorescence – unlike most of the other metal ions (e.g. platinum, copper, ruthenium…). Moreover, gold(I)-complexes display very interesting therapeutic properties[2]. In a first study[1], the synthesis of a first generation of gold-based aza-BODIPY probes has been reported. Three new complexes had been synthesized and the evaluation of different criteria of those probes as their IC_{50} and allowed us to determine the best design for those probes out of those three. This work proved that it was possible to design theranostic trackable *in vivo* and which display good anti-proliferative property *in vitro* and significant anticancer effect *in vivo*. The main drawback of this generation of theranostic is their limited accumulation in the tumor, due to the absence of vectorization. Thus, we decided to conceive a second generation of gold-based theranostic, that can be bioconjugated to a vector.



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Characterization and interaction with biomolecules of Cu^{II} and $V^{IV}O$ complexes of new 8-hydroxyquinoline Schiff bases

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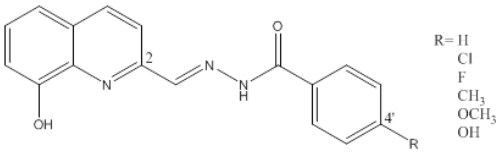
8-Hydroxyquinoline is a recognized chelator with several applications in the pharmaceutical field and its metal complexes have been studied as potential anticancer[1] and anti-infectious[2] agents. Substitution at the 2-position of this molecule with groups having coordinating elements expands the chelating ability providing interesting chemistry and opens additional possibilities for the development of new metallodrugs. Our aim is to explore such conjugation with benzohydrazides having different substituents at the 4'-position – **Scheme 1**. The compounds were synthesized and characterized by the conventional techniques. The dissociation constants (pK_a values) were determined by UV-Vis spectrophotometry in a 30% (v/v) DMSO/H_2O medium, as well as their lipophilicity. Complexation of these new compounds was achieved with Cu^{II} and $V^{IV}O$ centres, yielding a variety of coordination spheres and geometries. Absorption and emission spectroscopic techniques were used to evaluate the interaction of selected compounds with relevant biomolecules, namely albumin, DNA and glutathione. The compounds were tested for their cytotoxic activity in lung (A-549), melanoma (A-375) and breast (MDA-MB-231) human cancer cell lines. The copper complexes displayed activity in the low micro molar range.



Scheme 1 – The studied 8-hydroxyquinoline-2-carbaldehyde benzohydrazones

Overall, this work shows the structural diversity of the obtained hydrazone ligands, their complexes presenting ability to interact with the tested biomolecules and significant cytotoxicity against the tested human cancer cell lines.

Acknowledgments: Portuguese-Hungarian Scientific & Technological Cooperation 2018-2.1.15-TÉT-PT-2018-00002 and COST Action CA18202: NECTAR. *Fundação para a Ciência e Tecnologia* (projects UIDB/00100/2020, UIDP/00100/2020 and LA/P/0056/2020 and grant SFRH/BD/135797/2018).

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Aminocarboxylate functionalised silica nanoparticles for antibiotic delivery in Gram-negative bacteria

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Antimicrobial resistance is the cause of an estimated five million deaths worldwide annually, and along with its economic cost and the lack of new antibiotics in the pipeline is an increasing threat for society. [1] The well-known impermeability of Gram-negative bacterial species is a major barrier for successful treatment with known compounds.[2] Lack of new drugs in the pipeline and the rapid acquisition of resistance against new antibacterial agents, nanotechnology offers a potential solution using current antibiotics. Inclusion of therapeutic compounds in functionalised silica nanoparticles has been reported as alternative strategy to overcome membrane impermeability, due to their chemical stability, biocompatibility and tuneability regarding nanoparticle size, surface chemistry and porosity. [3] Destabilization of outer membrane structure, achieving higher permeabilization for antibiotic molecules and drug delivery system has been previously explored by surface functionalisation with proteins or polymers. However, addition of complex moieties onto nanoparticle's surface may also lead to higher toxicity and lower colloidal stability.

Herein, we present the design of a novel hybrid silica nanoparticles with therapeutic and tracking properties thanks to the simultaneous inclusion of vancomycin, unable to surpass Gram-negative bacteria outer membrane, and the red-luminescent photostable $Ru(phen)_3Cl_2$ (phen = 1,10-phenantroline) complex as targeting probe, allowing simultaneous nanoparticle tracking while vancomycin is being released. Ru(II) complexes have been previously included in silica nanoparticles for tissue[4] and flow[5] imaging. Moreover, to overcome the outer membrane of Gram-negative bacterial cells, we covalently modified the silica nanoparticles surface with aminocarboxylate moieties (Figure 1) to examine the effect of surface modification in nanoparticle cell uptake. Aminocarboxylate property for metal binding influences the structural destabilization of the bacterial outer membrane.

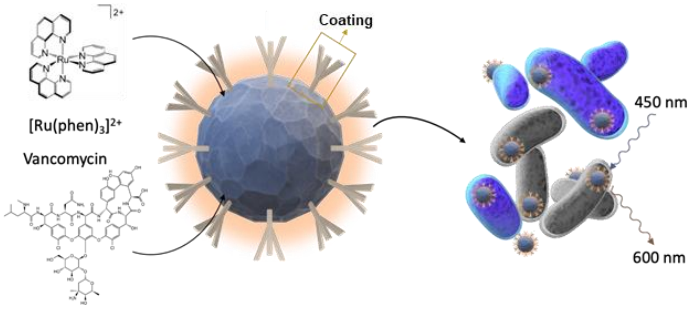

Figure 1. Hybrid- surface coated luminescence silica nanoparticles for vancomycin delivery

In this presentation, the studies of vancomycin release and nanoparticle uptake will be presented. Optical spectroscopic techniques have been used to monitor the release of the drug and the uptake in cells. Confocal fluorescence imaging of live bacterial cells incubated with designed nanoparticles reveals uptake in Gram negative bacteria (*E. coli*). Absence of coating, however, leads to no cell uptake in *E. coli*, highlighting the importance of surface coating for the nanoparticles to overcome outer membrane and release included cargos. Determination of MIC values for *S. aureus* and *E. coli* reveals high efficiency of coated hybrid nanoparticles compared with control samples. The presence Ru(II) complex allows tracking of the particles in cells.

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Red Luminescent Gold Nanoparticles for Imaging and Sensitive Detection in Cancer Cells

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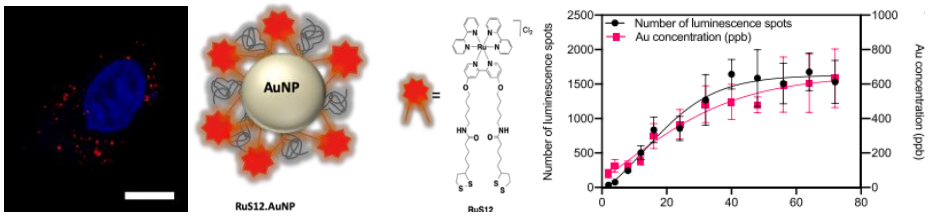
Gold nanoparticles (AuNP) are ideal scaffolds for developing imaging agents due to their water solubility, characteristic surface plasmon resonance band, low toxicity and high electron density. These properties make them well suited for multimodal imaging applications. They possess a large surface area and can be readily functionalized with luminescent organic and organometallic probes.[1] Ruthenium polypyridyl complexes are popular luminescent probes for imaging due to their strong light absorption in the visible region, displaying red to near infra-red emission. Moreover, ruthenium compounds have promising anticancer properties, prompting investigation into their use as novel chemotherapeutics.[2] We are interested in combining the attractive properties of nanoparticles and ruthenium for new imaging probes with potential in diagnosis and therapy.

In our approach we have demonstrated that high loading of gold nanoparticles is achieved with metal probes.[3] Their unique luminescent properties are translated in the nanoscale for imaging cancer cells by confocal luminescence and electron microscopies.[3] Furthermore, we have investigated the effect of the distance of the metal centre from thr surface of gold. The RuS12 (Scheme 1) has shown the highest luminescence lifetime enhancement on AuNP 13, 50 and 100 nm with a 70% increase of lifetime compared to smaller chains.[4] In this presentation, the detection properties of the RuS12AuNP will be presented in imaging and quantification of nanoparticles in A459 lung adenocarcinoma epithelial cancer cells.For the first time we show that confocal luminescence image analysis based on ruthenium luminescence signal can be correlated with ICP-MS data for quantification of gold.[5] Due to gold's high electron density we were also able to monitor the uptake of the RuS12 into the cancer cells by transmission electron microscopy, and propose the three most likely cellular uptake mechanisms of our system.[5] The development of the ruthenium gold nanoparticles to theranostic properties towards specific targetting of DNA, will also be presented. This approach offers the potential for the development of a powerful tool for both imaging and therapy within cancer research.



Scheme 1-Luminescence and quantification of a ruthenium complex in gold nanoparticles (RuS12.AuNP).

