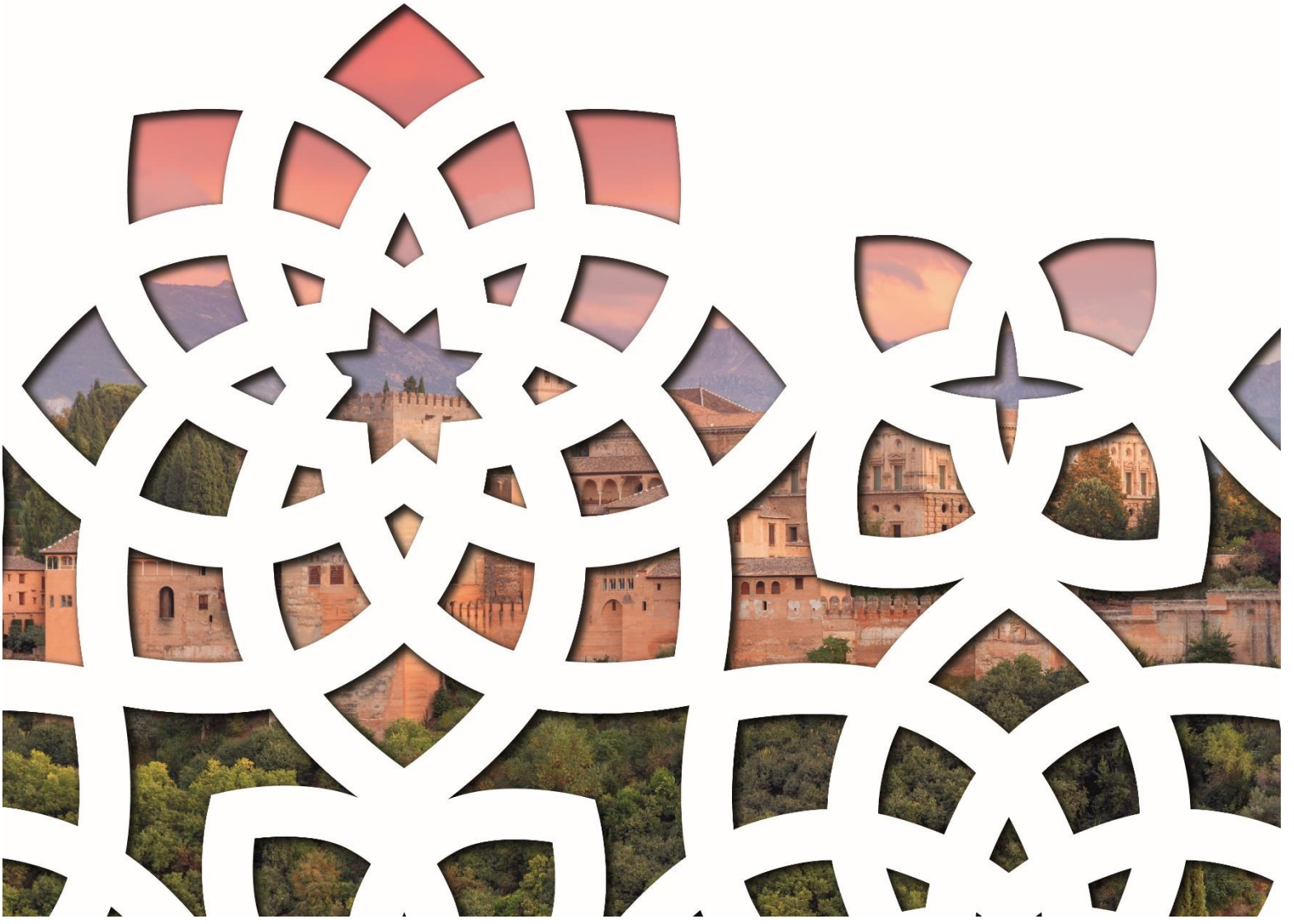
Granada 5 - 7 junio 2023

BOOK OF ABSTRACTS

BIOGranada23



XIII Reunión Científica de Bioinorgánica

BioGranada 2023

5-7 de junio de 2023

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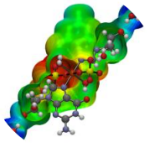

COMPLEJOS DE METALES DE TRANSICION CON INTERES BIOINORGANICO Y/O TERAPEUTICO

BIOMEC
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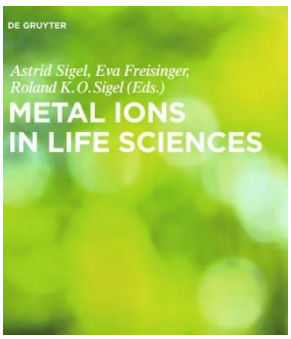

UNIVERSIDAD DE GRANADA

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		10:15-10:30	**OC-6**	10:15-10:30	**OC-17**
		10:30-10:45	**OC-7**	10:30-10:45	**OC-18**
		10:45-11:00	**OC-8**	10:45-11:15	**INV-05**
11:00-14:00	**Registration**	11:00-11:15	**OC-9**		
		11:15-11:45	**Coffee Break**	11:15-12:00	**PL-04**
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20:30	**Welcome Reception**	21:30	**Gala Dinner**		

CONFERENCIAS INTERNACIONALES / PLENARY LECTURES

Metal Complexes as Therapeutics

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Keywords: Anticancer, Metals in Medicine, Osmium, Photodynamic Therapy, Ruthenium.

Metal complexes are currently playing a tremendous role in medicine [1]. For example, the platinum complex cisplatin and its derivatives oxaliplatin and carboplatin are employed in more than 50% of the treatment regimes for patients suffering from cancer! Over the last years, our research group focused its attention on the development of novel metal complexes as imaging and therapeutic agents against cancer and parasitic/fungal diseases [2]. During this talk, we will present our latest results, including in vivo results, on the development of new osmium-based photosensisitzers for photodynamic therapy that can be activated at 740 nm [3] and ruthenium-based anticancer drug candidates [4].

Acknowledgements: This work was financially supported by an ERC Consolidator Grant PhotoMedMet.

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Expanding the Biocatalytic Toolbox with Salophen-Myoglobin Catalysts

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Keywords: Artificial metalloenzymes, salophen, myoglobin, biocatalysis.

First row transition metal salen and salophen complexes demonstrate catalytic activity in a range of synthetic reactions, including C-H bond functionalization and small molecule activation [1]. Due to the structural similarity to porphyrin cofactors, synthetic salen and salophen complexes can act as cofactor mimics for heme proteins and, thus, are attractive building blocks in the design of new artificial metalloenzymes (ArMs). When bound within the stereogenic protein scaffold, such synthetic cofactors hold the potential of equipping the active site metal centre with enhanced reactivity and high enantio- and/or regio-selectivity. To date, ArMs comprised of myoglobin and salophen complexes have only been employed in sulfoxidation reactions, therefore, the full scope of such systems as biohybrid catalysts remains underexplored [2]. Here we show that myoglobin acts as an efficient protein scaffold for non-covalent binding of Fe(III)-, Mn(III)- and Co(III)-salophen derivatives. Reconstitution of further rationally designed myoglobin variants with these metal-Schiff base complexes permits access to a new ArM candidate library. Spectroscopic (UV-vis, CD, fluorescence) as well as spectrometric tools (native nanoESI-MS) are used to monitor structural changes in the ligand-protein assembly and confirm the binding of metal-salophen complexes within the protein scaffold. Electrochemical studies have been undertaken to inform the potential range of catalytic reactions that could be accessed.

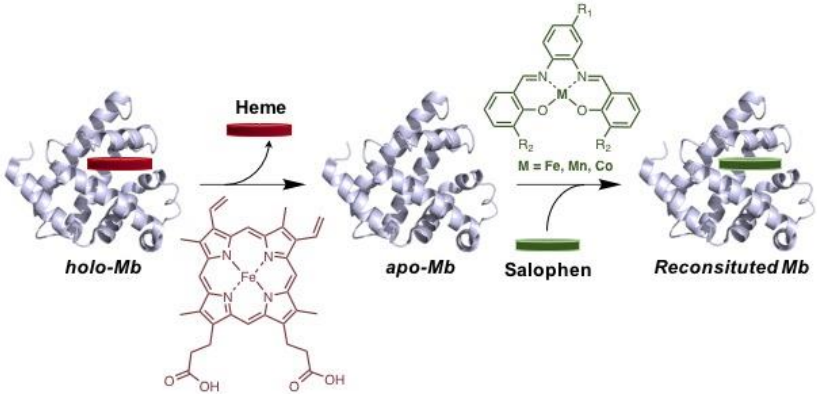

Figure 1. Reconstitution of myoglobin with synthetic salophen complexes.

Acknowledgements: This work was supported by funding from the UKRI (MR/S017402/1), the BBSRC through an EastBio DTP studentship to Evelinaa Venckute and an RSC Research Enablement Grant.

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Anti-cancer stem cell metal complexes

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Keywords: bioinorganic chemistry, medicinal inorganic chemistry, cancer stem cells

Cancer stem cells (CSCs) are a distinct population of tumour cells that have the ability to self-renew, differentiate, and form metastatic tumours [1]. CSCs effectively evade conventional chemotherapy and radiotherapy as these treatments specifically target fast growing cancer cells, and CSCs, due to their stem cell-like properties, divide more slowly [2]. After surviving treatment, CSCs are able to regenerate the original tumour and/or produce invasive cancer cells that are able to colonise distant organs. For these reasons, CSCs are widely thought to be responsible for cancer relapse. Therefore, to provide a durable response and prevent tumour recurrence, chemotherapeutics must have the ability to remove the entire population of cancer cells, including CSCs. Therapeutic strategies capable of selectively killing CSCs and disrupting the microenvironments supporting these cells are the focus of several research programmes [2]. Potential CSC therapeutic targets such as cell surface markers and various deregulated signalling pathways have been identified, but there is still no clinically approved drug that specifically kills CSCs at safe doses.[2] Most of the compounds undergoing pre-clinical or clinical investigation as CSC-specific agents are completely organic in nature.

Recent work by our group and others has shown that metal complexes are capable of potently and selectivity killing CSCs at clinically relevant concentrations [3-6]. Here we present a series of novel copper(II)-dithiacyclam and gold(I)-triphenylphosphine complexes bearing nonsteroidal anti-inflammatory drugs that can specifically kill CSCs *in vitro* and provide insight into their mechanism of action [6-7]. The ability of the gold(I)-triphenylphosphine complexes to inhibit tumour growth in a murine metastatic triple-negative breast cancer model will also be presented [7].

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Studying Metal Complexes in Biological Environments: Inorganic Chemical Biology

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Keywords: catalytic anti-oxidants or SOD mimics/mimetics, oxidative stress, mass spectrometry, X-fluorescent imaging, metal-carbonyle

Metal complexes are increasingly used for biological applications, as metal-centered probes for imaging or as metal-based drugs [1]. To be active a metal complex must reach its biological target that can be embedded in cells or organelles. The metal speciation in low-molecular weight complex, its intracellular quantification and intracellular distribution through imaging, as well as the evaluation of its activity directly in a cellular environment are key questions to be taken into account in the design of metal complexes with a bio-activity. They can be analyzed through the study directly in a cellular environment. These approaches can be delineated as “inorganic chemical biology”.

The talk will first discuss a series of Mn-complexes designed to reproduce the activity of the cell’s protective anti-oxidant metalloenzymes, the superoxide dismutases, so called SOD mimcs [2,3]. We will show how cellular models can be designed to evaluate their activity [4–6], and how chemical analyses through different approaches in mass spectrometry can help quantifyting and determining metal speciation [7,8].

We will then focus on application of metal-based probes and their use for multimodal imaging [9–11]. More specifically, probes consisting of a central metal-CO core, called SCoMPIs (for single core multimodal probes for imaging), can be mapped using unconventional imaging techniques such as IR and X-fluorescence imagings. Several examples, including a SOD mimic conjugated with a $Re(CO)_3$-based probe (and vector) [12], $Re(CO)_3$-based organelle trackers [13,14].

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CONFERENCIAS NACIONALES / INVITED LECTURES

Mimetics of defence enzymes against ROS: from aza-macrocyclic complexes to nano-structured systems

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Keywords: Polyamines, SOD, Catalases, macrocycles, Cu(II), Fe(II), Mn(II)

Manganese and copper have a prominent biological role participating in numerous biological processes, most of them related to dioxygen management and electron transfer. Among these functions, copper is involved as the electroactive metal in the active site of protective SOD1 and SOD3 enzymes, which along with the Mn-enzyme SOD2, are in charge of regulating superoxide radical concentration in mammals, getting rid of excess amounts of superoxide anions through their dismutation into hydrogen peroxide and dioxygen. Superoxide is the first product coming out from the reduction of dioxygen to give water. Imbalances between generation and clearance of superoxide anions give rise to the formation of all other Reactive Oxygen Species causing oxidative stress, which is related to a variety of health issues that include neurodegenerative disorders such as Parkinson's, Alzheimer's and Huntington's disease [1]. Administration of SODs is however not useful for therapeutic treatment due to their drawbacks such as the absence of oral activity. It has been reported that several copper complexes of aza-macrocyclic ligands have SOD activity in vitro which rank among the highest ones so far reported for synthetic systems [2,3]. A step forward to improve the activity, the likely-cell uptake and bio-distribution of these low molecular weight mimetics might be their incorporation in non-toxic nanoparticles. The grafting of the molecules to the surface of the nanoparticles may yield pre-concentration and amplification of the signal. Here we discuss the chemistry of Mn^{2+} and Cu^{2+} aza-macrocyclic complexes appropriately functionalized to permit their covalent anchorage to boehmite oxidic nanoparticles [4], and the parameters regulating the general SOD activity enhancement observed.