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Investigations on an unexpected side reaction during the synthesis of a cytotoxic diaminedicarboxylatoplatinum(II) complex

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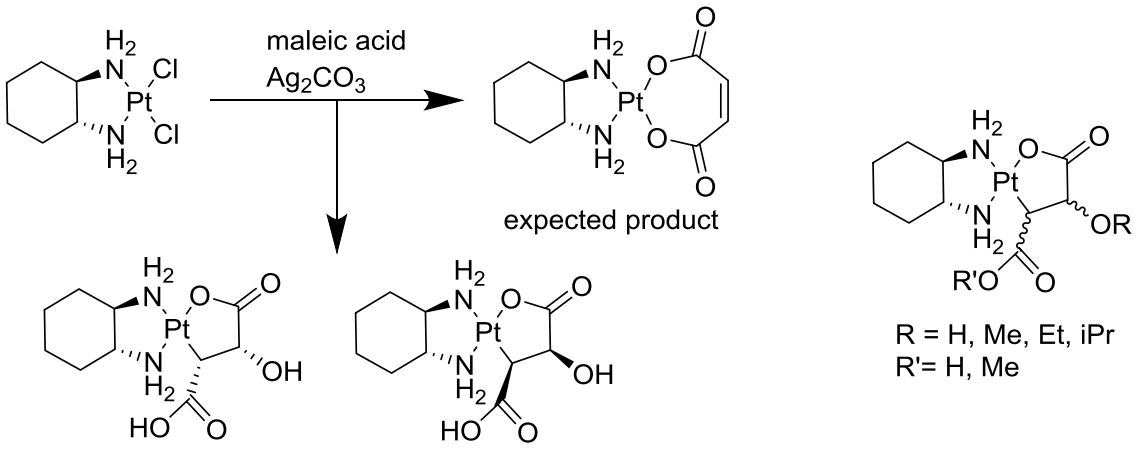
During the synthesis of a Pt(II) complex according to standard literature methods[1], we observed the formation of an unexpected by-product (Scheme 1) featuring a metal carbon bond.



Scheme 1: The planned reaction pathway, the unexpected side reaction and the general structure of the new complexes

To the best of our knowledge, there is only one report dealing with this substance class in the literature.[2] Starting from either maleic or fumaric acid, the inventor was able to produce either a mixture of the RR and SS or of the SR and RS carboxylato ligand.

Based on these findings, we report on the synthesis of new complexes, where R equals different alkyl moieties and R' equals H or Me, respectively. Additionally, the complexes were characterized *via* multinuclear NMR spectroscopy, elemental analysis and HR-MS. Crystallographic analyses, stability assessments *via* NMR and HPLC, and determination of cytotoxic properties are still ongoing as of now.

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Copper Pyrithione Complexes as Potent Bioactive Agents

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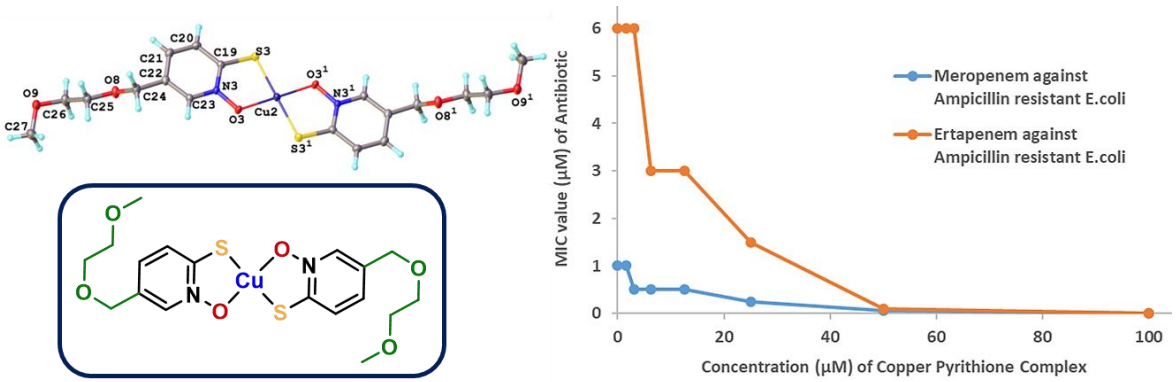
Regulation of enzymatic activities play a crucial role in survival of cellular systems. For example, bacterial resistance often arises due to enzymatic breakdown of antibiotics.[1] New Delhi metallo-β-lactamase (NDM-1) is a recently found class of such enzymes[2] and inhibition of this enzyme has been shown to overcome the bacterial resistance to carbapenem class of antibiotics.

Another class of enzymes, the deubiquitinases (DUBs), have been shown to be overexpressed in certain cancerous tumours. Inhibition of DUBs can potentially render protection against carcinoma. Copper(II) pyrithione ($CuPy_2$) has been studied as a potent inhibitor of both NDM-1[3] and DUBs[4]. However, the complex possesses high hydrophobicity and thus is unsuitable to use in the cytosolic system.



In this work, a series of substituted copper pyrithione complexes is presented that overcomes the limitations of the parent complex. Various substitution patterns allow a balance between solubility and lipophilicity, while maintaining biological activity. Antibacterial testing against the *ESKAPE* pathogens and antibiotic resistant *E. coli* has proved the new complexes to have efficient antibacterial activity against gram positive bacteria (*S. aureus*) and a synergy effect on the existing antibiotics (Figure). Furthermore, these complexes possess anticancer activity against pancreas and bone cancer cells with some selectivity over normal human cells. Within the series of complexes, we have established some initial structure to activity relationships.

We will present the synthesis, structural characterisation and physical properties of these copper based complexes. Enzymatic inhibition and biological activity will also be presented for the family of 20 complexes.

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Radicals coordinated to lanthanides for monitoring the redox status

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Lanthanide(III) complexes are widely used for bio- and clinical imaging due to their unique luminescent or magnetic (depending on the metal) properties. Although their use as a probe is widespread, there is one area in which they are struggling to emerge, redox imaging. This is explained by the natural tendency of these elements to adopt the (+III) oxidation state and hence to behave as redox-innocent centers. [1] Redox imaging is however a domain of primel importance since the oxidative stress is believed to contribute to the proliferation of diseases such as cardiovascular diseases, cancers or neurodegenerative diseases. We recently designed redox-sensitive ligands for overcoming the strong limitation imposed by the redox-innocence of most of the lanthanides. We demonstrated that a change in the redox state of the ligand can influence both the lanthanide-based luminescence and the relaxation times (coordinated water molecules) for magnetic resonance imaging (MRI).[2] We also prepared lanthanide-based spin traps for detecting reactive oxygen species by using EPR and luminescence. [3] We will summarize our recent results in the field in this communication (Fig. 1).

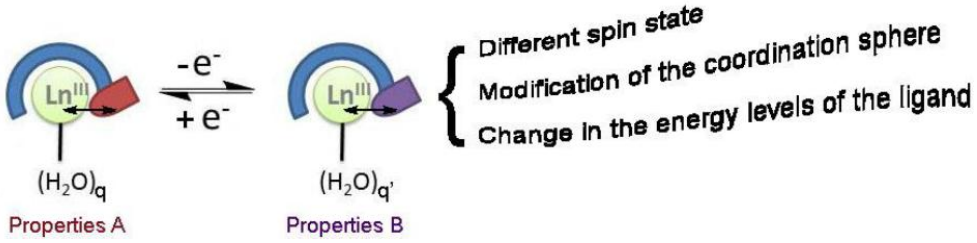

Fig. 1 General strategy for redox mapping with lanthanide complexes.

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Dual Action Cu(II) Histone Deacetylase Inhibitors

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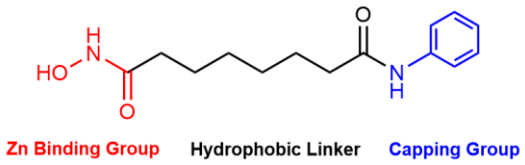
The reversible acylation of histone proteins is a vital regulator of gene expression which may act by modifying the accessibility of transcription factors to DNA through conformational changes in the nucleosome.[1] The reversible acylation is mediated by two enzymes, histone acetyl transferase (HAT) and histone deacetylase (HDAC), which catalyse the respective transfer and removal of an acetyl group to the histone protein.[2]

The inhibition of HDAC enzymes has garnered considerable attention, with four HDAC inhibitors in clinical use, owing to the 11 known HDAC isoforms that contain Zn(II) in the active site.[3] The key principles for HDAC inhibitor design are illustrated in Figure 1, whereby the inhibitor molecule constitutes three key features: a zinc binding group, hydrophobic spacer and a head group.



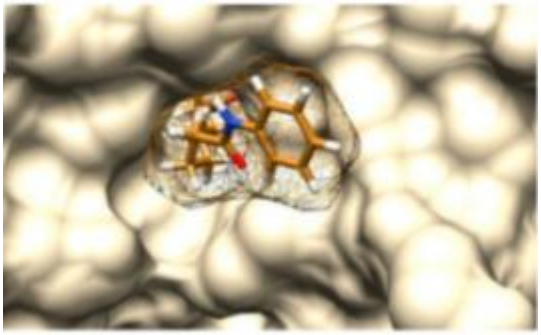


Figure 1: HDAC inhibitor structural motif and mode of HDAC enzyme inhibition, illustrated using the clinically approved suberoylanilide hydroxamic acid drug (SAHA).[4]

The scope for future HDAC inhibitor design lies in the promise of a dual action compound that can target both HDAC and HAT enzymes. A previous study has displayed Cu(II) mediated inhibition of HAT, leaving huge opportunity to explore a series of dual action inhibitors that incorporate the classical HDAC inhibitor framework and a source of Cu(II).[5] Herein, we report the synthesis and characterisation of a series of novel Cu(II) HDAC inhibitors, where the HDAC inhibition potency and selectivity between the HDAC isoforms will be analysed. Finally, we will report their anticancer activities and compare the Cu(II) complexes against their organic analogues.