Acknowledgements: Funded by the Spanish MICIN, National Research Agency, FEDER funds from the EU (PID2019-110751RB-I00, RED2018-102331-T) and the Conselleria de Innovación, Universidades, Ciencia y Sociedad Digital of the Generalitat Valenciana (PROMETEO Grant CIPROM/2021/030). This contribution is also supported by COST Action CA18202 – NECTAR (European Cooperation in Science and Technology).

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Complejos de bases Schiff con Re(I)/Tc(I) y Ga(III) en el Diseño de Radiofármacos

A. Lorenzo-Martínez, S. Argibay, R. Carballo, E.M. Vázquez-López

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Palabras clave: Galio(III), Renio(I), Tecnecio(I), Bases de Schiff

El uso de radionúclidos en el diagnóstico de patologías de muy diversa naturaleza es una herramienta fundamental para la adopción de un determinado tipo de terapia. El diseño y obtención de este tipo de medicamentos viene determinado por la naturaleza del elemento usado, mayoritariamente metales y la necesidad de conseguir preparaciones extemporáneas en medios biocompatibles. En definitiva, en la mayoría de los casos, la obtención del radiofármaco implica la formación de un compuesto de coordinación con unas características estructurales determinadas.

Debe tenerse en cuenta además, que para la mayor parte de este tipo de fármacos en uso clínico, la capacidad de penetración en los tejidos/órganos es diferente según esté sano o enfermo permitiendo así evaluar el estado funcional del mismo. Sin embargo en algunos tipos de enfermedades, como por ejemplo el cáncer, sería deseable que el radiofármaco presentara una alta afinidad por biomoléculas directamente relacionadas con esa patología de forma que permitieran determinar la distribución y localización de las áreas enfermas.

En nuestro grupo de investigación, hemos abordado el diseño de radiofármacos con afinidad específica basados en ligandos bases de Schiff usando diferentes aproximaciones sintéticas y centros metálicos de Re(I)/Tc(I) y Ga. Los resultados más relevantes serán examinados en esta comunicación.

Agradecimientos: Ministerio de Ciencia e Innovación (PID2019-110218RB-I00)

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

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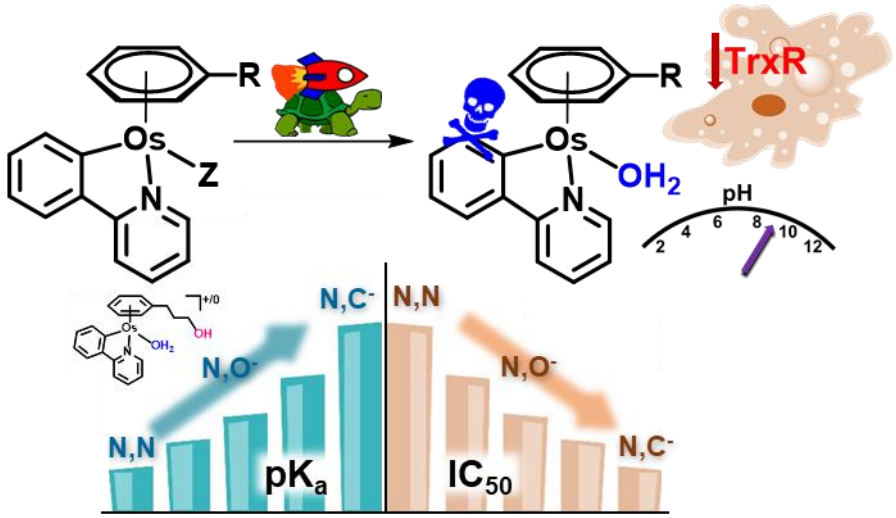
Complexes of the formula [Os(η^6-arene)(C,N-phenylpyridine)Z] (where Z is chlorido or a tethered oxygen) undergo very fast Os−Z hydrolysis (<5 min), and the high basicity of the coordinated water molecule of the aqua adducts (Os−OH_2; pK_a > 8) very much contrasts with previously reported Os-aqua adducts bearing NN- and NO-chelating ligands (pK_a < 6) [1]. The Os−Cl bond is unreactive in pure DMSO, yet the complexes readily form DMSO adducts upon aquation when dimethyl sulfoxide is present. Such a peculiar aqueous behavior is directly related to the negatively charged CN ligand. Potent Os-CN compounds (but not their Os-NN analogues) are particularly reactive; they bind to cysteine in vitro and decrease the activity of thioredoxin reductase (TrxR) in living cancer cells [2].



By revealing some interesting structure−activity relationship on Os-CN vs Os-NN complexes, we start uncovering the molecular rationale for the successful biological applications of osmium(II) half-sandwich compounds.

Acknowledgements: We acknowledge funding from the EC (FP7-PEOPLE-2013-CIG, no. 631396), from the Spanish MINECO (RYC-2012-11231, SEV-2016-0686, CTQ2017-84932-P, and PID2020-117766GB-I00), and the Comunidad Autónoma de Madrid (Scholarship PEJD-2016/IND-2608 and Professorship of Excellence 2016-T3/IND-2054).

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Biopolymer-Metal-based Hydrogels for Biomedical applications

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Keywords: hydrogels, amyloid nanofibers, metallic nanoparticles, biomedical applications

Our work explore the synthesis of hydro- and aerogels based-on biopolymers, such as amyloid proteins, bacterial cellulose and polysaccharides, to address specific health challenges. Taking advantage of their extraordinary properties: biocompatibility, antibacterial, biodegradability, absorbency, and skin compatibility, biopolymer hydrogels are more sustainable than the oil-derived traditional ones.

The use of protein and polysaccharide-based hydro- and aerogels meet the increasing demand of eco-friendly products, conjugating the reduction of the environment impact with increasing material biocompatibility. Furthermore, the use of natural renewable biopolymer sources and inorganic nanoparticles will provide new advanced functionalities, such as antibacterial, cell growth, wound healing, tissue engineering and drug delivery. Herein, we show the use of different biopolymers to form hydro- and aerogels incorporating different metallic nanoparticles (Figure 1) thus introducing new functionalities in these fascinating biomaterials with potential new applications.

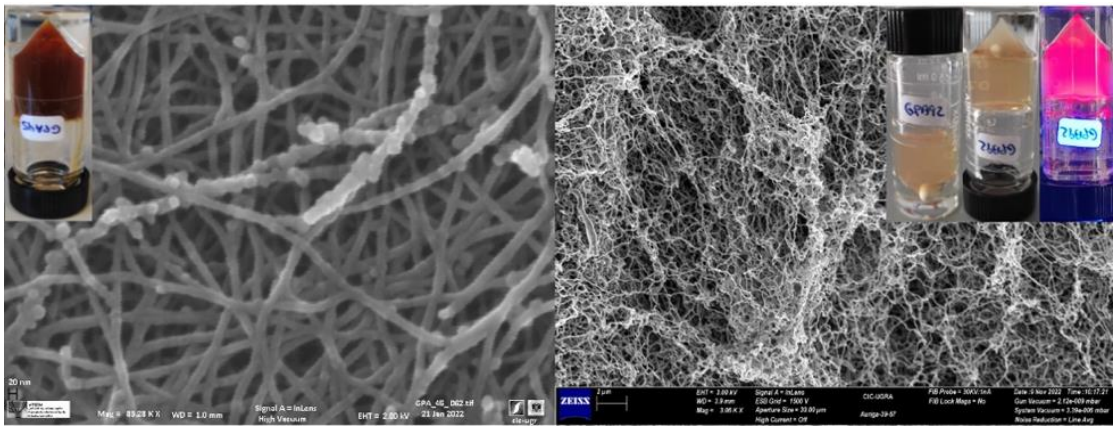

Figure 1. SEM images of: (left) Maghemite- and (right) QD-functionalized protein-hydrogel.

Acknowledgements: This work was funded by the Junta de Andalucía Project P11- FQM-8136 and MINECO Project CTQ2015-64538.

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Theranostic Systems based on Multifunctional Nanostructured Materials loaded with Metallodrugs

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Keywords: theranosis; metallodrugs; nanomaterials; anticancer; antimicrobial

Theranosis (*ther*apy + diag*nosis*) is the combination of therapy and diagnosis and is being currently applied in biomedicine in a wide variety of diseases, especially in cancer, because an early and easy diagnostic is as important as a good therapeutic approach. Therefore, an interesting and appropriate delivery system should combine the therapeutic (drugs) with the diagnostic (molecular imaging fragments) in a single platform. In this context, in recent years our group started to combine the therapeutic properties of metallodrugs of different metals with different imaging agents to tackle cancer or bacterial infections. Thus, we have recently described the preparation of several theranostic systems based on mesoporous silica nanoparticles (MSN) or fibrous silica particles (FSP) functionalized with organotin(IV) compounds or copper(II) agents, which, adequately decorated with targeting agents, have been studied both *in vitro* and *in vivo* in different cancer or bacterial models with promising results. In this communication, our latest results in the field will be described, paying special attention not only to the synthesis and characterization methods but also to the influence of the different structural features on the biological activity against the studied diseases.

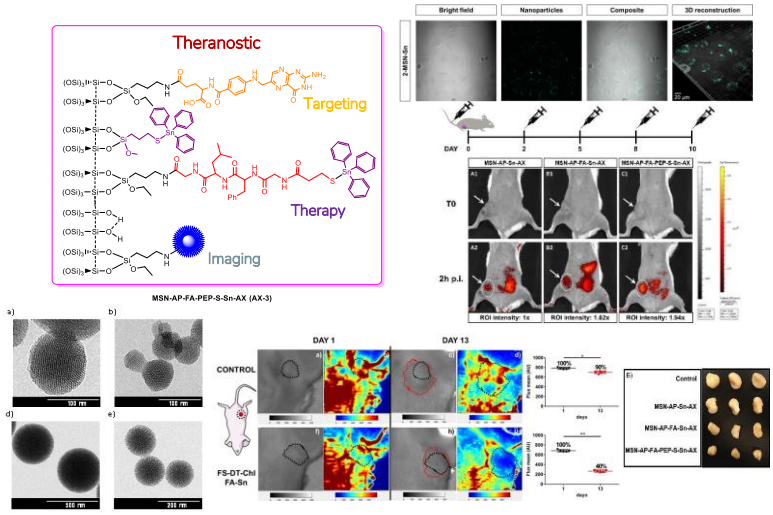

Figure 1. Theranostic properties of nanomaterials functionalized with organotin(IV) compounds.

Acknowledgements: We would like to thank MCIN/ AEI /10.13039/501100011033/ and by "ERDF A way of making Europe" for the project RTI2018-094322-B-I00 and the MCIN/ AEI /10.13039/501100011033/ for the Research Network "Red Metalbio 2022" RED2022-134091-

COMUNICACIONES ORALES / ORAL COMMUNICATIONS

An Ir(III)-Phthalocyanine Conjugate as Advanced Photosensitiser for Photodynamic Therapy

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Keywords: Iridium(III), phtalocyanines, PDT, drug design, anticancer agents, nanoencapsulation

Phthalocyanines (Pcs) present an excellent ability to act as photosensitizers (PS) in photodynamic therapy (PDT) [1]. Herein, we report the synthesis of a new zinc-phthalocyanine derivative bearing attached a cyclometalated iridium complex (**Ir-ZnPc**) (Figure 1) and its encapsulation into amphoteric polyurethane–polyurea hybrid nanocapsules (**Ir-ZnPc-NCs**) with the aim of developing novel nanoPDT agents. The photogeneration of cellular oxidative stress by **Ir-ZnPc-NCs** under both normoxia and hypoxia will be discussed in comparison with a reference ZnPc without iridium complex.

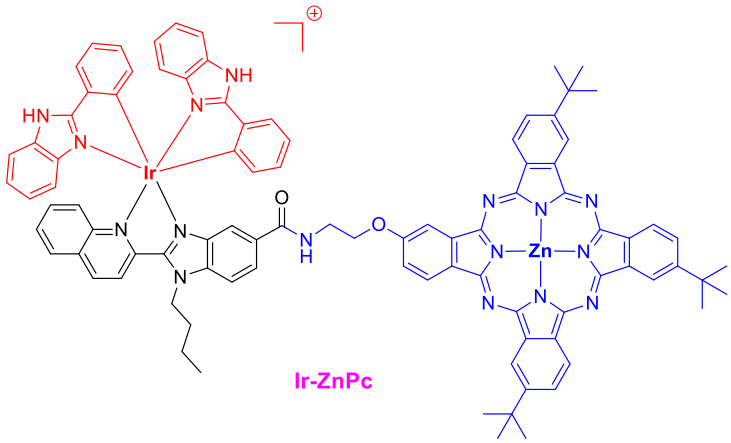

Figure 1. Structure of the new Ir-ZnPc conjugate.

Acknowledgements: this work was supported by funds from the Spanish Ministerio de Ciencia e Innovación-Agencia Estatal de Investigación (MCI/AEI/10.13039/501100011033) and FEDER funds (projects PID2020-117508RB-I00, PID2021-122850NB-I00). E.O.-F. thanks AECC (PRDMU19003ORTE).