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Bis-histidine phenanthroline based ligands highlight the significance of Cu(I) in the mechanism of Aβ-bound Cu ROS production in Alzheimer's disease context

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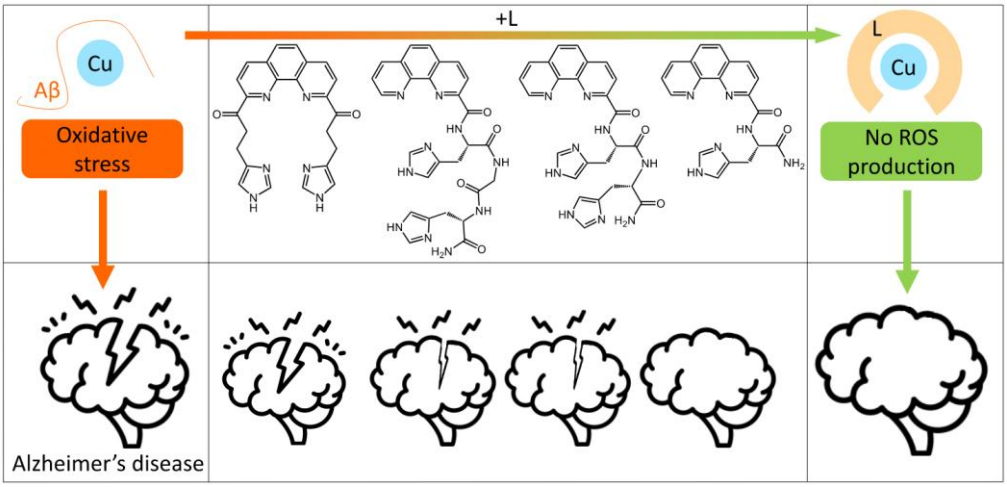
Alzheimer's disease is a neurodegenerative disease, which affects more than 40 million people worldwide. One of the principal physiological hallmarks of this dementia is the extraneuronal deposition of β-amyloid peptide (Aβ) aggregates, known as senile plaques[1]. These senile plaques are enriched in metal ions, particularly Zn and Cu ions, the latter being able to redox cycle in presence of dioxygen and ascorbate, consequently producing reactive oxygen species (ROS) and inducing oxidative stress. To avoid this phenomenon, a new class of potential drug candidates, targeting copper and its redox cycling, has been developed: these are ligands, able to extract copper ions from Aβ and to keep it stable in a single oxidation state[2]. In this study, we report different properties of a set of ligands composed of a phenanthroline with two histidines or histamines moieties, compared to a reference ligand with only one histidine[3]. The latter had previously been studied, showing unexpected results (the decrease of Cu(Aβ) ROS being lessened in excess of ligand) because of a mechanism of formation of a $Cu(I)L_2$ complex at Cu:L stoichiometry higher than 1:1[4]. First, the complexes formed by these ligands in presence of Cu(II) were analyzed using UV-visible and EPR spectroscopies. The ligands were then tested for their ability to stop ROS production, in absence and in presence of Zn and Aβ. Finally, the mechanism of action of the ligands was explored by cyclic voltammetry.



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Metals for Biological and Medical Diagnostics: Dual-mode Near-infrared Optical and Photoacoustic Imaging Agent based on Low Energy Absorbing Ytterbium Complex

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Medical and Biological Diagnostics are in great needs of non-invasive imaging approaches with responses in real-time using small footprints instruments. Photoacoustic (PA) and near-infrared (NIR) luminescence are novel imaging techniques that can uniquely address these requirements. They take advantage of the NIR light operating in the biological transparency window as an excitation source. The creation of dual-mode imaging agents would allow to combine the advantages of the two techniques: high sensitivity and high resolution of the NIR luminescence imaging with high signal detection depth of the PA imaging.

Lanthanide complexes formed with NIR-absorbing chromophores are promising candidates for the creation of the dual-mode agents. Lanthanide ions possess unique luminescence properties which makes them excellent candidates for the luminescence imaging. However, they have small values of molar excitation coefficients, so organic chromophores have to be used for the sensitization of the luminescent lanthanide ions. At the same time, organic chromophores can create the photoacoustic signal by dissipating the part of the excitation energy of the non-radiative processes. The presence of both the NIR-emitting lanthanide ion and the organic chromophore in the lanthanide complex allows using the same molecule for the creation of the bimodal imaging agents.

In this work, we present a new dual-mode photoacoustic and NIR luminescence imaging agent as polystyrene nanoparticles loaded with NIR-emitting lanthanide complexes containing NIR-absorbing chromophores. Evaluations of the performances of these new PA and NIR imaging agents for non-invasive detection in in biological systems were evaluated with the help of a phantom.

Stimuli responsive release of immunogenic cell death inducers: Exploiting disulfide based synthetic platforms for Pt^{IV} prodrugs

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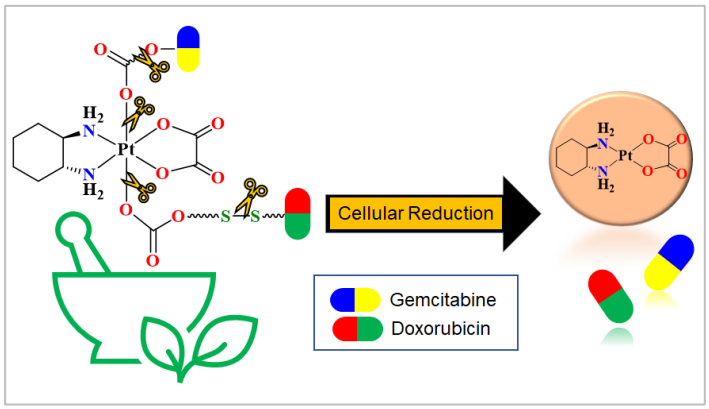
Pt^{II} complexes (cisplatin, carboplatin, oxaliplatin) are cornerstone anticancer agents in clinical use.[1] Over time, several Pt based complexes have been evaluated as potential antitumor agents, however, relatively few have progressed to clinical trials.[2] Albeit current cancer treatment strategies have significantly improved patients survival rate, serious side effects and acquired ressistance of Pt based chemotherapy remain a significant barriers to human health.[3] Immunotherapy offers an effective and promising treatment option that has helped to overcome these limitations in recent past. A cell death pathway called immunogenic cell death (ICD) involves stimulation of patient's immune response and offers promise by exploiting immunomodulation to fight against tumor relapse and cancer metastasis.[4] Although Pt chemotherapy has been traditionally viewed as immunosuppressive, oxaliplatin is reported to induce ICD.[5]

In the past two decades '*multi-action*' Pt^{IV} prodrugs have been developed that following cellular activation simultaneous release several bioactive agents along with the cytotoxic Pt^{II} moiety. In an attempt to combine cytotoxic agents with ICD inducers we conjugated the first reported ICD inducer, doxorubicin, to oxaliplatin forming a dual-action prodrug. We were able to do so by conjugating two drugs by self immolative linkers (carbamate, carbonate and S-S linkers). Moreover, we have added another FDA approved drug (gemcitabine) to form a triple-action prodrug. We prepared the compounds, checked their stability, studied their reduction kinetics with DTT (that reduces the S-S bond but not the Pt^{IV}) and with ascorbate that only reduces Pt^{IV}, and verified the nature of the reduction products. The chemistry and the biological properties of these compounds will be discussed.



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Mechanistic studies of the arene-ruthenium(II) complexes with carbathioamido pyrazoles as alternative for antibiotics

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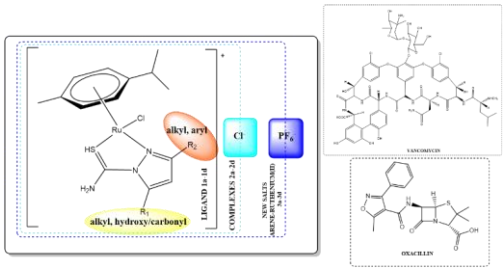
One of the most prevalt threats to patients is posed by antibiotic resistance. Almost all clinical strains are becoming resistant to one or more classes of antibiotics due to overuse of antibiotics. The resulting selection pressure favors the persistence and spread of resistant bacteria, including *S. pneumoniae* strains resistant to penicillin and third generation cephalosporins, *S. aureus* resistant to methicillin, and enterococci resistant to high concentrations of aminoglycosides, vancomycin and linezolid [1–4]. There is, therefore, a pressing need for a multidirectional response to counter this threat, including an intensive search for new drugs and development of more effective therapeutic strategies [5]. In response to the demand for alternatives of already widely used antibiotics, an attempt has been made to search for new compounds with antimicrobial activity. These role can be fulfill complexes arene-ruthenium(II) due to very promising results in microbial area.



Scheme 1. Selected structures of antibiotics and arene-ruthenium(II) complexes with carbathioamidopyrazoles (**2a**–**2d**) [17] and (**3a**–**3d**).

The aim of the present study was evaluate into the antibacterial properties of arene-ruthenium(II) complexes with carbathioamidopyrazoles containing various groups in C-3 and C-5 position pyrazole ring and their hexafluorophosphate salts. The activity against a wide range of microorganisms, expressed as MIC/MBC/MFC, was determined using broth microdilution. To understand the mechanism of action of the most promising compounds, their ability to induce bacterial cell death was evaluated, as well as their influence on DNA, and time-kill experiments were conducted. In the present work examines also their synergistic antimicrobial effect in combination with commonly used antibiotics e.i. vancomycine and oxacilline. In addition, the cytotoxicity of the compounds was also investigated against normal human foreskin fibroblasts (HFF-1), as well as their antioxidant properties.

We hope that arene-ruthenium(II) complexes presented here will prove useful in the treatment of bacterial diseases, especially for people affected by cancer or for patients after surgeries dealing with wounds that are difficult to heal in this future.

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Tumour Selective Activation of DNA Intercalator

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Cancers affect life expectancy and life quality across the globe, being the 2nd highest cause of death worldwide and the leading cause in high-income countries.[1] Chemotherapies represent key treatment options and broad spectrum cytotoxics (such as metallo-drug cisplatin that targets nuclear DNA and is used to treat as many as 70% of all cancer patients), frequently deployed as combinations, remain the go-to agents for clinicians to treat many cancers. They are effective because they interfere with so many processes within the cancer cells. Yet they are associated with systemic toxicities and side effects due to lack of tumour selectivity[2] and developed drug resistances.[3] To overcome resistance mechanisms, new modes of action are needed: indeed there is an urgent need for new agents that bind nucleic acids in unprecedented ways to tackle not only resistant cancers, but potentially the DNA/RNA of viral diseases too. Background work has identified a new way of binding DNA by wrapping DNA about an anionic gold nanoparticle (AuNP).[4] It achieves this effect by locating intercalators on the curved surface of the nanoparticle that bind the DNA and hence wrap it round the nanoparticle (like an artificial histone – a histone is about 11 nm in diameter; the nanoparticles used are ~14 nm). This is exciting because DNA that is wrapped away cannot be processed, and indeed the particles show exciting anti-proliferative activity in cancer cell lines. Yet this background research creates a cytotoxic agent that could potentially affect all cells. Herein we will show our first steps towards creating non-toxic pro-drug nanoparticles which are activated into toxic DNA-coiling species by an enzyme present in elevated levels in specific cancerous tissues.[5]

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Glycosylated iron(III)-boron-dipyrromethene conjugates for lysosome targeted photodynamic therapy in red light

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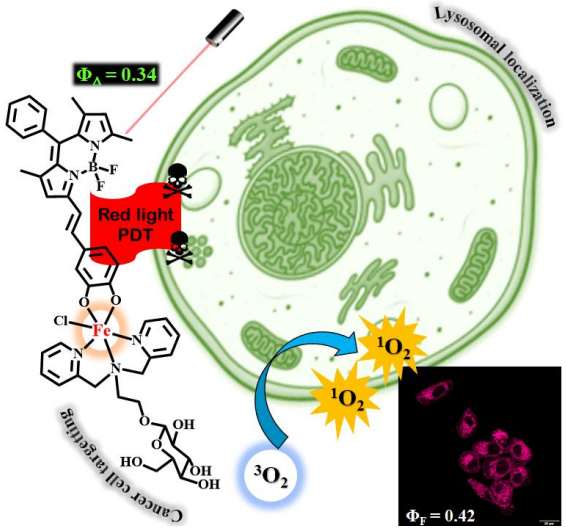

Being a bio-essential element, iron does not possess the systemic toxicity often encountered by heavy metal (Pt/Ru) based photosensitizers. To explore the use of iron in metal-based PDT (photodynamic therapy) agents, two iron(III) complexes [Fe(L^1)(L^3)Cl] (**1**) and [Fe(L^2)(L^3)Cl] (**2**), where L^1 and L^2 are tridentate NNN-donor benzyl-dipicolylamine and its glycosylated analogue, respectively, and L^3 is BODIPY (boron-dipyrromethene) appended catecholate ligand, were synthesized, characterized, and their photocytotoxicity studied. The complexes showed intense absorption spectral bands near 585 nm (ε ≈ 55000 M^{-1} cm^{-1}) in 1:1 DMSO/DPBS (Dulbecco's phosphate-buffered saline) buffer. The binding of catecholate moiety to Fe(III) pushes the absorption of the complexes into the clinically relevant red light zone due to the Fe(III)-catecholate LMCT band. Upon red light irradiation (30 J/cm^2, 600−720 nm), the complexes gave a singlet oxygen quantum yield (Φ_Δ) of ~0.34 in DMSO. Complex **2** exhibited apoptotic PDT activity (IC_{50} ≈ 0.08 μM) with high photocytotoxicity index (PI) value of > 1200 in red light in HeLa and H1299 cancer cells. They are less toxic in HPL1D non-cancerous cells and in dark conditions. A differential uptake of **1** and **2** was observed due to the targeting glucose moiety. The emissive complex **2** (1 μM) exhibited excellent cellular imaging with lysosomal localization. Formation of both singlet oxygen and radical species as the reactive oxygen species (ROS) was evidenced from pUC19 DNA photo-cleavage studies and SOSG (Singlet oxygen sensor green) assay. Drug accumulation was studied in 3D multicellular tumor spheroids, showing that it reaches the spheroid core within 8 h, with excellent fluorescence. The complexes are, hence, new iron-based lysosome-targeted PDT agents showing ROS-mediated red light photocytotoxicity at nanomolar concentrations.

Reactive Intermediates of Copper Bound Aβ peptides and Their Association with Alzheimer's Disease

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Alzheimer's disease (AD) is a terminal neurodegenerative disease that has generally been associated with the accumulation of amyloid beta (Aβ) peptides and characterized by the loss of neurons and neurotransmitters.[1-3] Transition metals like copper is found in abnormally high concentration in the oligomers and plaque of Aβ of AD affected brains. This invokes the possible involvement of copper in AD. Copper can bind Aβ peptides and coexists in two different pH dependent forms at physiological pH.[4] We recently demonstrated that Cu-Aβ exhibits peroxidase activity[5] and can oxidize neurotransmitters like serotonin (5-HT) in the presence of H_2O_2, a biological oxidant. Reactive copper oxygen intermediates are supposed to be the active oxidants for the oxidative process. Cu-Aβ reacts with lower concentration of H_2O_2 to form a mixture of bis-μ-oxo-dicopper(III) and mononuclear end-on hydroperoxo copper(II) (Cu(II)-OOH) while in the presence of excess H_2O_2, Cu-Aβ generates only the mononuclear end-on hydroperoxo intermediate. Both these intermediates have been characterized using UV-Vis, EPR and Resonance Raman (rRaman) spectroscopy. Among these two Cu/O species, the mononuclear Cu(II)-OOH intermediate is the reactive oxidant and accountable for the oxidation of the neurotransmitter, serotonin. Moreover, H_2O_2 produced by the reaction of O_2 with reduced Cu(I)-Aβ species can also oxidize serotonin. The role of second sphere Tyr10 residue in the oxidation of 5-HT by Cu-Aβ and H_2O_2 has also been investigated using 3-nitro modified Tyr (3-NT). Results indicate that inclusion of an electron withdrawing group to Tyr10 increases the rate of serotonin oxidation. The ability of Cu-Aβ to oxidize neurotransmitters may provide a possible explanation for the observed neurodegeneration associated with AD.

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Cu(I)-targeting ligand in Alzheimer disease context

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Alzheimer disease (AD) is the most common cause of dementia, affecting more than 30 million people in the world. AD is characterized by a brain deterioration leading to difficulties with memory, behavior, and thinking. According to the "amyloid cascade hypothesis" an abnormal amyloid deposit formation composed of amyloid-β peptides (Aβ), a 40-42 amino acids peptide, occurs in AD brain in extracellular locations at the early stage of the disorder.[1] Aggregation of Aβ is linked to an accumulation of the peptide induced by an imbalance between its clearance and its production. Due to the presence of a huge concentration of d-metal ions in the senile plaques (up to mM) and an overall disturbed metal homeostasis, the role of metal ions in AD has been widely studied.[2]

It has been shown over the last decade that Cu ions bound to Aβ is able to catalyze the production of reactive oxygen species (ROS) through incomplete reduction of dioxygen.[3, 4] This ROS production in assumed to be part of the enhancement of the oxidative stress found in AD brain that drives the disease.

These findings led to the development of therapeutic approaches based on the chelation of Cu(II) with the description of a large number of ligands. Promising effects have been observed with different class of ligands such as hydroxyquinoline moieties, stilbene-like molecules, benzothiazole derivatives, macrocyclic and peptidic ligands.[5, 6] Nevertheless, until now, attempts to use Cu ligands in AD clinical treatment have failed. While most of the ligands studied were designed to target Cu(II), Cu(I) ligands have been overlooked and might be the missing piece of the puzzle for the strategy to be effective. Indeed, the targeting of Cu(I) in the therapy by chelation approach is an emerging and promising idea as Cu(I) is the entity directly reacting with O_2.

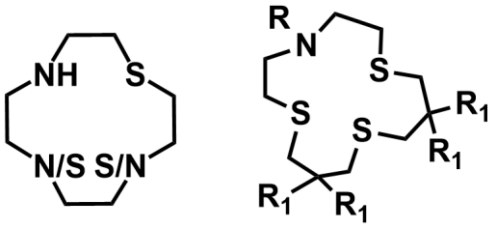

Figure: General structure of the ligand studied in this work

Here we will present the ability of [S, N] containing macrocycle ligands (Figure) to inhibit the Cu-Aβ induced ROS production.

ANR JCJC **"Copperation"** is gratefully acknowledge for funding

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New organometallic gold(III) complexes based on (C^C) chelates and NHC ligands: synthesis and anticancer investigations.

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Keywords : anti-cancer treatments, gold(III) complexes, structure-activity relationship.