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Exploring chirality in fighting-cancer metallodrugs

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Keywords: chirality, amino-oxime ligands, glyco-conjugation, antimetastatic metallo-drugs

Cancer is the second most frequent cause of death in the world. Research on a variety of metal compounds has demonstrated that the unique properties of metal ions can be exploited for anticancer-drug design [1]. The incorporation of active biological ligands in the metal compound is well-documented: Metallo-drugs can exhibit differential target binding affinity and biological activity compared to their parent organic ligands, but they can, as well, fine-tune toxicity and affect other properties, such as antimetastatic behavior. Within this context, the stereochemistry of metal compounds has been recognized to have an important role in determining cytotoxicity, and should be considered in the design, modification, and improvement of active compounds [2]. On the other hand, hydrogen bonding can improve solubility in water and effectively enhance site and base recognition, not only of nucleic acids but also of proteins and enzymes that are crucial to metastatic processes. In this regard, glycoconjugation is an anticancer strategy that has gained great interest in recent years. The presence of carbohydrates can improve water solubility but also allow selective interactions with carbohydrate-binding proteins involved in cell adhesion, migration, and angiogenesis-related processes, all closely related events to metastasis [3].

In this communication, recent results from the research group will highlight some strategies used in the design of Ti(IV), Ru(II), and Pd(II) compounds containing chiral ligands with strong hydrogen-bonding abilities. The results will be discussed with a special focus on some derivatives that have shown relevant antitumor activity *in vitro* and *in vivo*. We will report the results obtained with two types of ligands: on the one hand, we have used optically active amino oxime ligands derived from natural terpenes and, more recently, glycoconjugated scaffolds based on polypyridyl chelating ligands, which are being investigated as potential targets for the stabilization of DNA-G4 quadruplexes [4].

Acknowledgements: Funding from Spanish MICINN (PID2019-108251RB-I00) and UAH (PIUAH22/CC-028, CCG20/CC-026) is gratefully acknowledged. ETR is grateful to MICINN for her FPU/03617 fellowship.

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Breast Cancer Stem Cell Potent Copper(II) Coordination Complexes

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Keywords: metallopharmaceuticals, cancer stem cells, copper, phenanthroline, reactive oxygen species

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 [2,3].

CSCs maintain low intracellular levels of reactive oxygen species (ROS) [4]. 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 polypyridyl and Schiff base or hydroxyaldehyde ligands [5-7]. 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 resulting in breast CSC death. Our work shows that redox modulation of CSCs using coordination copper complexes could be an effective therapeutic method to pursue.

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Highly Efficient Cleavage of DNA Replication Foci in Cell Nuclei by ATCUN-Functionalized Peptide Helicates

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Keywords: non-canonical DNA; DNA nucleases; anticancer drugs; helicates; metallopeptides

Recently, we have completed a research project on the design of a series of Cu(II) peptide helicates that show extremely selective nuclease activity towards 3WJ-DNA *in vitro*, and are also capable of cleaving DNA replication foci into functional nuclei, thus acting as selective metallo-nucleases for 3WJ-DNA *in cellulo* [1,2]. To our knowledge, this is the first example of a nuclease agent selective for DNA-3WJ, both *in vitro* and *in cellulo*. Moreover, the amino-terminal Cu(II)/Ni(II) binding motif (ATCUN) is a small metal-binding site found at the N-terminus of many natural proteins and exhibits excellent dsDNA cleavage properties as well as antitumor activity due to ROS formation. We believe that the efficiency of 3WJ cleavage by our Cu(II) peptide helicates could be improved by adding an ATCUN motif at the N-terminal end of the peptide strand (Figure 1) and in this communication we present our findings on this research project.

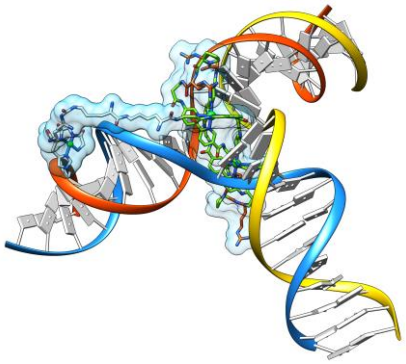

Figure 1. Hypothetical model of an ATCUN-derived peptide helicate bound to a DNA-3WJ.

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Metal-DNA Nanosystems with Programmable structures

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Keywords: DNA, silver, nanostructures, nucleobases, Watson-Crick.

The ability to control the shape and size of DNA-based systems allows high versatility to design and prepare customized nanostructures with biological applications [1]. In addition, if these DNA nanostructures can host metal ions at specific locations without changing their structural organization, such as Ag(I), high-organized metal nanostructures could be obtained, holding new physicochemical properties and opening new development fields for application in nanotechnology and biomedicine.

This communication presents the results of a novel strategy we developed to create customized and stable Ag-DNA structured nanosystems. The challenge is to prepare metallized nanostructures *on demand* following natural DNA self-recognition rules, i.e., complementary base recognition. These new systems could act as delivery systems of Ag(I) ions in living organisms, as DNA structures can be customized to penetrate cell membranes.[1b] To demonstrate the viability of this methodology, we have initially prepared a DNA junction (Holliday Junction) where Ag(I)-coordination bonds replace Watson-Crick hydrogen bonds between base pairs (Figure 1). To do this, we have used deaza-DNA molecules where 7-deazaadenine and 7-deazaguanine bases replace purine bases (adenine and guanine). This modification allows the natural hybridization of the strands and the interaction of Ag(I) inside the double helix forming silver-modified base pairs without changing its natural pairing organization [2].

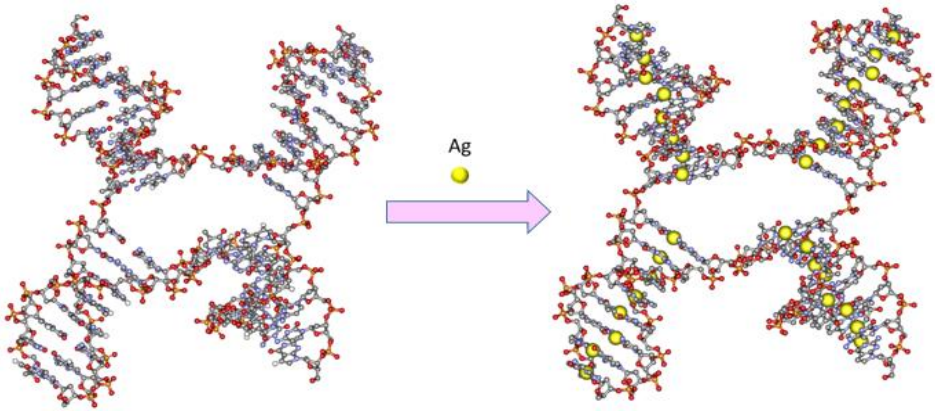

Figure 1. Structure of DNA Junction formed by base pairs mediated by Ag(I).

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Complejos Dinucleares de Pd(II)/Ditiobiurea con Potencial Actividad frente a Cáncer Gástrico

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Palabras clave: paladio, ditiobiurea, cancer gástrico, cisplatino

El cáncer de estómago o cáncer gástrico es uno de los de mayor incidencia y mortalidad a nivel mundial y aunque los tratamientos principales se basan en cirugía, la quimioterapia adyuvante con cisplatino es necesaria en muchos casos [1].

Los fármacos de platino en clínica presentan limitaciones que han impulsado la búsqueda de nuevos compuestos metálicos con mayor eficacia y/o selectividad. Una de las vías de investigación se basa en el desarrollo de compuestos usando iones metálicos del grupo del platino con ligandos de interés farmacológico. En este sentido ligandos derivados de tioamidas, como las tiosemicarbazonas, han despertado un gran interés por sus características químicas, reactividad y propiedades biológicas, sin embargo, las ditiobiureas, $[–NH(CS)NH-]_2$, han sido escasamente estudiadas [2].

En este trabajo hemos diseñado compuestos dinucleares de Pd(II) con ligandos ditiobiurea y coligandos cloruro y trifenilfosfina (Fig. 1). Uno de los complejos sintetizados muestra citotoxicidad selectiva en células AGS (adenocarcinoma gástrico) comparado con HEK293T (células embrionarias humanas de riñón) y AC16 (cardiomioblastos humanos). También presentamos estudios de su interacción, con modelos de ADN, y el análisis del ciclo celular, por citometría de flujo, que sugieren que el compuesto puede tener otras dianas además del ADN.

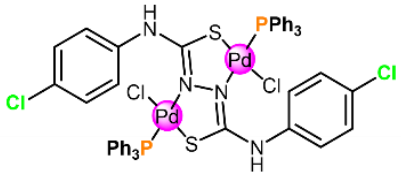

Figura 1. Representación del complejo derivado del ligando 1,6-(4-clorofenil)-2,5-ditiobiurea

Agradecimientos: Trabajo financiado por el Ministerio de Ciencia, Innovación y Universidades (PID2019-106220RB-I00, RED2018-102471T) y COST Action NECTAR CA18202.

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Novel Ru-Coumarin Photosensitizers for Combating Hypoxic tumors with PDT

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Keywords: metallodrug, coumarin, PDT, photosensitizer, hypoxia

A new family of photosensitizers (PSs) has been developed by taking advantage of the well-established anticancer properties of transition metal complexes and of the rich and tunable photophysical properties of coumarin fluorophores [1]. The compounds are non-toxic in the dark but become highly phototoxic when irradiated at different wavelengths within the phototherapeutic window, even with highly-penetrating far-red and NIR light. In general, the Ru-coumarin PSs exhibited IC_{50} values in the very low nM range (e.g., 7.4 nM at 645 nm) and impressive PI values (PI > 34000) after red light irradiation. In addition, the PSs display a good phototoxicity profile with highly penetrating NIR light (e.g., IC_{50} = 0.26 μM at 770 nm), and retain an excellent photoactivity under hypoxia, being particularly phototoxic in light-window of 540-670 nm (PI values around 2900-3300). Finally, it is worth noting that the PSs are aqueous-soluble, highly photostable and can be prepared in high purity from straightforward syntheses, which are also highly desirable attributes for further preclinical development. Thus, the newly developed PSs are promising candidates for treatment of large and deep-seated hypoxic tumors, which is the cornerstone of PDT.

Acknowledgements: This work was supported by funds from the Spanish Ministerio de Ciencia e Innovación-Agencia Estatal de Investigación (MCI/AEI/10.13039/501100011033) and FEDER funds (PID2020-117508RB-I00), the Departament de Recerca i Universitats de la Generalitat de Catalunya (2021 LLAV 00083) and the Fundació Bosch i Gimpera (F2I-PdC_2022-007).

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Platinum Complexes for Combined Chemotherapy and Immunotherapy

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Keywords: Bioinorganic Chemistry; Cancer; Chemotherapy; Immunogenic Cell Death; Medicinal Inorganic Chemistry

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

Acknowledgements: J.K. gratefully acknowledges the financial support with a Liebig fellowship from the Chemical Industry Fund of the German Chemical Industry Association.

Controlled Release of Single-Stranded DNA from Protein-Coated Gold Nanoparticles

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Keywords: DNA, gene delivery, gold nanoparticle, laser-triggered response, protein corona

Gene and antisense therapy works at the genetic root of a disease by replacing or deactivating defective or harmful genes. In the pursuit of higher therapeutic efficiency, the future of gene therapy relies on the design of delivery vectors that are selective, protect the transported oligonucleotides from degradation and allow “on-command” release of the cargo [1]. Gold nanoparticles are interesting gene delivery carriers due to their biocompatibility, well-known bioconjugation chemistry, and optical properties, the latter allowing light-responsiveness [2].

In this communication, we present our latest results on the preparation of gold nanoparticles with double-stranded DNA and a protein corona for light-triggered gene therapy, and the subsequent thermal and photothermal release studies.

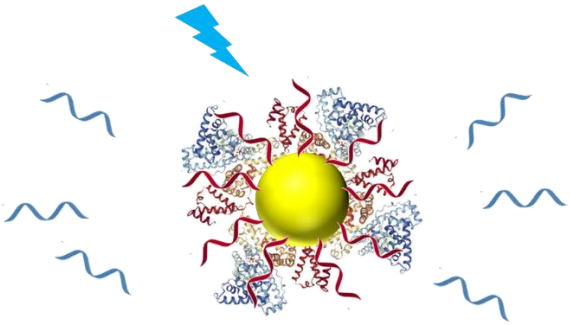

Figure 1. Light-responsive release of genetic material.

Acknowledgements: Financial support by Ministerio de Ciencia e Innovación of Spain (Project PID2020-115537RB-I00) is kindly acknowledged.

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Synthesis and biological evaluation of novel Re(I) complexes against cancer cells and *Caenorhabditis elegans*

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Keywords: Rhenium(I), 4-dimethylaminopyridine, anticancer activity, apoptosis, C. elegance.