Metal-based anti-cancer treatments appeared in the late 1970s with the appearance of platinumbased compounds.[1] Although these treatments are used in therapy today, they have many limitations. This results in the appearance of side effects or development of resistance.[2] For this reason, studies have been conducted by replacing platinum(II) by isoelectronic gold(III). Thus, many gold(III)complexes with (C^N) or (C^N^C) ligands have been synthesized and then tested on cancer cell lines. These compounds were found to have anticancer activity in the micromolar range.[3] Moreover, the presence of these cyclometalated ligands have improved the redox stability of gold(III) in the presence of strong natural reducing agents such as glutathione.[4] However, of the four available coordination sites of the complexes, three are blocked by the cyclometalated ligand, leaving only a small possibility for functionalization or for direct coordination of gold(III) with biomolecules. The objective here is to synthesize a new family of gold(III) complexes, replacing the (C^N^C) ligand. After an initial study of compounds with a biphenyl ligand (C^C) and a dinitrogen ligand (N^N),[5] we focused on the synthesis of a new family of complexes composed of a biphenyl ligand (C^C), a chlorido ligand and pyridinylNHC ligands based on imidazole and benzimidazole scaffolds. These new organogold complexes have been screened for their anticancer activity on a panel of human cancer cells along with analogs without pyridine ring substituents. A preliminary structure-activity relationship could be established.

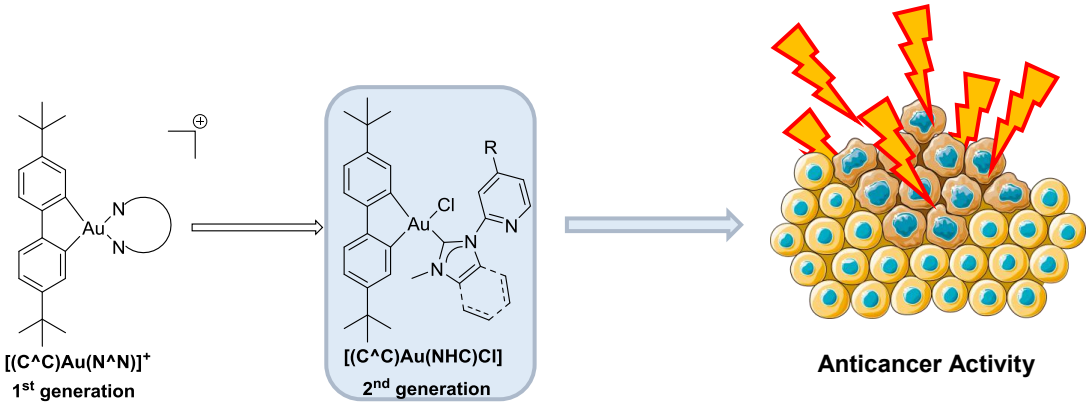

Fig. 1 Optimization of gold(III) complexes with pyridinyl-NHC ligands and assays for anticancer activity

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BODIPY-Tagged Platinum(II) Curcumin Complexes for Endoplasmic Reticulum-Targeted Red Light Photodynamic Therapy

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Cisplatin remains the frontline chemotherapeutic agent and the nuclear genome is believed to be its main target. Its reduced efficacy such as off-target activity and drug resistance can be enhanced by combining its chemotherapeutic potential with photodynamic therapy (PDT) and sending it to organelles other than nucleus respectively. Additionally, near-infrared light (600−800 nm) active PDT agents have deep tissue penetration proficiency, reduced scattering, and can eradicate autofluorescence interference of tissue successfully. Combining these rationales, platinum(II) curcumin complexes having 2-pyridyl-benzimidazole ligands with red light active BODIPY (**RBC** and **IRBC**) were designed, synthesized and studied. Along with the medicinal influence of curcumin, BODIPY complex, **IRBC** with λ_{abs} at >600 nm and high values of ε and Φ_{Δ}, showed remarkable apoptotic PDT activity in A549, HeLa and MDA-MB-231 cells [IC_{50}: 1.3-2.4 μM, λ = 600-720 nm red light]. Further, **IRBC** displayed a novel mechanism of generation of two types of ROS, namely, hydroxyl radicals from the curcumin ligand and $^1O_2$ involving the BODIPY moiety when excited in blue and red light, respectively. Interestingly, **RBC** was found to localize predominantly in the endoplasmic reticulum (ER). The complexes resulted in apoptosis as evidenced by the sub-G1 population on cell-cycle analysis and caused ER stress and disruption of mitochondrial potential as observed by the Fluo-4 AM calcium release assay and JC-1 assay respectively. **RBC** and **IRBC** as newly designed platinum(II)-BODIPY conjugates exemplify multifunctional red light photosensitizers having therapeutically beneficial curcumin dye as a stable moiety showing photo-selective multiple cell-killing pathways, thus providing scope for further investigations toward cancer treatment and cure.[1]

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Oxoplatin-B, a cisplatin-based platinum(IV) complex with photoactive BODIPY for mito-specific "chemo-PDT" activity

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Serendipitous discovery of cisplatin by Rosenberg followed by its FDA approval in 1978 has stimulated the research based on platinum-based drugs. Despite pervasiveness present in classical platinum drugs, several attendant drawbacks including dose-dependent toxicity and intrinsic or acquired drug resistance against certain types of cancer. In this context Pt(IV) prodrugs can overcome the undesirable drawbacks related to the platinum(II) drugs. Pt(IV) having low-spin d^6 system is kinetically inert and resistant to ligand substitution. Herein, we present a cisplatin-derived platinum(IV) prodrug, namely, Oxoplatin-B of formulation $[Pt(NH_3)_2Cl_2(OH)(\mathbf{HL^1})]$, where $\mathbf{HL^1}$ is visible light activable boron-dipyrromethene (BODIPY) pendant. The complex is synthesized and its application as synergistic chemo-PDT agent has been explored. $[Pt(NH_3)_2Cl_2(OH)(\mathbf{HL^2})]$, where $\mathbf{HL^2}$ is methyl benzoic acid is used as control. The BODIPY complex displayed strong absorption band at 500 nm ($\varepsilon \sim 4.34 \times 10^4$ $M^{-1}cm^{-1}$) and emission band at 515 nm (λ_{ex}=488 nm, Φ_F=0.64) in 1% DMSO/DMEM medium. Titration experiments using 1,3-diphenylisobenzofuran (Φ_Δ = 0.28) and mechanistic pUC19 DNA photocleavage study in visible light revealed its singlet oxygen generation ability. It showed high stability in dark but undergoes activation on visible light irradiation generating active Pt(II) species. It displayed remarkable apoptotic photocytotoxicity in visible light (400-700 nm) with IC_{50} value ranging from 1.1 to 3.8 μM against MCF-7, HeLa and A549 cancer cell lines. Photocytotoxicity of the complex substantially attenuated in non-cancerous HPL1D cell line. The emissive complex showed predominant mitochondrial (mito) localization with Pearson's correlation coefficient (PCC) value 0.96. This observation is of importance as mitochondrial disruption could trigger intrinsic pathway leading to apoptosis. Mitochondria lack any defence repair mechanism such as nucleotide excision repair (NER) which operates only in nuclear DNA. Mito-localization thus helps prodrug to overcome cisplatin resistance. JC-1 and annexin V-FITC/PI assays reveal apoptotic cell death by mitochondrial dysfunction. This work exemplifies a combo "PACT-PDT-Chemotherapy" process

that opens an emerging direction towards designing PDT active platinum-based multimodal therapeutic agents.[1]

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Novel Silver-based Therapeutics: Biological Activity and Stability

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While antibiotic-resistant bacterial infections are a widely recognised global health threat, much less media attention has been given to drug-resistant fungal infections. Globally, more than 300 million people suffer a serious fungal infection causing over 1,350,000 deaths.[1] *Candida* is a leading cause of healthcare-associated bloodstream infections in US hospitals.[2] Some types of *Candida* are becoming increasingly resistant to first- and second-line antifungals which is incredibly concerning. Clearly new therapeutic agents are required and work in our group focuses on designing antimicrobial metal complexes with different modes of action to existing therapeutics. Previous work in our group has reported a phenanthroline-oxazine ligand with atypical DNA binding abilities[3] and antimicrobial activity against *S. aureus* and *E. coli* which is greatly increased by improving lipophilicity by means of increasing the chain length **R** (**Figure 1**)[4]. These studies also showed enhanced antimicrobial activity against MRSA by complexation to copper(II). In this poster we report on the synthesis, solution characteristics and biological activity of a related family of silver complexes of the phenanthroline-oxazine ligands. I will present data on the solution stability of silver phenanthroline-oxazine complexes and their biological activity against *C. albicans* in nutrient rich and nutrient poor media. I will discuss the stability of the silver complexes in biological media as determined by UV-visible spectroscopy and the solution behaviour as determined by NMR spectroscopy.

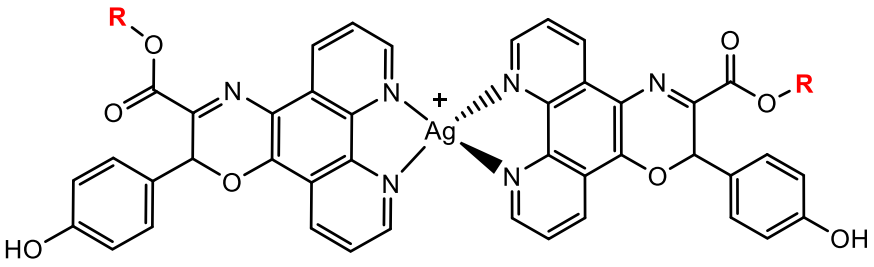

Figure 1: Silver complex of L-Tyrosine ester derived phenanthroline-oxazine, where R = methyl, propyl, hexyl.

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Modulating Metal-Binding Affinity in Multifunctional Molecules for Reactivation of Mutant p53

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The p53 protein plays a major role in cancer prevention, and over 50% of cancer diagnoses can be attributed to p53 malfunction.[1] p53 incorporates a structural Zn site that is required for proper protein folding and function.[2] In many cases, point mutations around the structural Zn binding site leads to loss of the Zn^{2+} ion, which causes destabilization of the tertiary structure and eventual fibril-like amyloid aggregation.[2] We have synthesized lead compounds which act as small molecule stabilizers of mutant p53 or act to prevent its aggregation, and feature Zn-binding fragments to chaperone Zn to the metal depleted site and restore wild-type function.[3,4] However, many zinc metallochaperones (ZMCs) have been shown to generate intracellular reactive oxygen species (ROS) through Fenton-like chemistry by chelating redox-active metals such as Fe and Cu.[5,6] Generating high levels of ROS can lead to off-target effects and general toxicity. Careful tuning of ligand zinc affinity and the affinity for other endogenous metals is critical for on-target mutant p53 activation.[6] We are optimizing lead compounds by using donors which we hypothesize will increase the relative affinity for Zn in comparison to Cu. This presentation describes the design and optimization of a series of ligands containing phenols for interaction and stabilization of the p53-Y220C surface cavity, and Zn-binding fragments for metallochaperone activity. Recent results will be presented.

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Antioxidant activity of ruthenium cyclopentadienyl complexes bearing different imidato ligands

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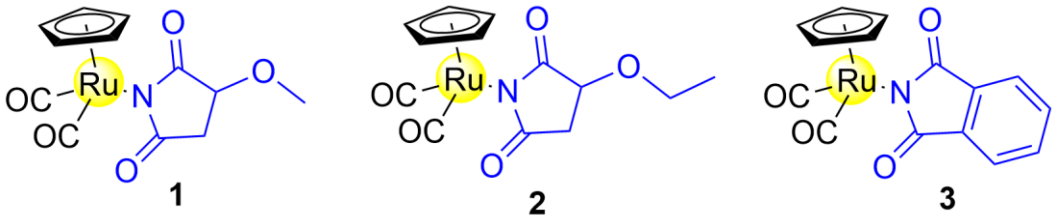
Over the past few decades, half-sandwich ruthenium complexes have played a significant role in the field of organometallic chemistry and medical sciences[1].

Cyclic imides contain bisamide linkages with a general structure of [-CO-N(R)-CO-]. Cyclic imide derivatives show a wide range of biological properties such as antibacterial, antifungal, antiviral, antitumor, anti-inflammatory and muscle relaxant activities[234]. Therefore, why they are privileged pharmacophores and important building blocks for the synthesis of natural products, drugs, and polymers.

In the presented studies, organometallic ruthenium complexes that carry different imidato ligands (η^5-cyclopentadienyl)Ru$(CO)_2$-*N*-methoxysuccinimidato (**1**), (η^5-cyclo-pentadienyl)Ru$(CO)_2$-*N*-ethoxysuccinimidato (**2**), and (η^5-cyclopentadienyl)Ru$(CO)_2$-*N*-phthalimidato (**3**) have been synthesized and tested for their antioxidant activity. We found that ruthenium complexes **1**-**3** have antioxidant activity without cytotoxic effect at low concentrations[5].



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Direct Monitoring of Doxorubicin Release via sensitization of NIR-emitting Ytterbium Liposomes

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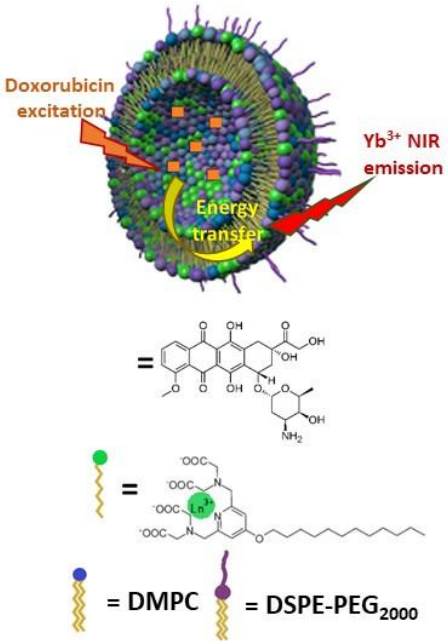
Liposomes are widely used as drug carriers, and offer the possibility of combining therapeutic and diagnostic properties within a single unit; enabling drug delivery follow-up. The encapsulated drugs become bioavailable only upon their release from the nanocarrier, alleviating out-of-target tissue damage. Thus, a controlled and localized release of the drug is crucial. The previously reported methods rely mostly on indirect monitoring of drug release, typically by co-loading a contrast agent into the liposome, that is co-release with the drug and its signal detected.[1]

Following our previous work on lanthanide-based lipoparticles,[2] we report here on liposomes composed of amphiphilic Yb^{3+} chelates encapsulated with doxorubicin, the anti-cancer agent in the clinically used liposomal drug Doxil®. We show that doxorubicin can sensitize Ytterbium (Yb^{3+}) and generate its near infrared (NIR) emission.[3] Indeed, the sensitized emission of Yb^{3+} is dependent on the presence of both the Yb^{3+} complexes and the doxorubicin within the liposome, and thus on the integrity of the particles, which can be used to monitor drug release. We also established the first demonstration that the NIR Yb^{3+} emission signal is observable in living mice following intratumoral injection of the Yb^{3+}-doxorubicin-liposomes, using a commercial macroscopic setup equipped with a near-infrared camera.



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New Nuclear Medicine Imaging Radiotracer ^{64}Cu(II) for diagnosing Hypoxia Conditions Based on the Cellular Copper Cycle

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Cancer is a disease characterized by uncontrolled cellular proliferation. Accumulation of the abnormal cells creates a tumor that can migrate to other places in the body producing metastases. Treating cancer is difficult as it may return even after treatment and in late stages of disease the cancer cells develop resistance, often because of the increased rate of proliferation leading to the formation of new genetic mutations. Detection of cancer is of importance, allowing a stronger chance of cure. With the help of early detection, it will be possible to adapt the treatment to the person and the condition of the illness. Tumors are characterized by hypoxic conditions (a low oxygenation environment), which also lead to aggressive phenotypes. Radiotracers are radioactive biomarkers that characterize a biological phenome within the cell. When the biological phenome behaves differently in cancer and normal cell, quantitative characterization of the cell's state can be achieved using PET-CT and PET-MRI imaging. Here, we develop a new radiotracer for hypoxic cells based on the copper oxidation-reduction process in the cells and the cellular copper transfer mechanism. We designed a ^{64}Cu(II) based complex which holds high affinity to the main human copper transporter, hCtr1. This complex Is integrated in the copper cellular metabolism. This research involves both cold and hot experiments, as well as in-vitro and in-vivo studies. We hope that in the future, we will be able to offer a radiotracer for detection of cancerous tumors by imaging of hypoxia and with that, we can better match the treatment to the patient.

Breast Cancer Stem Cell Active Copper(II) Coordination Complexes

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Despite progress in treatments, cancer continues to be a huge socio-economic burden, killing millions of people a year. A large number of cancer deaths are associated with cancer metastasis and cancer recurrence. These phenomena are thought to be caused by a small population (1-3%) of cancer cells called cancer stem cells (CSCs), which can survive treatments and eventually regrow tumours. Most chemotherapeutics target fast-dividing cells that make up the bulk of tumours, however CSCs can survive these treatments, in part due to their slow-dividing stem-like nature.[1] Although CSC specific targets have been identified, there are currently no clinically approved CSC-specific treatments. There is a clear need to develop new chemotherapeutic agents which can kill CSCs at safe doses, in order to increase long-term treatment success. We and others have shown the promise of metal complexes as cytotoxic agents towards CSCs.[2]

CSCs maintain low intracellular levels of reactive oxygen species (ROS).[3] Due to this, they are more susceptible to oxidative damage compared to bulk cancer cells. Copper is an endogenous metal which is redox-active in physiological conditions and has the potential to disrupt this finely tuned redox balance, causing a cytotoxic effect.

Here we present the synthesis, characterisation, and anti-breast CSC properties of a variety of Cu(II) complexes bearing phenanthroline, terpyridine and Schiff base ligands.[4–6] These Cu(II) complexes kill breast CSCs at low or sub-micromolar doses and are more toxic towards breast CSC mammospheres than salinomycin (up to 34-fold), an established anti-CSC agent. Upon short exposure times these compounds elevate intracellular levels of ROS, disrupting cellular functions and leading to cell death in a variety of mechanisms, depending on the coordinating ligands. Our work shows that redox modulation of CSCs using coordination copper complexes could be an effective therapeutic method to pursue.