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

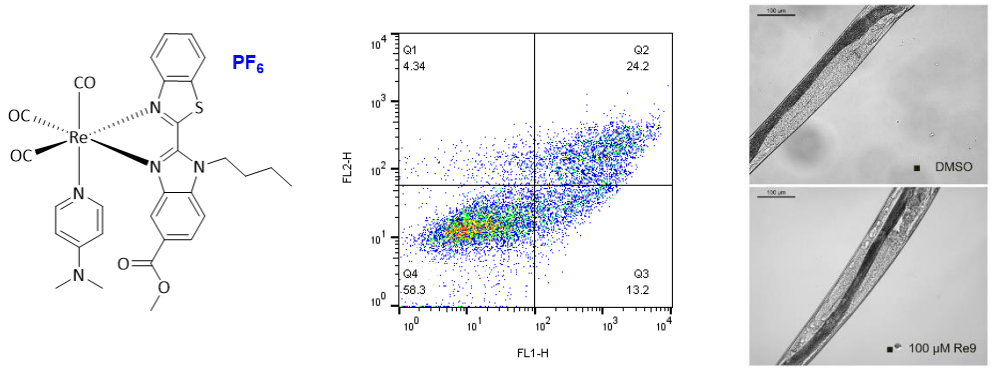

Figure 1. Structure of Re(I) compound inducing apoptosis and reducing gonad tumor growth in *C. elegnas.*

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

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Platinum Iodido complexes affect mitochondrial function and induce ROS and senescence in gastrointestinal cancer cells

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Keywords: Platinum Iodido Complexes, ROS, Metabolism, Senescence, Mitochondria.

Gastrointestinal cancers are one of the main leading causes of cancer death worldwide, and while platinum-based compounds represent the most common selected chemotherapy used for these types of cancer, problems such as high toxicity and resistance are commonly associated with these treatments. Thus, the development of new antitumor metallodrugs able to overcome different clinical barriers in platinum-based chemotherapy is a public healthcare priority [1]. We studied the mechanism of action of the isomers *trans* and *cis*-[PtI_2(isopropylamine)$_2$] (I5 and I6, respectively) against gastrointestinal cancer cells (i.e., gastric, and pancreatic cancer). We demonstrate that both I5 and I6 modulate mitochondrial metabolism, decreasing OXPHOS activity (and glycolysis in the case of I5), and negatively affect ATP-linked oxygen consumption rate. Consequently, I5 and I6 generated Reactive Oxygen Species (ROS) in a more efficient way than cisplatin, provoking oxidative damage and eventually the induction of senescence (β-galactosidase, CDKN1A, IL-6, MMP1 induction). Thus, herein we propose a triple accumulative loop with three interconnected processes modulated by these iodido agents: (i) mitochondrial dysfunction and metabolic disruptions; (ii) ROS generation and oxidative damage; and (iii) cellular senescence (Figure 1). Our results indicated that both iodido agents represent new potential chemotherapeutics for gastrointestinal cancers, warranting future preclinical studies in animal models of gastrointestinal tumors.

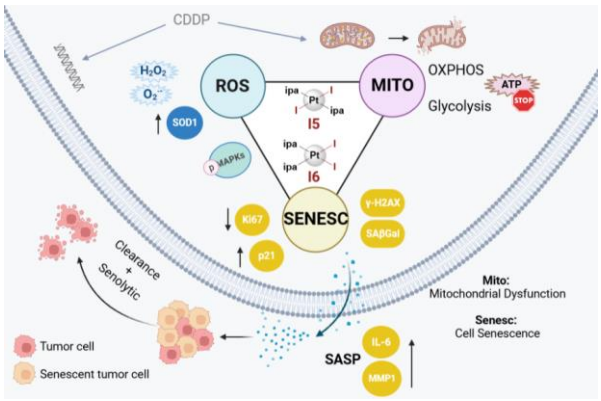

Figure 1. Graphical Summary.

Agradecimientos: This research was funded by Spanish MICINN grant number PID2019-106220RB100. JMH FPI-UAM 2021 from UAM (Molecular BioSciences PhD programme).

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Silver-based Terpyridine Complexes as Antitumor Agents

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Keywords: Cancer; Cytotoxicity; Silver; Polynuclear compounds; Terpyridine

The antimicrobial properties of silver compounds and nanoparticles have been widely recognised and have been incorporated into medicinal drugs due to their high antimicrobial activity. However, in recent years, it has been observed that silver complexes also exhibit good cytotoxic activity against many cancer cells. Furthermore, the synthesis of silver(I) compounds has gained importance because of their lower toxic effects on healthy cells and promising anticancer effects.

The study of the anticancer properties of silver complexes with terpyridine or tetra-2-pyridinylpyrazine ligands is scarce, despite the possibilities of combining the properties of the metal and the ability of the ligands for DNA binding. We study, the antiproliferative activity, stability, CT-DNA binding and mechanism of cell death of these types of derivatives. High cytotoxicity against different tumour cells was observed, and, more important, a great selectivity index has been detected between tumour cells and healthy Lymphocytes T for some of these compounds. The CT-DNA interaction study has shown that these derivatives are be able to interact with CT-DNA via moderate intercalation. Furthermore, cell death studies indicate that these derivatives promote the apoptosis *via* mitochondrial pathway. Therefore, we consider that these results contribute to corroborate that silver derivatives have a great potential for the future development of new anticancer agents [1].

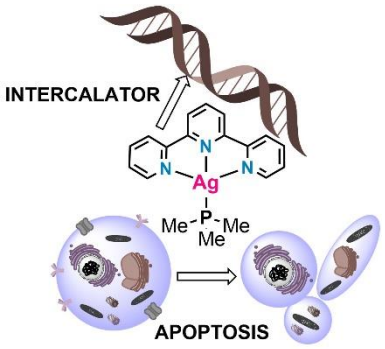

***Figure1**: Mechanism of action of silver complexes*

Acknowledgements: Authors thank the Agencia Estatal de Investigación (AEI), projects PID2019-104379RB-C21, PID2019-104379RB-C22 / AEI /10.13039/501100011033 for financial support.

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New β-Carboline-based Ir(III) and Ru(II) photosensitizers with mitochondria-targeted anticancer activity

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Keywords: Photodynamic Therapy; Iridium; Cancer.

In this work, we synthesize and characterize three Ir(III) complexes **1-3** of general formula $[Ir(ppy)_2(N\text{^}N')]Cl$ (N^N' = β-Carboline; ppy = 2-phenylpyridinate) and six Ru(II) complexes **4-9** of general formula $[Ru(bpy)_2(N\text{^}N')](PF_6)_2$ or $[Ru(TAP)_2(N\text{^}N')](PF_6)_2$ (N^N' = β-Carboline; bpy = 2,2'-bipyridyl; TAP = 1,4,5,8-tetraazaphenanthrene).

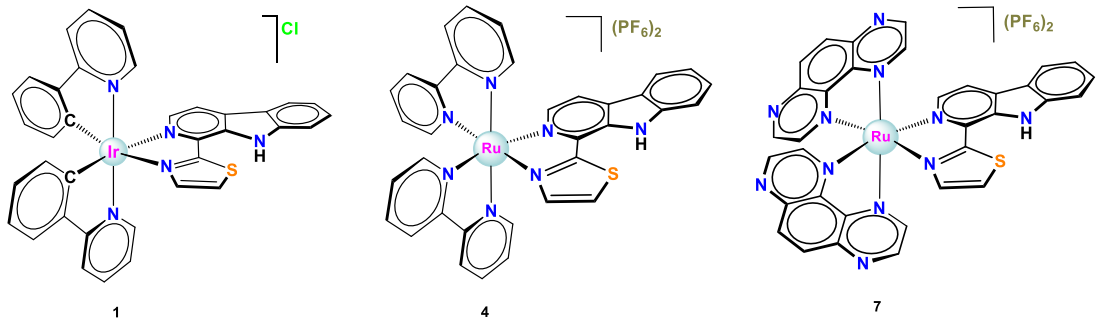

Figure 1. Molecular structure of **1**,**4** and **7**.

The cytotoxic activity of these complexes was evaluated in five different human cell lines under either dark conditions or light irradiation. Ir(III) complexes **1**-**3** exhibit lower $IC_{50,light}$ values in the nanomolar range under blue light irradiation and phototoxicity indexes (PI) around 100. Furthermore, **1**-**3** showed fast uptake by the cells and accumulation in mitochondria and lysosomes. The generation of reactive oxygen species (ROS) inside the cells leads to mitochondrial dysfunction, lysosomal damage, and cell death by apoptosis.

Acknowledgements: We want to acknowledge funding from Ministerio de Ciencia, Innovación y Universidades (PID2021-127187OB-C21) and from Universidad de Burgos (2019/00002/008/001).

Biscyclometalated Ir(III) Complexes with π-extended C^N ligands as Potent Anticancer PDT Agents

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Keywords: anticancer, photodynamic therapy, iridium, π-extended.

Octahedral Ir(III) complexes have been widely studied in medicinal chemistry as luminescent probes and/or anticancer agents. Some of them have shown anticancer activity under light irradiation via $^1O_2$ photoproduction, through a process named photodynamic therapy (PDT) [1]. In this work, new octahedral Ir(III) complexes with π-extended ligands have been prepared (Figure 1) and their anticancer activity explored.

Complexes **1** and **2** differ in only one fused ring in the C^N ligand, but **1** has a high fluorescence emission while **2** has a very low emission (ϕ_{em} = 8.9 and 0.1% respectively). The quenching in **2** could be due to a higher degree of aggregation through the C^N ligands, as it was observed in solution (^{1}H NMR and fluorescence emission) and in solid state (X-ray difraction). Both complexes are good $^1O_2$ photosensitizers (ϕ_Δ = 41 for **1** and 91% for **2** under blue light). Biological studies in different cancerous cell lines show cytotoxicity in the dark for both complexes ($IC_{50} \leq 3$ μM) and under blue light this cytotoxicity was improved in both cases (PI = $IC_{50,dark}/IC_{50,light}$ up to 140). Differences in the internalization degree were observed for **2** depending on the specific cell line (ICP-MS studies). The high emission of **1** enabled us to confirm, by confocal microscopy, that drugs are accumulated in mitochondria. After that, light irradiation causes an intracellular ROS increment which finally induces the cell death.

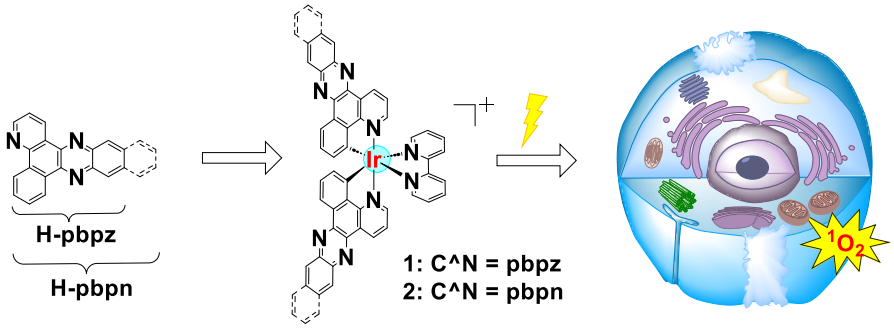

Figure 1. Cell death via mitochondrial damage by $^1O_2$ photosensitizers.

Acknowledgements: MICIN-FEDER (RTI2018-100709-B-C21 and RTI2018-100709-B-C22), Junta de Comunidades de Castilla-La Mancha-FEDER (JCCM) (grant SBPLY/19/180501/000260). C. G.-N. thanks to FSE+ founds and Plan Propio de I+D+i-UCLM for a predoctoral contract (2022-PRED-20649).

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Nucleobases as coformers in pharmaceutical multicomponent solids involving diclofenac

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Keywords: Pharmaceutical multicomponent materials, diclofenac, nucleobase.

The long, tedious and expensive process of developing new drugs has forced the pharmaceutical industry to explore alternative strategies to improve the properties of already-known drugs. In this field, pharmaceutical multicomponent materials have demonstrated incredible potential with a collection of new solids with tailored properties already approved by FDA and EMA [1].

Diclofenac (DIC) is a non-steroidal anti-inflammatory (NSAID) drug widely used for the treatment of pain and inflammatory diseases. However, due to its poor solubility, the use of high dosage is necessary to achieve the minimal effective concentration, increasing the probability of side effects [2]. In this work, DIC was used in the formulation of three novel multicomponent solids with the nucleobases Adenine (ADE), Cytosine (CYT) and Isocytosine (ICT) as coformers. Fast and inexpensive syntheses were conducted by liquid-assisted grinding (LAG), while crystal structures were characterized by X-Ray diffraction (XRD) techniques. Differential scanning calorimetry (DSC), stability and solubility studies demonstrated enhanced solubility and thermal stability for the new DIC-materials as a consequence of the DIC:DIC dimer disruption, present in the parent drug, and the crystal morphology observed in the novel materials [3].

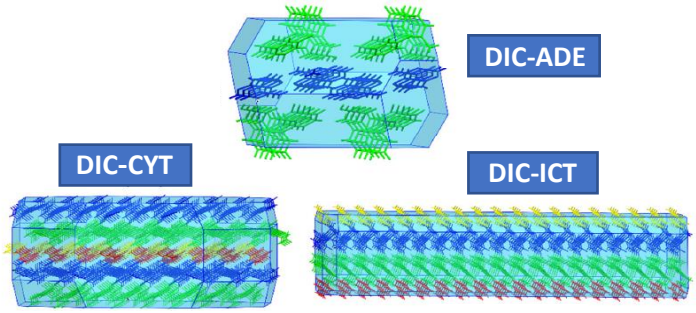

Figure 1. BFDH-predicted morphologies of cocrystals.