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Intracellular cryo-correlative XRF imaging of innovative nano-hybrids designed for X-ray photodynamic therapy

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Radiation therapy (RT) remains a major part of the anti-cancer arsenal as more than 50% of cancer patients undergo RT through their standard-of-care. However, because of radiation toxicity and a lack of specificity for tumor tissues, delivering a high-dose of X-rays with tolerable toxicity to the surrounding tissues remains a challenge that has yet to be overcome to improve the clinical management of cancer. New X-ray based treatment known as X-rays activated Photodynamic Therapy (X-PDT) involving specific probes (photosensitisers) which after activation with X-rays are able to generate reactive oxygen species that can locally kill cancer cells [1]. Indeed, thanks to such innovative nanohybrids, X-rays irradiation only becomes the “catalyst”, opening the possibility to treat deep tissues that cannot be reached with classical PDT. We have evaluated in vivo that ultra-small GdF3 nanocrystals are stable efficient contrast media for imaging with the Spectral Photon Counting Scanner CT (SPCCT) scanner clinical prototype and suitable for preclinical studies, with a biodistribution study on mice and K-edge imaging on rats [2]. Compared to the organometallic gadolinium complexes, these nanoparticles feature a very high stability with no possible gadolinium leakage and show a high payload of gadolinium ions. These systems provide thus a very high local density of active ions, making them efficient probes for various imaging modalities. Our nanohybrids aim at providing a “all-in-one” methodology to allow the use of only one device the SPCCT scanner, within the same period of time for precise imaging/radiotherapy. Yet, the distribution of nanoparticles within the tumor cells vs. healthy cells, and a quantitative intracellular distribution in close relation to organelle location, is not known and being of particular importance considering the PDT effect. Using cryo-correlative optical and hard X-ray ID16A nanoprobe as well as MISTRAL soft X-ray microscope we could obtained better understanding of their intracellular behavior and this will contribute to more efficient development of the imaging/therapy on X-ray SPCCT.

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Unprecedented Kinetic Inertness for a Mn(II)-Bispidine Chelate : A Novel Structural Entry for Mn(II)-Based Imaging Agents

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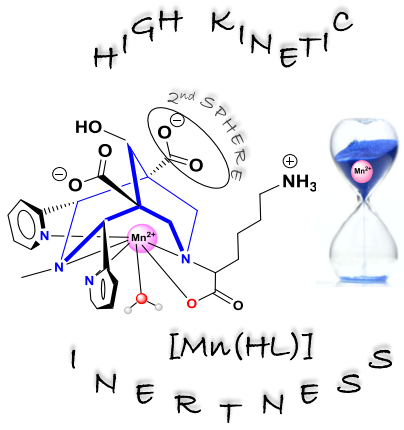
Gd^{3+}-based contrast agents have been recently the subject of public health concerns, due to the potential *in vivo* release of free and toxic Gd^{3+}.The causal link of nephrogenic systemic fibrosis to Gd^{3+} exposure of patients has so far led to the withdrawal of Gd^{3+} complexes formed with linear chelators.[1] The search for more biocompatible alternatives to Gd^{3+}-based MRI agents, and the interest in ^{52}Mn for PET imaging call for ligands that form inert Mn^{2+} chelates.



Given the labile nature of Mn^{2+}, high inertness is challenging to achieve. The strongly preorganized structure of the 2,4-pyridyl-disubstituted bispidol ligand L endows its Mn^{2+} complex (see Scheme) with exceptional kinetic inertness and despite a moderate thermodynamic stability, [Mn(HL)] is the most inert monohydrated Mn^{2+} complex known to date. Indeed, the Mn^{2+} complex did not show any dissociation for 140 days in the presence of 50 equiv. of Zn^{2+} (37 °C, pH 6). In addition, the relaxivity of [Mn(HL)] (4.28 $mM^{-1}.s^{-1}$ at 25 °C, 20 MHz) is remarkable for a monohydrated, small Mn^{2+} complex, which might be related to a second sphere relaxivity contribution induced by the non-coordinating carboxylates functions. In vivo MRI experiments in mice and determination of the tissue Mn content evidence rapid renal clearance of the chelate. Additionally, the ligand could be radiolabeled with ^{52}Mn and the radiocomplex revealed good stability in biological media.[2]

The bispidine-based L chelator constitutes a very promising structural entry for the development of Mn-based imaging agents for both MRI and PET. Most importantly, it can provide excellent kinetic inertness which so far could not be achieved within the more traditional ligand families.

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Water-stable bimetallic copper (I) helicate as artificial chemical nuclease

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DNA and proteins are the main targets for metal complexes with cytotoxic properties against cancer cells. The interaction of a complex with DNA could damage its structure or block its replication process, thus inducing to cell death.[1] Copper complexes are a promising alternative to classic platinum compounds used as anticancer metallodrugs.[2] The design and evaluation of copper compounds as metallodrugs has been dominated by Cu (II) complexes. Studies based on Cu (I) complexes are limited, mainly due to the difficulty to stabilize the 1+ oxidation state in aqueous media.[3]

In this work, we synthesized a water-soluble bimetallic Cu (I) helicate complex, $[Cu_2(L)_2](Cl)_2$ (L is a bis-phenanthroline ligand, Fig. 1A), which is stabilized respect to oxidation by intramolecular π-stacking interactions and steric effects, as observed by UV-Vis and NMR-^{1}H spectroscopies. Electrophoresis experiments with plasmid DNA show that the bimetallic Cu (I) helicate can act as an artificial chemical nuclease, whose activity depends on the complex concentration and incubation time. The nuclease activity is greatly enhanced in the presence of H_2O_2, while EPR studies with DMPO probe confirmed the production of hydroxyl radicals, suggesting an oxidative DNA-cleavage mechanism through a Fenton-like reaction. Our preliminary results make this Cu (I) helicate as a potential anticancer agent. The impact of the intrinsic chirality of helicates on the affinity to bind DNA is currently under evaluation.

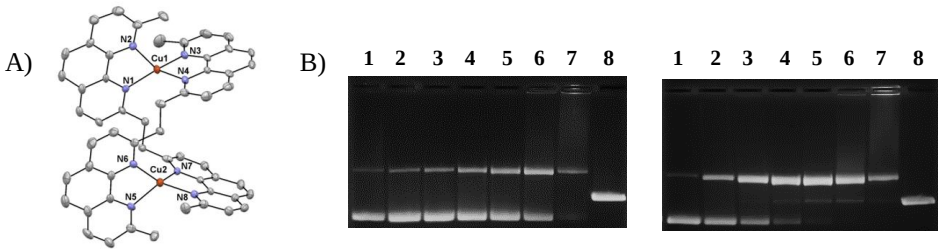

Figure 1. A) Cationic crystal structure of the Cu(I)-helicate (P-enantiomer). B) Effect of the helicate concentration on the nuclease activity against pBR322 DNA, in absence of H_2O_2 (left), and in the presence of 100 μM H_2O_2 (right). Lane 1: control DNA (40 μM bp), lane 2-7: 1 μM, 2.5 μM, 5 μM, 10 μM, 25 μM and 50 μM, respectively of [Cu2(L)2](Cl)2, lane 8: control linear DNA (24 μM).

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Novel potential MRI Contrast Agent based on Mn^{2+} complex of macrocyclic ligand with increased thermodynamic stability

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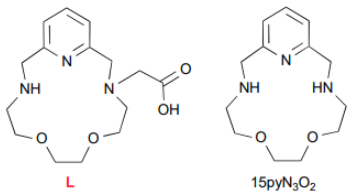
Magnetic resonance imaging (MRI) is one of the most common methods used in the field of diagnostic medicine. Its low sensitivity can be improved by use of contrast agents (CA) where the majority of clinical CAs are Gd(III) complexes.[1]

Recent research of Nephrogenic Systemic Fibrosis (NSF) revealed that some Gd(III) complexes had to be withdrawn.[2] As their alternatives, Mn(II) complexes were studied in the past years because of suitable properties, such as five unpair d electrons, long electronic relaxation times and labile water exchange.[3] However, there is a struggle between thermodynamic stability and kinetic inertness, so the ligand design is considered as a challenge. Macrocyclic ligands provide higher thermodynamic stability of their complexes in comparison with non-cyclic ligands. Moreover, presence of pyridine moiety leads to a higher rigidity and additional increase of complex stability. Thus, several 15-membered pyridine based macrocycles were examined previously and provided seven-coordinate Mn(II) complexes with two inner-sphere water molecules, but their thermodynamic stability was not sufficient enough.[4] Therefore, in this work, we decided to modified the parent 15-membered pyridine-based macrocycle ($15pyN_3O_2$,) with one acetic pendant arm, i.e. to increase the denticity of the ligand **L** and to increase its complex solubility as well as thermodynamic and kinetic stability.



Prepared Mn(II) complex was examined using several methods such as ^{17}O NMR, ^{1}H NMRD profile, measurement of kinetic inertness and potentiometry and obtained results will be discussed within the presentation.

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Molecular nanoparticles of ferric-tannic complexes enhance brain magnetic resonance imaging and activate brain clearance pathways

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Iron-containing drug can be considered beneficial for non-invasive magnetic resonance imaging (MRI) and induction of essential biochemical processes. Herein, we present a new type of iron-containing drug, based on molecular nanoparticles of ferric-tannic complexes (so-called FTs), that could be used to enhance non-invasive brain MRI and to modulate brain clearance pathways. Once intravenously administered into healthy Wistar rats, the maximum enhancement of T_1-weigthed MRI signal was observed at 0.5 h post-injection, corresponding to their maximum accumulation in the brain. After that time, FTs were rapidly cleared by the brain, which was possibly modulated by organic anion transporters present at the blood-brain barrier. This result describes the 'come-and-run' concept of FTs, which could be utilised as brain-targeting agent for various proposes. Although the 'come-and-run' mechanism allows them to have a short half-life in the brain, they remain long enough to activate brain clearance pathways such as autophagy, lysosomal function and cellular clearance. Therefore, FTs could be considered a new clinically translatable pharmaceuticals for brain MRI and prevention of brain ageing and related diseases.