Acknowledgements: This work was funded by the project B-FQM-478-UGR20 (FEDER-UGR, Spain).

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Gold Compounds as *cys*-targeting Inhibitors: Mechanisms and New Directions

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Keywords: gold, protein inhibition, catalysis, C-S coupling, bioconjugation

Gold-based compounds have promising applications in chemical biology, being able to selectively inhibit distinct classes of disease-related proteins and enzymes. Over the years we have developed structurally-diverse Au(I) and Au(III) compounds with diffferent ligands such as phosphines, N^N-bidentate ligands, and cyclometallated compounds as metalloprotein inhibitors, with a particular interest in viral and cancer-related zinc finger (ZnF) proteins [1–3]. We have also dedicated significant effort into understanding the mechanism of ZnF inhibition, making use of "dual-probe" (Au, Zn) X-ray absorption spectroscopy (XAS), time-dependent density functional theory (TD-DFT) and traveling wave ion mobility (TWIM) mass spectrometry (MS) as powerful tools for elucidating the differential substitution pathways of Au(I) and Au(III) compounds reacting with biologically relevant ZnFs [2,3].

In terms of biological endpoints, the series of gold(I)-phosphine compounds was shown to selectively inhibit growth of the tumorigenic CEM leukemia cell line, with low micromolar IC_{50} values. An analysis of the effects of $[Au(dmap)(Et_3P)]^+$, where dmap = 4-dimethylaminopyridine, on protein expression profile of treated CEM cells revelead proteolytic degradation of caspase-3 and poly(ADP-ribose)-polymerase (PARP), DNA strand-break induced phosphorylation of Chk2 Thr68 and increased p53 ser15 phosphorylation, a wide range of cellular responses that activate apoptosis [4].

More recently we found that the cyclometallated gold(III) compound $[Au(bnpy)Cl_2]$ inhibits the full-length HIV NCp7 ZnF by a brand new reaction mechanism, a C–S coupling to cysteine residues [5]. Ongoing work on cyclometallated gold(III) compounds for (metallo)protein inhibition will also be discussed.

Acknowledgements: REFP acknowledges "la Caixa" Foundation (ID 100010434) for the Junior Leader Fellowship LCF/BQ/PI22/11910033. The Donostia International Physics Center receives support from the "Severo Ochoa" Program for Centers of Excellence in R&D (Grants CEX2018-000867-S) run by the Spanish State Research Agency.

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Copper proionophores for the selective targeting of cancer cells

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Keywords: copper, ionophore, prodrug, enzyme, activation, cuproptosis

Conventional cancer drugs 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]. Cuproptosis defines Cu-dependent cytotoxicity (with a unique mechanism) leading to cell death [3]. In this context, we studied systems that could act as prodrugs. In particular, proionophores are molecules that have to be activated to release the metal ionophore, increasing the selectivity of the drug (Figure 1). In particular, stimulus-responsive prodrugs of 8-substituted quinolines were evaluated in vitro. The released 8-hydroxyquinoline moiety can act increasing the copper content of cancer cells and causing cell death.

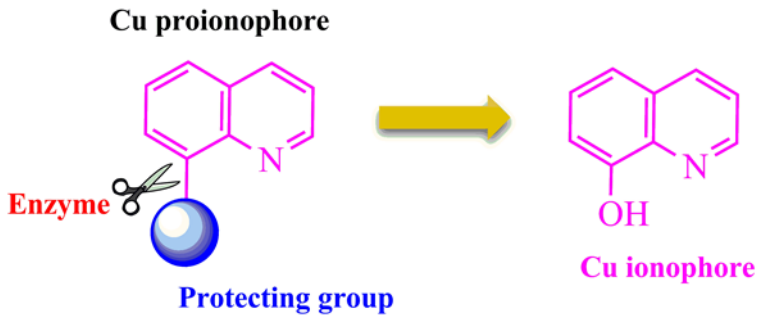

Figure 1. Cu proionophore has to be activated by a specific stimulus (i.e. enzymes) to release the Cu ionophore

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Structural and Thermodynamic Study of the B_{12}-Riboswitch from *Klebsiella Pneumoniae*

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Keywords: RNA, riboswitch, ITC, in-line probing, gene regulation

RNA Riboswitches, sited in the 5'-UTR (untranslated region) of mRNA, are able to regulate gene expression via changing the RNA conformation upon interaction with a specific metabolite. They are formed by an aptamer, where the metabolite is bound, and the expression platform, which finally causes the gene expression regulation.

A presumable *btuB* riboswitch sequence was bioinformatically found in the genome of *Klebsiella pneumoniae*, and afterwards validated as a B_{12} riboswitch by in-line probing experiments. In the gene-on conformation, the ribosome binding site (RBS) is free, therefore the *btuB* gene can be expressed. On the other hand, after the AdoCbl interaction, the RNA is shifted to the gene-off conformation, in which the RBS is masked in a base paired region, proving the sequence as a riboswitch and suggesting a translation inhibition mechanism. The inhibition translation mechanism was also proved by coupling the riboswitch to a red fluorescent protein (*mCherry*). The protein synthesis was inhibited after increasing amounts of AdoCbl were added to the culture media.

Isothermal titration calorimetry (ITC) experiments were used to determine the thermodynamic parameters of the RNA-metabolite interaction with two different constructs: one carrying the whole riboswitch (246 nt.) and another one which contains only the aptamer (214 nt.). Results suggest that the RNA-AdoCbl interaction is exothermic and follows a 1:1 stoichiometry. The obtained enthalpy values are in consonance with a sum of several weak interactions such as H-bond and π,π- stacking, while the presence of the expression platform in the construct stabilizes the interaction of the *btuB* riboswitch with the AdoCbl [1].

The effect of the ancillary ligands' integrity over translation was also assesed using cyanocobalamin and cobyric acid instead of the entire coenzyme. Finally, we have been able to extract and purify descobaltocobalamin and descobaltocobyric acid from cultures of *Allocromation vinosum*, anaerobically grown in a deficient cobalt medium, with the aim to synthetize an antivitamin of Cbl, which could be a candidate to a novel antibiotic via Trojan horse approach.

Acknowledgements: The authors would like to acknowledge funds received from the "Govern de les Illes Balears" to set up a RNA research lab and to R.K.O. Sigel from University of Zurich for their advice and support. Special thanks to Roger Tsien for supplying us the mCherry plasmid.

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PREMIOS AEBIN /
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Potent Anticancer Activity of an Iridium Metallodrug via Oncosis

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Keywords: anticancer drug; Caenorhabditis elegans; iridium; metallodrug; oncosis.

Most anticancer drugs induce cell death *via* apoptosis. However, cancer cells often evade apoptosis, showing resistance not only to cell death but also to chemotherapy [1]. In this study, we report a novel rationally designed mitochondria-targeted iridium(III) complex (**Oncolr**) which can induce oncosis (**Figure 1**). Oncosis (from Greek *ónkos*, meaning "swelling") is a non-apoptotic cell death associated to the depletion of cellular energy stores. Besides inducing potent anticancer activity, **Oncolr** exhibited an apoptosis-independent mechanism involving energy depletion, mitochondrial damage and cellular swelling that matched with the oncotic process [2]. Furthermore, an *in vivo* tumoral model was developed using *Caenorhabditis elegans*, which allowed us to verify that the antitumor activity of **Oncolr** was derived from oncosis induction. Indeed, **Oncolr** reduced the tumoral area by 41% *in vivo* and extended the mean lifespan of the animals by 18%. Altogether, these findings may shed light on the development of anticancer metallodrugs with non-conventional mechanisms such as oncosis, which are of particular interest to tackle apoptosis-resistant cancers.

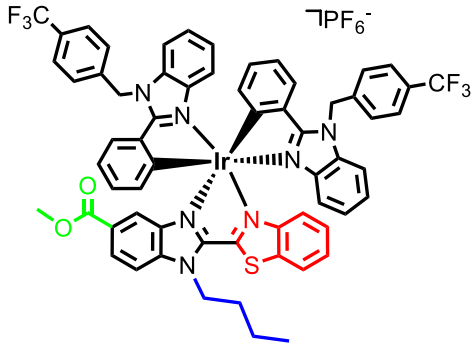

Figure 1. Chemical structure of **Oncolr.**

Acknowledgements: *This work was supported by the Spanish Ministerio de Ciencia e Innovación-Agencia Estatal de Investigación (MCI/AEI/10.13039/501100011033), FEDER funds (Projects PID2021-122850NB-I00, AGL2017-86526-P and MultiMetDrugs network RED2018-102471-T) and Fundación Séneca-CARM (Projects 21989/PI/22 and 19893/GERM/15). E.O.-F. thanks AECC (PRDMU19003ORTE).*

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Probiotic Bacteria as Carrier of Metallic Nanoparticles for Magneto-optical Hyperthermia

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Keywords: probiotic bacteria, magnetic nanoparticles, gold nanoparticles, hyperthermia, colon cancer.

Nanoparticles-mediated hyperthermia consists of single gold or magnetic nanoparticles, which after exposure to laser irradiation or magnetic fields, respectively, produce heating. In the current work, probiotic bacteria were used as carriers of gold nanoprisms (AuNPR) and superparamagnetic maghemite nanoparticles (MNP) to develop innovative oral agents for hyperthermia cancer therapy. The adsorption of metallic nanoparticles takes place in the biofilm, an extra-bacterial conglomeration of products, composed mainly of extrapolysaccharides (EPS), that surrounds the bacterial wall of the probiotic bacterium.

The hybrid nanostructures produced have adequate features to act as dual agents in magnetic hyperthermia and photothermal therapy.

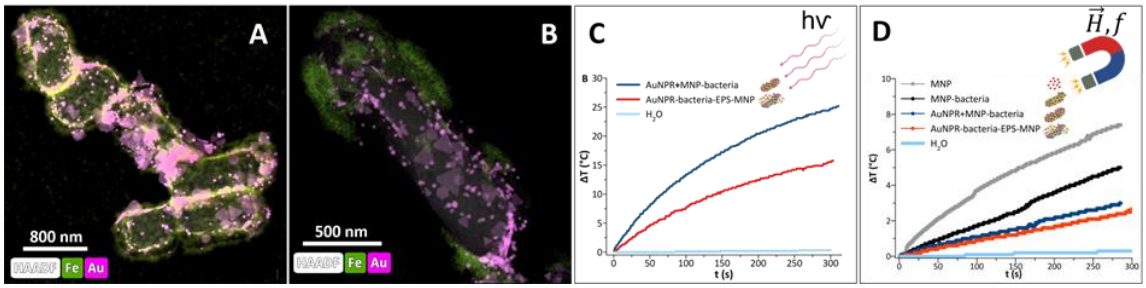

Figure 1. HAADF-STEM/EDX images of the AuNPR+MNP-bacteria (A) and AuNPR-bacteria-EPS-MNP-bacteria (B) (Au, pink; Fe, green). Heating curves after laser irradiation of samples in A and B (C). Magnetic hyperthermia-heating curves of MNP, MNP-bacteria, and samples in A and B (D).

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COMUNICACIONES PÓSTER / POSTER COMMUNICATIONS

Celulosa Bacteriana como filtro UV para protección de la piel

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Palabras clave: Celulosa bacteriana; UV; probiótico; filtro; LMs; Materiales Hibridos Vivos; bacteria; Komagataeibacter xylinus; Lactobacillus fermentum

Los Materiales Híbridos Vivos (LMs) representan uno de los temas de mayor importancia en las investigaciones recientes sobre nuevos materiales. Los LMs están basados en un sistema mixto de un componente abiótico y un componente vivo [1]. *Komagataeibacter xylinus* (*Kx*) es una bacteria capaz de sintetizar, en la interfase líquido-gas en presencia de oxígeno, Celulosa Bacteriana (BC), un biopolímero biocompatible de elevada resistencia mecánica, pureza y alta capacidad de absorción [2,3]. Kx genera esta celulosa como método de supervivencia para protegerse de las radiaciones UV [4]; así, BC presenta un potencial uso como filtro de UV biocompatible. Con el fin de desarrollar LMs con propiedades mejoradas, *Kx* puede co-cultivarse con otros microorganismos quedando estos encerrados en la matriz fibrilar de celulosa, como es el caso de *Lactobacillus fermentum* (*Lf*), propocionando propiedades antimicrobianas a este material (BC-*Lf*) frente a microoganismos patógenos, propiedad que no se observa en el material resultante de la simple suma de ambos componentes (BC+*Lf*) [5]. En este trabajo se ha demostrado el efecto de protección de BC sobre probióticos encerrados en la matriz fibrilar (BC-*Lf*) y expuesto en su superficie (BC+*Lf*) frente a radiación UV en comparación con un cultivo libre de *Lf*.

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Nuevos Complejos ciclometalados Heterolépticos de Ir(III) como Agentes Fototerapéuticos

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Palabras clave: benzotiazol, cáncer, iridio, fotosensibilizador, terapia fotodinámica.

Recientemente ha proliferado el desarrollo de compuestos con metales de transición para tratamientos como la Terapia Fotodinámica (PDT), en la que se emplea un fotosensibilizador (PS) con el que se generan especies reactivas de oxígeno (ROS) y/u oxígeno singlete ($^1O_2$), que conducen a la muerte de las células cancerosas [1]. En este caso, se ha seleccionado el iridio para formar complejos aplicables en PDT por: favorecer el cruce entre sistemas, exhibir una alta población en estado excitado, generar ROS y/u $^1O_2$, y por absorber y emitir en la región visible del espectro electromagnético en forma de complejos ciclometalados [2].

Teniendo en cuenta estos antecedentes, se han sintetizado una serie de nuevos complejos de Ir(III) (Figura 1) con ligandos N^N derivados de la fenantrolina, empleando como ligando C^N el: 4-difenilaminobenzo[d]tiazol. Además de su caracterización química, se han estudiado sus propiedades ópticas por espectroscopía de absorción UV-visible y de emisión, así como su (foto)estabilidad en distintos medios.

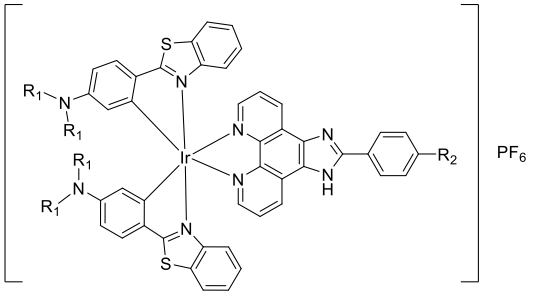

Figura 1. Estructura química de los nuevos complejos de Ir(III) de estequiometría $[Ir(C^N)_2(N^N)]PF_6$.

Agradecimientos: al Ministerio de Ciencia e Innovación -Agencia Estatal de Investigación (MCI/AEI/10.13039/501100011033) y fondos FEDER (proyecto PID2021-122850NB-I00). Isabel Romero Castellón agradece a la Fundación Séneca su contrato predoctoral (21854/FPI/22).

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Bimetallic Photosensitizers based on Ir^{III}- Au^{I} Carbenes

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Keywords: PDT, Iridium complexes, ROS, Carbene, Confocal microscopy

Medicinal inorganic chemistry has attracted great attention in the recent years due to the development of novel metallodrugs derived from gold, platinum and ruthenium species among others [1,2]. Within this context, a growing interest is devoted to the design of heterometallic complexes, which are expected to contribute to the realization of personalized cancer therapy [3]. A synergic effect is feasible to take place when both, a bioactive and an emissive metallic fragment are combined and thus, delivering novel trackable metallodrugs [4].

This work describes the development of a new variety of heterometallic complexes based on the combination of both, Ir^{III} and Au^{I} fragments, using as a linker an N-heterocyclic carbene phenanthroline ligand, Figure 1. Their emissive properties, photocytotoxic activity in tumor lines, cell distribution, mechanism of death, as well as their singlet oxygen production have been thoroughly investigated.

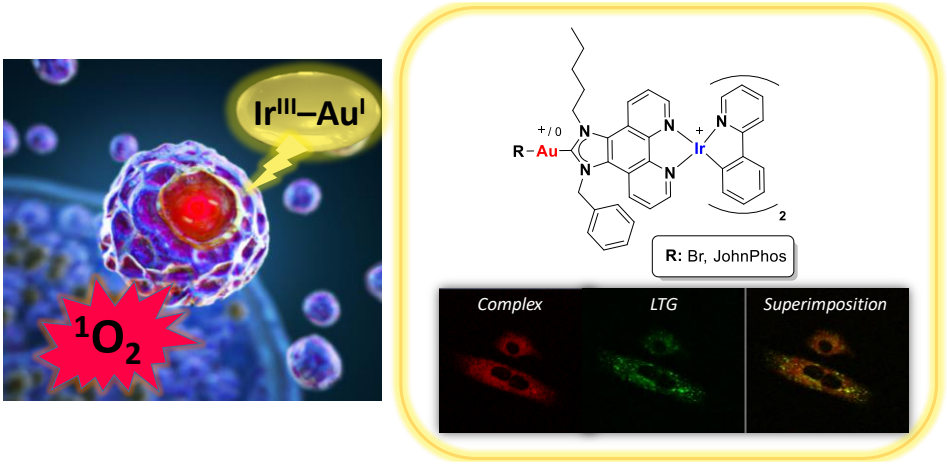

Figure 1. Schematic representation of the heterometallic photosensitizers.

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Materiales Fotoelectrocrómicos como Sensores de Biomoléculas en Suelos

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Palabras clave: POMs, sensor colorimétrico, nitratos, nitritos, amonio

Los polioxometalatos (POMs) son materiales electrocrómicos descritos como clústeres aniónicos o fragmentos moleculares de óxidos metálicos capaces de aceptar electrones mediante procesos químicos o fotoquímicos, dando lugar a especies coloreadas de valencia mixta. Los organismos vivos y algunas biomoléculas pueden actuar como donantes de electrones para estos materiales, de modo que las propiedades cromáticas de los POMs pueden relacionarse directamente con una determinada actividad biológica o con la presencia de una biomolécula en una determinada muestra. Esta propiedad los hace candidatos ideales para el diseño de sensores colorimétricos tales como los que ya hemos desarrollado en nuestro grupo de investigación [1].

Otro campo de posible aplicación de este tipo de sensor podría ser en agricultura, ya que el uso de fertilizantes, es a día de hoy el único recurso para mantener la correcta nutrición de plantas y cultivos. Sin embargo, el aprovechamiento de los mismos no es total y esto hace que numerosos iones inorgánicos (sobre todo nitratos, nitritos y amonios) queden en exceso en suelos o que lleguen a contaminar aguas [2].

En la búsqueda de alternativas que permitan evitar estos procesos contaminantes, está la rápida detección del exceso de sales inorgánicas. En este sentido, este trabajo pretende diseñar un nuevo sensor colorimétrico basado en el empleo de las propiedades colorimétricas de los POMs para la detección de nitratos, nitritos y amonios de forma más rápida, sencilla y económica que los métodos tradicionales existentes para el mismo fin.

Agradecimientos: Trabajo financiado mediante proyecto TED2021-130392A-I00, Ministerio de Ciencia e Innovación.

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Sensores de biomoléculas con interés en salud basados en polioxometalatos electrocrómicos

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Palabras clave: polioxometalatos, sensores, biomoléculas

Los polioxometalatos (POMs) son materiales electrocrómicos que pueden aceptar electrones mediante procesos químicos o fotoquímicos, dando lugar a especies coloreadas de valencia mixta. Los organismos vivos y algunas biomoléculas pueden actuar como donantes de electrones para estos materiales, de modo que las propiedades cromáticas de los POMs pueden relacionarse directamente con una determinada actividad biológica o con la presencia de una biomolécula específica. Basándonos en esta idea, hemos diseñado varios sensores de fácil uso y bajo coste para cuatro aplicaciones biomédicas diferentes.

1. Estudio del efecto de fármacos en la microbiota. Hemos evaluado el efecto de fármacos sobre la viabilidad del probiótico *L. fermentum* correlacionando su fuerza metabólica con su capacidad reductora. El color azul del PMO sintético ($Na_6[P_2Mo^{VI}_{18}O_{62}]$) se obtuvo sólo en las muestras en las que la actividad metabólica no se veía afectada. Esta prueba puede ser una buena forma de detectar actividad bacteriana [1].

2. Diagnóstico de vaginosis bacteriana (VB). En la VB, la flora vaginal típica formada por bacterias lactobacillus, que secretan ácido láctico en el medio, se ve alterada por el crecimiento de bacterias anaerobias patógenas, que secretan ácido acético como metabolito más abundante. Así en una muestra sana que contiene ácido láctico, el PMA ($H_3[P(Mo_3O_{10})_4]\cdot xH_2O$), cambia de amarillo a azul en presencia de luz UV. Cuanto más intenso es el color azul más sana es la muestra. Esta prueba proporciona un diagnóstico rápido, exacto y preciso de la infección [2].

3. Monitorización de la dosis de radiación UV. Se ha utilizado la reacción PMA-ácido láctico para diseñar una pulsera que monitoriza la dosis de radiación UV a simple vista. De este modo, se pueden detectar todos los tipos de radiación UV (UVA, UVB y UVC), e incluso el sensor puede ser personalizado para todos los tipos de piel [3].

4. Detección de etanol en el sudor y la saliva. Utilizando la capacidad del etanol para reducir el PTA ($H_3[P(W_3O_{10})_4]\cdot xH_2O$) bajo la radiación de luz UV, hemos diseñado un dispositivo reutilizable para detectar y cuantificar la cantidad de etanol en el sudor y la saliva. La integración de la tecnología de análisis de imágenes digitales permite su uso potencial como test de alcoholemia para conductores [4].

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Photo-Controlled Delivery of Cisplatin Catalyzed by riboflavin

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Keywords: fotochemistry, Pt(IV) prodrugs, catalysis, polymers, drug delivery

The photoactivation of transition metal complexes has been successfully tailored to kill cancerous cells by novel mechanisms of action that may help overcoming downsides connected to metallodrugs [1]. In this context, our group has recently demonstrated that flavins and flavoproteins are capable of functioning as photosensitizers and photocatalysts for the conversion of Pt(IV) prodrugs into active Pt(II) anticancer drugs in the presence of electron donors. These reactions have shown bioorthogonal selectivity, high efficiency and have been employed to kill cancer cells *in vitro* with minimal light doses [2][3].

Herein, I will describe how to engineer new biocompatible polymers with flavins and Pt(IV) prodrugs so to desing new photocatalytic biomaterials for the administration of platinum-based anticancer drugs [4]. I will discuss how this unconventional catalysis can be exploited to devise innovative strategies for photochemotherapy and drug photodelivery.

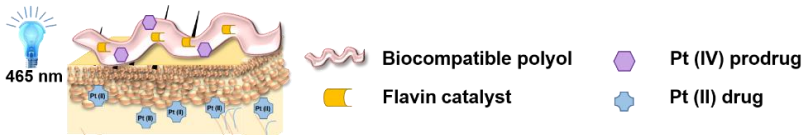

Figure 1. Robust photocatalytic device for the liberation of Pt(II) drugs

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New NanoPS based on Ir complexes encapsulated into nanogels with PDT behaviour for cancer treatment

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One of the most successful therapies to treat cancer is chemotherapy. However, it shows some limitations such as: i) the prodrugs must pass through several barriers (bloodstream, tissues and cells); ii) they show poor aqueous solubility; iii) they can be cleared rapidly from the blood circulation; iv) they display indiscriminate body distribution, causing more side effects. To overcoming these limitations, it is required the development of new systems. One strategy is the photodynamic therapy (PDT), based on the administration of a photosensitizer (PS) which ideally is innocuous in the absence of light, but under irradiation with light it can produce ROS species at cytotoxic levels. A different approach to improve the limitations is the protection of the drug through encapsulation into carriers, showing several benefits such as: i) protection of the molecules against premature degradation, ii) increase their aqueous solubility, iii) sustained release, iv) higher accumulation in the solid tumour due to the EPR effect, v) requirement of lower concentrations, and vi) lower toxicities on healthy cells. Different systems have been used as carriers to encapsulate and deliver a large range of drugs. In particular, hydrogels have also shown enormous potential. They are 3D polymer crosslinked containing porous networks with high amounts of water, able to retain their structure unbroken even at low concentration.

In this work we present a family of complexes of formula $[IrCp^*(C^N)L]^{n+}$ (L = Cl, imidazolyl-derived ligands, n = 0 or 1) with cyclometalated π-extended ligands, possessing outstanding PTD properties with photoindex values (PI) > 1000 under blue light. The generation of ROS is increased by irradiation. The cell death is by apoptosis. On the other hand, nanogels based on PEG polymers, with size between 100-200 nm, are obtained as platforms to encapsulate these complexes, showing good encapsulation efficiencies and great stabilities under solution. When the complexes are encapsulated into nanogels, the cytotoxicity under light of the species was kept, and they even achieved similar PI values to those of the corresponding free complexes, indicating the encapsulation does not inhibit the generation of ROS and its damage to the cells. Interestingly, the cytotoxicity in the dark is notably reduced with the encapsulation.

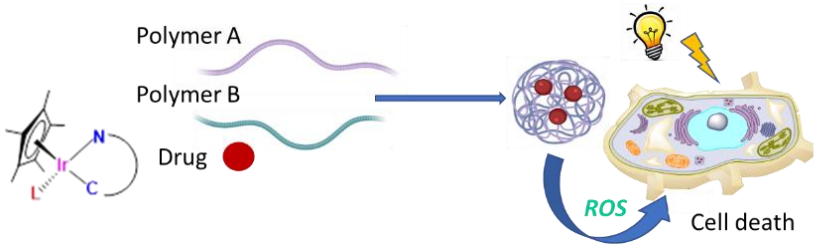

Figure 1. Encapsulation of drugs into nanogels and selective photoexcitation of the Ir species.