Novel Gold(I)-thiosemicarbazone compounds as potential anticancer and antiparasitic agents

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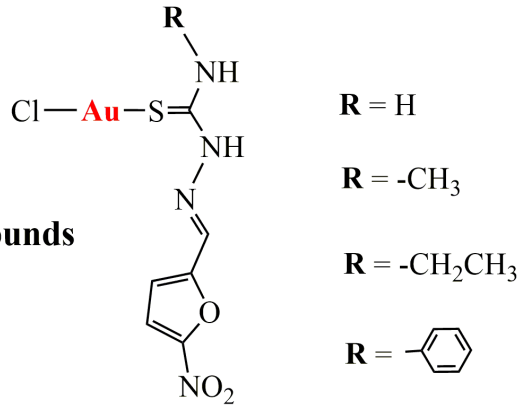
Cancer is one of the major health concerns and currently remains the second leading cause of death worldwide. Gold(I) compounds have emerged as promising drugs due to their ability of altering the redox homeostasis of cancer cells and for their inhibition metastasis ability. Chagas's disease is caused by the parasite *Trypanosoma cruzi* and affects more than 7 million people in the world. Current chemotherapy still relies on old and toxic drugs that require quite long treatment. Our group has developed a family of 5-nitrofuryl containing thiosemicarbazones (HL) whose main mode of trypanocidal action is through ROS generation. Considering the metabolic similarities between both highly proliferative cells, in this work we synthesized four new gold(I) compounds including this thiosemicarbazones bioactive ligands. The [AuCl(HL)] complexes were fully characterized in solid state and solution. The stability in solution of the compounds was evaluated by ^{1}H-NMR spectroscopy, UV-Vis absorption spectroscopy and Cyclic Voltammetry. The antiproliferative activities were evaluated *in vitro* against renal, ovarian and Triple Negative Breast (TNB) cancer cell lines, and on the infective stage of *T. cruzi* (trypomastigotes). Additionally, cytotoxicity was evaluated on normal lung cells and VERO cells. The anti-metastatic properties of the compounds were evaluated on renal cancer cells by migration, invasion and angiogenesis essays. Electrochemical and EPR studies were performed to evaluate the free radicals generation ability of the compounds, ROS generation in *T. cruzi* cellular culture was confirmed.

[AuCl(HL)] compounds



Catalysis of chlorite disproportionation by iron porphyrins and a low-tech source of disinfecting chlorine dioxide

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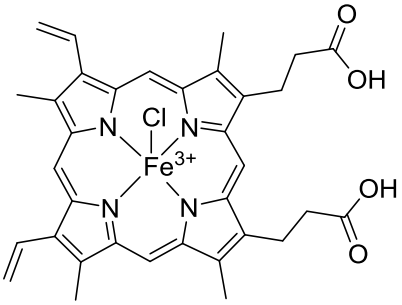
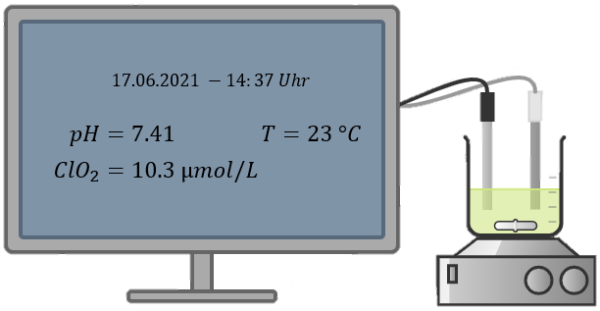
Cutaneos leishmaniasis (CL), a non-lethal skin disease ever spreading due to climate change and the migration of people, harms people with open wounds and leaves disfiguring scars. Currently patients are mostly treated either with affordable antimony(V) drugs causing severe side effects or the expensive antibiotic paramomycin.[1]



In cooperation with a local non-profit organisation (*Waisenmedizin e.V.*[2]), a new CL treatment using a hydrogel containing pharmaceutical sodium chlorite has been developed and already undergone several trials with CL patients. So far, enhanced wound healing was clearly observed but the mode of action of the new wound dressing is not clear. In the 1980s, Elstner *et al.*[3,4] investigated the reactions of chlorite in the presence of haemoglobin and hemin (see structure above) in detail. Based on their results, the formation of an unknown very oxidizing oxo species from chlorite was postulated.



Using an amperometric chlorine dioxide sensor (right), we found that hemin is able to catalyse the formation of significant concentrations of chlorine dioxide from chlorite, probably via the following disproportionation reaction:

$$3\ ClO_2^- + 3\ H^+ \xrightarrow{cat.} 2\ ClO_2 + HClO + H_2O$$

In this contribution, we will present investigations on the catalysis of chlorite disproportionation under “wound conditions”, i.e. by iron porphyrins and / or by the mildly acidic conditions often found in wounds. In addition, UV/Vis monitoring, pH detection and the monitoring of oxohalide concentrations by ion chromatography offers some insights into reaction pathways and mechanisms.

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Enzyme-responsive Copper Proionophores as anticancer agents

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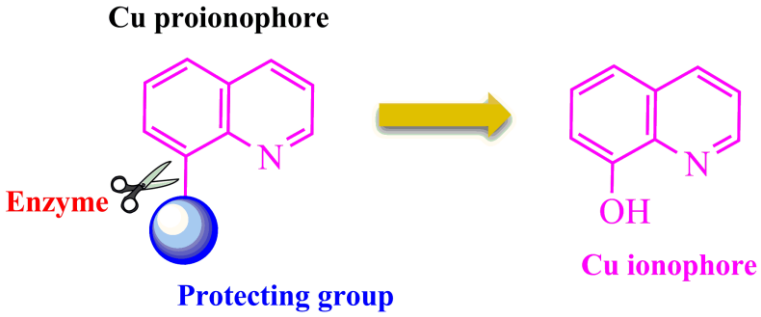
Current cancer therapies suffer from severe off-target effects because most of them target critical facets of cells that are generally shared by all rapidly proliferating cells. The development of new anticancer drugs should aim to increase selectivity and therefore reduce side effects.[1] In addition, these agents should overcome cancer cell resistance and target cancer stem cells. Some copper ionophores have shown promise in this direction thanks to an intrinsic selectivity in preferentially inducing cuproptosis of cancer cells compared to normal cells.[1,2] In this context, new systems that could act as proionophores are reported. Proionophores are molecules that have to be activated to release the metal ionophore, increasing the selectivity of the drug. In particular, enzyme-responsive prodrugs of 8-substituted quinolines were evaluated. β-Glucuronidase was one of the chosen enzymes as it is overexpressed in the microenvironment of solid tumors and therefore represents a privileged target in cancer prodrug monotherapy.[3] Currently, this is the first example of glucuronidation applied to copper ionophores.



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A redox switch candidate based on pyridyl nitroxide radicals complexes with metal transition

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The development of novel redox switches as sensitive probes has been growing due to their ability to provide a distinct and easily detectable response, which represents an attractive tool in the study of species such as reactive oxygen species (ROS). These species have been implicated in differences in ROS concentration or in oxidation potiential between healthy and diseased tissues in several diseases such as cancer.[1,2]

This work presents a series of metal complexes based on a pyridyl-based ligand containing two nitroxide groups, which were characterised by electrochemical, optical and magnetic properties to determine whether they can be employed as a redox switches.

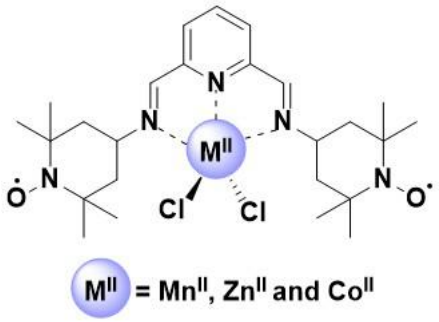

Figure 1. M^{II} (Mn^{II}, Zn^{II} and Co^{II}) complexes of the pyridyl-based ligand containing nitroxide groups.

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Anaerobic hydrogen peroxide detoxification and NHC compounds with antimicrobial activity

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Escherichia coli and *Staphylococcus aureus* are considered by CDC to be urgent health threats and are classified by WHO as high priority pathogens for R&D of new antibiotics, due to the emergence of strains resistant to most of the available antibiotics. Thus, there is a need to develop new antimicrobial compounds, for which metallodrugs have demonstrated promising results in *in vitro* studies. Silver and copper are known to possess antimicrobial proprieties since antiquity and are excellent candidates as potential antimicrobial due to its high abundance, relatively low price, and low toxicity, when compared to other metals. Complexes of Ag and Cu using N-heterocyclic (NHC) carbenes, as a mean to stabilize the metal, in some cases potentiate an increase in their antimicrobial activity.

Pathogenic bacteria use molecular systems to detoxify ROS and copper as a strategy to evade the human immune system. In *E. coli*, YhjA a non-classical bacterial peroxidase as the dual role of reducing hydrogen peroxide to water and it as the final electron acceptor under anaerobic respiration[1,2]. Thus, these enzymes can be considered promising drug targets.

In here, the biochemical and kinetic characterization of YhjA, a quinol peroxidase[3] composed by a C-terminal domain homologous to the classical dihaem bacterial peroxidases, with an additional N-terminal domain, binding one *c*-type haem and a transmembrane helix, is presented.

We present a new family of Ag(I) and Cu(I) complexes bearing NHC carbenes with an acenaphthene backbone. The activity of both the ligands and complexes will be studied against the *S. aureus* and *E. coli* to address the effect of the compounds in different bacterial membrane compositions. The effect of the complexes on the inhibition of growth was screened by disk diffusion, and the minimum inhibitory concentration was determined for the ones with higher activity. The impact of the ligands and complexes were additionally evaluated regarding its capacity to prevent the formation of biofilms and in its disintegration.

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