Photodynamic Therapy with Mitochondria-targeted Biscyclometallated Ir(III) Complexes. Multi-action Mechanism and strong Influence of the C^N Ligand

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Keywords: Photodynamic Therapy, Cancer, Iridium, Mitochondria

Photodynamic therapy is an alternative to classical anticancer chemotherapy based on the activation of a photosensitizer (PS) through local irradiation with light to reduce side effects. The PS* then interacts with O_2 and generates ROS. Ir(III) biscyclometallated complexes are promising PSs due to their outstanding photophysical properties and their ability to target mitochondria. Four photostable Ir(III) biscyclometallated complexes of formula $[Ir(C^N)_2(N^N')]Cl$, (N^N' = **L1**, **L2**; C^N = **ppy**, **dfppy**) have been prepared and studied as PSs. Their electrochemical and photophysical properties are modulated by the C^N and the N^N' ligands. The **dfppy** derivatives yielded the lowest λ_{em} and the highest PLQY and τ. All PSs generated $^1O_2$ in aerated solutions upon irradiation. Biological studies revealed that these PSs have a moderate cytotoxicity in the dark against different human cancer cells: prostate (PC-3), colon (CACO-2) and melanoma (SK-MEL-28), and against non-malignant fibroblasts (CCD-18Co). However, **[1a]-[2a]** yielded a relevant photodynamic activity upon light irradiation (450 nm), with phototoxicity indexes of 20.8 and 17.3 in PC-3 cells, respectively. These PSs are taken up by cells through endocytosis and accumulate in mitochondria. Upon photoactivation, the PSs induced MMP loss and DNA damage, triggering apoptosis. This mitochondria-targeted photodynamic mechanism inhibits efficiently the reproductive ability of cancer cells [1].

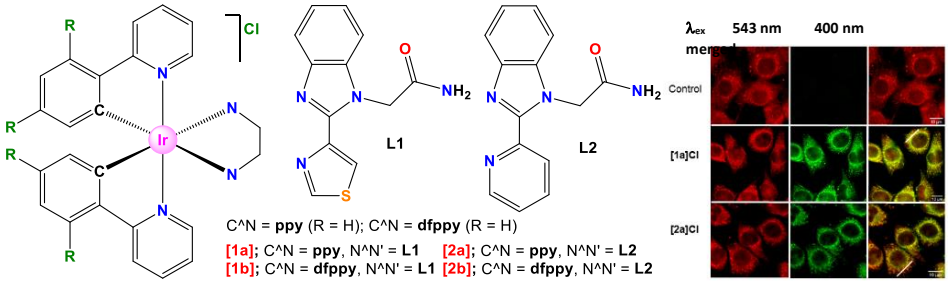

Figure 1. Molecular structure of the Ir(III) PSs and Subcellular localization of **[1a]Cl** and **[2a]Cl**.

Acknowledgements: Project **PID2021-127187OB-C21**.

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A Novel Near-IR absorbing Ruthenium(II) complex and its Cetuximab Bioconjugates as Targeted Photosensitizers for Photodynamic Therapy

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Keywords: cyclometalated complexes, ruthenium, photodynamic therapy, bioconjugation, antibody.

Photodynamic therapy (PDT) is an approved medical technique based on the combined effect of a photosensitizer (PS), molecular oxygen and light and it has been recently used in anticancer therapies [1]. One feature for a PS to be suitable for PDT is to absorb light in the red or NIR region of the spectrum (> 600 nm), so that complexes can be irradiated with low energy. To approach this aim, we have used cyclometalation since this strategy lowers the energy of the triplet metal-to-ligand charge transfer state (^{3}MLCT), and thus, causes a bathochromic shift in the absorption [2].

In this work, a novel Ru(II) cyclometalated photosensitizer (PS), Ru-NH_2 and its cetuximab (CTX) bioconjugates, were synthesised and characterised as potential agents for PDT. The photophysical properties of Ru-NH_2 revealed absorption up to 725 nm and generation of singlet oxygen ($^1O_2$) upon light irradiation ($^1O_2$ quantum yield of 0.19). Preliminary *in vitro* experiments revealed that Ru-NH_2 was nontoxic in the dark in CT-26 and SQ20B cell lines but showed outstanding phototoxicity when irradiated, reaching interesting phototoxicity indexes (PI) at 740 nm for CT-26 cells. The cetuximab bioconjugates, however, were not as photoactive as the Ru-NH_2 complex.

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Ligand photoejection and cytotoxic behaviour of 2,2'-dipyridylamine-containing ruthenium(II) polypyridyl complexes as photosensitizers in photoactivated chemotherapy (PACT)

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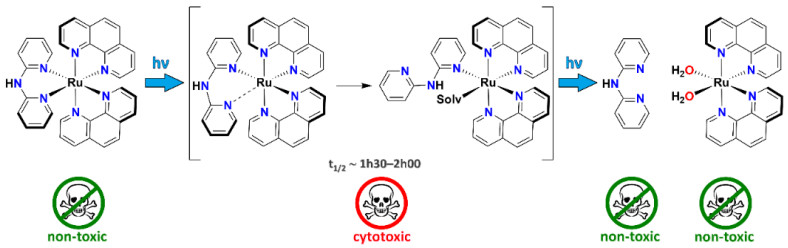
Keywords: Ruthenium(II), Photochemistry, Ligand Photorelease, Light Activation, Cytotoxicity

Numerous transition-metal-containing photosensitizers have been described in the literature for potential utilization in photodynamic therapy (PDT) and photoactivated chemotherapy (PACT). It is also widely accepted that PACT with Ru(II) polypyridyl complexes involves the photoinduced release of a ligand, producing cytotoxic species.[1,2] The toxicity may be due to the free ligand, or the generation of (di-)aquated Ru(II) species that can, for instance, bind to DNA. Furthermore, it is also believed that the increase of steric bulk near the metal center favors the photodissociation of the ligand from the distorted octahedral complex. Polypyridyl ruthenium(II) compounds represent a highly promising family of photoactive complexes [1-3].

In the present study, two ruthenium(II) polypyridyl complexes were prepared from the $\{Ru(phen)_2\}^{2+}$ moiety and a third sterically non-hindering bidentate ligand, namely 2,2'-dipyridylamine (dpa) or N-benzyl-2,2'- dipyridylamine (Bndpa). Hence, complexes $[Ru(phen)_2(dpa)](PF_6)_2$ (**1**) and $[Ru(phen)_2(Bndpa)](PF_6)_2$ (**2**) were obtained and the effect of the slight ligand difference on their photochemical behaviour, interaction with DNA and associated photocytotoxic properties was investigated.

For both complexes, a highly efficient ligand ejection is observed upon light irradiation, as already observed for other non-sterically hindered ligand complexes. DNA-binding studies (using various techniques) revealed distinct complex behaviours. Cytotoxic studies with two different cancer cell lines also showed rather striking results. Localization of the compounds in living cells was achieved by confocal microscopy.



Scheme 1. Proposed two-step ligand photorelease leading to significantly cytotoxic transient Ru species, ultimately producing non-toxic free ligand and Ru complex.

Acknowledgements: Financial support from the Spanish Ministerio de Ciencia e Innovación (PID2020-115537RB-I00 MCIN/AEI/10.13039/501100011033) and Generalitat de Catalunya (FI-SDUR) is kindly acknowledged

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Photoredox Catalysis For The Bioorthogonal Activation Of Pt(IV) Anticancer Complexes

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Keywords: Photochemotherapy, Photocatalysis, Platinum drugs, Flavins

In this contribution, we will summarize our most recent achievements in the use of flavin photoredox catalysis as a strategy for the bioorthogonal activation and delivery of platinum anticancer drugs.

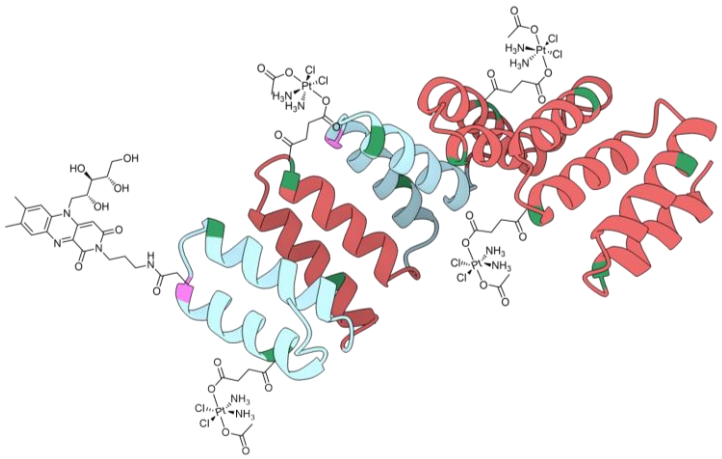

Figure 1. Artificial flavoprotein for the photoactivation and delivery of Pt drugs.

Acknowledgements: We acknowledge financial support from the Spanish State Research Agency (PID2019-109111RB-I00 and CEX2018-000867-S), the Basque Government (PIBA_2021_1_0034), the Diputación Foral de Gipuzkoa (RED 2021) and the EU Horizon 2020 Research and Innovation Programme (Marie Sklodowska-Curie Actions grant no. 101024838).

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Phosphonium Gold(I) Complexes as Antitumor agents Targeting Mitochondria

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Keywords: Gold, antitumor complex, phosphonium, chromophore, mitochondria

The new generation of antitumor drugs is based on metals such as Ru, Au, Ti or Ga. Gold(I) complexes have proven to be effective against certain human diseases and can be designed to target specific overexpressed receptors in tumor cells. Mitochondria play an essential role in the regulation of cancer, cell apoptosis and metabolism, as they provide the energy for cancer cell growth. Targeting them can directly inhibit energy supply for cancer cells, resulting in cancer cell death. Therefore, the search for specific agents to target mitochondria has attracted considerable attention as an effective therapeutic strategy [1].

The phosphonium groups promote transmembrane transport of cationic compounds, such as those with high lipophilicity and large ionic radius [2].

This work focuses on the functionalization of phosphonium salts with specific moieties, such as chromophores, followed by deprotonation to afford gold ylide derivatives (Figure 1). This will provide complexes with multiple functionalities for targeting the mitochondria of cancer cells.

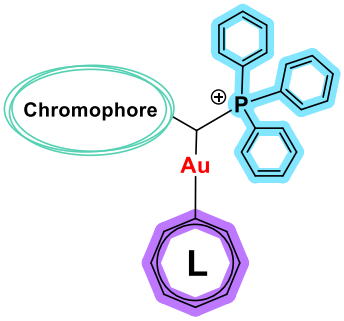

Figure 1. General structure of antitumor gold complexes.

Acknowledgements: Authors thanks to the AEI, project PID2019-104379RB-C21/AEI/ 10.13039/501100011033. N.R. thanks the Gobierno de Aragón for a predoctoral fellowship.

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The Anti-Breast Cancer Strem Cell Properties of Cobalt(III)-Non-Steroidal Anti-Inflammatory Drug Complexes

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Keywords: Cobalt(III) complexes, Hypoxia, Cancer Stem Cells

Cancer is a serious health problem worldwide and is one of the most common causes of death in developed countries. Cancer stem cells (CSCs) are a subpopulation of cells within the tumour responsible for cancer recurrence and metastasis after surgery, chemotherapy and radiation therapy [1]. Because of their stemness properties, CSCs have the ability to self-renew and differentiate [2]. During the rapid reproduction and growth of solid tumours, the imbalance in oxygen supply and consumption leads to the occurrence of hypoxia in solid tumors, which is associated with poor prognosis. Hypoxic microenvironments in tumours can maintain the undifferentiated state of CSCs by controlling the asymmetric division of CSCs as well as preventing their differentiation into bulk cancer cells [3]. Therefore, cytotoxic compounds that can accumulate and be activated in the hypoxic microenvironment associated to CSCs could offer a solution to overcoming CSCs.

Our group has previously developed several cobalt(III) complexes capable of killing CSCs in hypoxic-like conditions [4-6]. In this poster, we present the synthesis, characterisation, and anti-breast CSC potency of cobalt(III) complexes with non-steroidal anti-inflammatory drugs (NSAIDs). Specifically, we report a cobalt(III)-cyclam complex bearing two flufenamic acid moieties and a series of cobalt(III) complexes bearing polypyridyl and salicylate ligands. The cobalt(III) complexes kill monolayer-cultured breast CSCs at sub-micromolar doses and inhibit the formation of three-dimensional tumour-like mammospheres. Mechanistic studies revealed that cobalt(III) complexes are bio-reductively activated, resulting in the release of (i) the NSAID component which inhibits cyclooxygenase-2, and (ii) a reduced Co(II) form which damages genomic DNA. Our work shows that cobalt(III) complexes with reduction-activatable properties have the potential to effectively kill breast CSCs.

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Complejos de Ir(III) con actividad antimetastásica y antiproliferativa frente al cancer de mama triple negativo

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Keywords: Iridio(III), terpiridina, metástasis, anticancer, EMT, TNBC, esferoides 3D.

Uno de los tipos de cáncer de mama con peor prognosis es el cáncer de mama triple nagativo (TNBC) debido a su potencial capacidad para generar metástasis. En esta situación los fármacos basados en platino o la doxorubicina suelen fracasar en su tratamiento, por tanto, es muy importante desarrollar compuestos tanto con actividad antiproliferativa como antimestastásica. En este sentido, los complejos basados en Ir(III) pueden ser una extraordinaria herramienta ya que ofrecen la posibilidad de actuar con mecanismos de acción diferentes a los fármacos de referencia en uso clínico.

En esta contribución se describe una serie de complejos octaédricos de Ir(III) del tipo $[Ir(N^N^N)(C^N)Cl]PF_6$, donde N^N^N es el ligando tridentado 4'-(p-tolil)-2,2':6',2''-terpiridina y C^N contiene el esqueleto 2-arilbenzimidazol.

Los ensayos realizados muestran que el complejo más activo (Figura 1) es más eficiente y más selectivo que la doxorubicina frente modelos 2D y esferoides multicelulares 3D de células de TNBC. Además, los datos obtenidos indican que **1** no sólo presenta actividad antiinvasiva sino que también tiene capacidad para suprimir su diseminación.

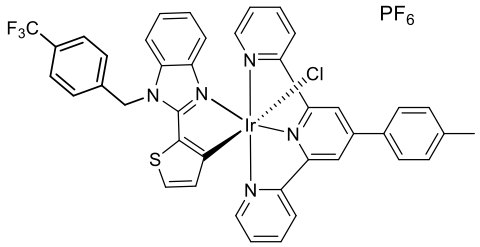

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Figure 1. Complejo de Ir(III)

Acknowledgements: This work was supported by funds from the Spanish Ministerio de Ciencia e Innovación-Agencia Estatal de Investigación (MCI/AEI/10.13039/501100011033) and FEDER funds (Project PID2021-122850NB-I00) and MultiMetDrugs network RED2018-102471-T. A. M. thanks Fundación Séneca-Región de Murcia for a grant (project 21234/FPI/19).

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Emissive cyclometallated Ir(III) Drugs with Potential as Anticancer Agents: Synthesis and Biological Activity in Lung Cancer

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Keywords: photosensitizers, bioimaging, metallodrugs, anticancer, iridium

Cyclometallated Ir(III) drugs are emerging as great alternative to traditional anticancer agents. Their prospects in chemotherapy and photodynamic therapy (PDT) [1], together with their intrinsic photophysical properties, make these complexes very appealing for the development of multimodal probes [2]. To this end, emissive cyclometallated Ir(III) complexes with the general formula of $[Ir(C^N)_2(N^N)]^+$, containing different phenyl-benzoimidazole derivates as C^N ligands and a thiazol/pyridine benzoimidazole funtionalised with a chromophore have been synthesised (Figure 1). Their biological activity was studied in lung cancer A549 cells, revealing their great potential as chemotherapeutic and photosensitiser (PS) agents. Moreover, their highly emissive character allowed to elucidate their celular biodistribition using fluorescence microscopy.

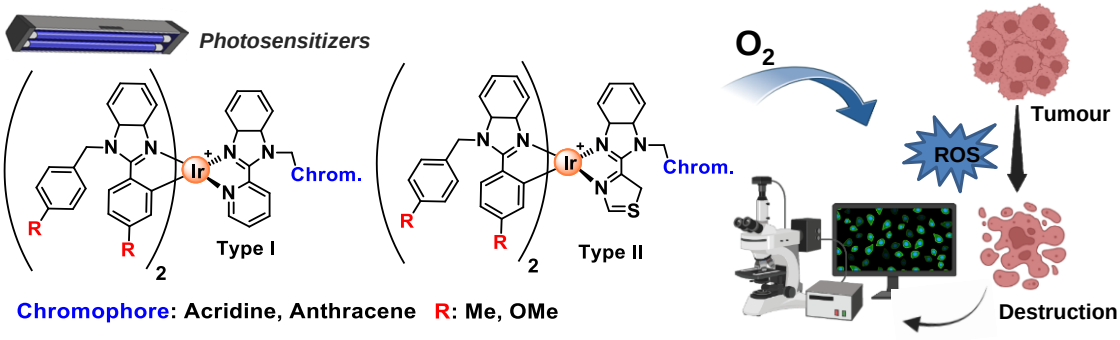

Figure 1. Chemical structure of reported Ir^{III} complexes.

Acknowledgements: Proyect RYC2018-025872-I

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Preliminary *in vitro* antiproliferative assays over human tumor cells of a new silver(I) complex with 6-(trifluoromethyl)uracil

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Keywords: 6-(Trifluoromethyl)uracil, Silver(I), Antiproliferative agents.

Metal complexes are used in medical practice for different purposes. Silver complexes, as silver sulfadiazine, have been used to treat bacterial infections for a long time [1]. More recently, new silver complexes have been prepared and studied as alternatives for the treatment of non-melanoma skin cancers [2]. One of the strategies for the synthesis of novel bioactive compounds is the combination of metals, such as silver, platinum and copper, among others, with ligands that already possess medicinal applications [2]. Nucleotide analogs are a class of bioactive molecules used in medicine as antiproliferative agents. One representative nucleotide analog used in the treatment of cancer is 5-fluorouracil (5-FU) [3]. Recently, our research group described the synthesis of a silver complex with 5-FU and its acivities over multi-resistant NCI/ADR-RES ovarian tumor cells [3,4]. In this work we present the synthesis, characterization and antiproliferative profile over tumor cells of a new silver complex with 6-(trifluoromethyl)uracil. The complex was prepared by the reaction of 1.0 mmol of an alkaline aqueous solution 5-(trifluoromethyl)uracil with 1.0 mmol of silver nitrate. The reaction was carried out under magnetic stirring for 2 hours without heating. The complex was collected by filtration, washed, and dried. The composition found for this complex was $Ag_2C_5H_2F_3N_2O_2$. Anal. Calcd.: C 15.25%; H 0.26%; N 7.11%. Found: C 15.70%; H 0.26%; N 7.17%. Infrared (IR) and solid-state ^{13}C nuclear magnetic resonance (NMR) spectroscopies suggest coordination of the ligand to silver by oxygen and nitrogen atoms of the ligand in a bidentate mode. The Ag-6TFMU complex showed potent *in vitro* antiproliferative activity against prostate PC3 cells, with TGI value 0.9258 μmol L^{-1} and ovarian adenocarcinoma NCI/ADR-RES, with TGI 15.7 μmol L^{-1}, being more active than doxorubicin against the considered cell lines.

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Complejos Fluorados de Ir(III) derivados de Benzimidazol como potenciales Agentes Oncóticos

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Palabras clave: iridio · ciclometalado · agente antitumoral · oncosis · flúor

En la actualidad, numerosos tumores han desarrollado resistencia frente al mecanismo apoptótico de muerte celular. Este hecho plantea la necesidad de buscar fármacos que desencadenen la muerte de las células tumorales por otras vías, entre las cuales se encuentra la oncosis, consistente en el hinchamiento de la célula y la formación de protuberancias [1]. Los complejos ciclometalados derivados de metales de transición se han postulado como prometedores agentes teragnósticos en quimioterapia debido a la fácil modulación de sus propiedades fotofísicas y fotoquímicas [2]. Siguiendo esta línea, nuestro grupo está centrado en la síntesis de complejos ciclometalados derivados de benzimidazol, una subestructura ampliamente utilizada en el diseño de agentes antitumorales [1]. Dado el escaso número de estos complejos como agentes oncóticos, y basándonos en una publicación reciente del grupo [1], se han preparado tres complejos ciclometalados de Ir(III) con potencial actividad oncótica. Para ello, los complejos han sido funcionalizados con grupos fluorados con el fin de aumentar su potencia inhibitoria [3].

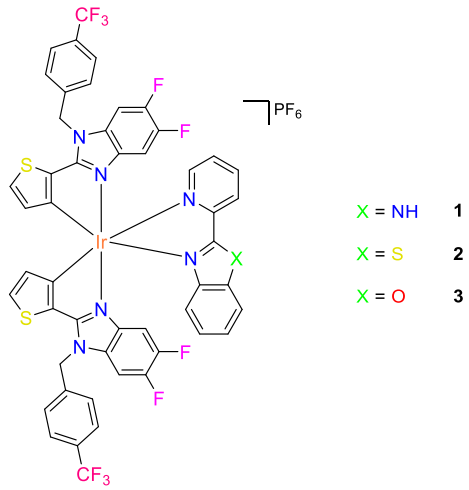

Figura 1. Estructura de los complejos ciclometalados de Ir(III) preparados.

Agradecimientos: al Ministerio de Ciencia e Innovación-Agencia Estatal de Investigación (MCI/AEI/10.13039/501100011033) y fondos FEDER (proyecto PID2021-122850NB-I00). A. Linero agradece asimismo a la Universidad de Murcia su contrato predoctoral (100159/2021).

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Exploring the Cytotoxicity and Photocytotoxicity of cyclometallated Ir(III) Complexes for Cancer Treatment and Bioimaging

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Keywords: photosensitizers, bioimaging, metallodrugs, anticancer, iridium

The development of efficient anticancer agents has become an urgent need in our society, and medicinal bioinorganic chemistry is a useful tool in the search for novel strategies to deal cancer. Besides the commonly used metallodrug, cisplatin, there are other complexes such as those derived from Au(I) (auranofin) or Ru(III) (KP1019 and TLD-1433) that are at different stages of clinical trials for various cancer diseases. Within this context, cyclometallated iridium complexes, with the general formula [Ir(C^N)2(N^N)]+, have also shown their great potential in medicine, not only in chemotherapy but also in photodynamic therapy [1]. Furthermore, these species are generally emissive and, therefore, can be used as luminescent tags in bioimaging, which allows the collection of key information using non-invasive techniques [2].

Herein, we present two families of Ir(III) complexes containing cyclometallated ligands, either 2-phenylbenzothiazole (family Type I) or 2-(2-pyridyl)benzothiophene (family Type II), and series of benzoimidazol deriatives funtionalised with a chromophore (antracene or acridine). Cytotoxicity and photocytotoxicity were investigated via MTT assays, revealing very promising results for some of the complexes. Furthermore, the biodistribution was analysed by fluorescence microscopy.

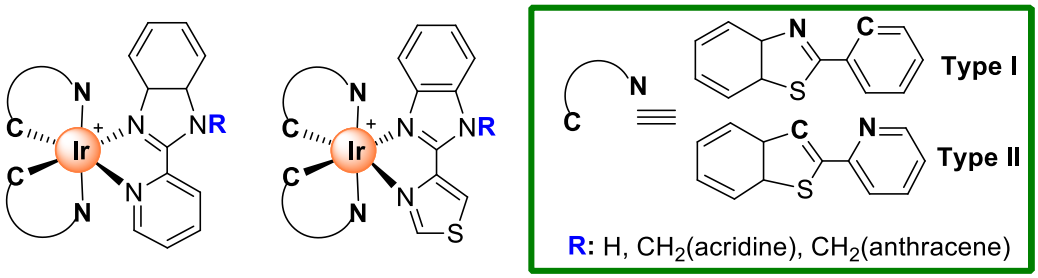

Figure 1. Synthesised Ir(III) complexes

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Exploring the Potential of Coinage Complexes with Nucleobase Ligands for Anticancer Applications

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Keywords: Bioinorganic Chemistry, Copper, Silver, Gold, Nucleobases

Cisplatin's fortuitous discovery revolutionized metallodrugs for anticancer use. However, despite its effectiveness against numerous types of tumors, cisplatin has notable side effects [1].

Coinage metals are of particular interest in this regard due to their biocompatibility. Achieving high stability in physiological conditions is essential for enhancing the delivery and transport of these complexes to tumor cells. Ancillary ligands play a critical role in this regard, as their stereoelectronic properties can be easily modulated [2].

In addition, the interaction of nucleobases with transition metals has attracted much attention over the past few decades in understanding bioinorganic processes. Nucleobase derivatives have also shown promise as therapeutic agents, and the combination with metal complexes offers numerous potential pharmaceutical applications [3].

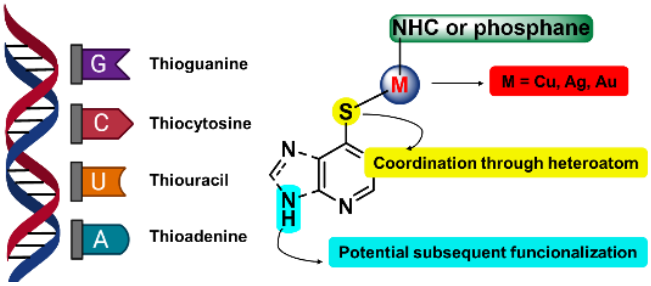

Figure 1. Graphical abstract of the new coinage metal complexes

This article presents a novel approach to synthesizing new Cu, Ag, and Au complexes containing an ancillary ligand such as N-heterocyclic carbenes (NHCs) or phosphanes, and a nucleobase modified with a thiol group as the coordination point through the heteroatom. The presence of multiple amino groups in the nucleobase skeleton allows for further modification of their properties by introducing other pharmacophore and/or chromophore groups (Figure 1).

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Carbohydrate-modified metal complexes effect on metastasis-related processes

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Keywords: metal-glycoconjugates, ruthenium polypyridyl, palladium, antimetastatic metallo-drugs

Cancer is the second most frequent cause of death in the world. Research on a variety of metal compounds have demonstrated that the unique properties of metals can be exploited and used for cancer cell-targeted approaches. Within this field, functionalization of drugs with carbohydrates is an anticancer strategy that has gained great interest in recent years [1]. The presence of carbohydrates can improve solubility and allow selective interactions with carbohydrate-binding proteins involved in cell adhesion, migration, and angiogenesis-related processes, all closely related events to metastasis [2]. On the other hand, polypyridyl compounds such as 1,10-phenanthroline are powerful bidentate metal chelating ligands able to act as DNA intercalators and groove binders. Furthermore, they serve as scaffolds for several potent stabilizers of DNA G-quadruplexes, which are being investigated as potential targets for anticancer drug development [3].

In contrast with other complex carbohydrate functionalization reactions reported, we have used an efficient and stereoselective N-glycosylation of 5-amino-1,10-phenanthroline, which allows the one pot synthesis of N-(1,10-phenanthrolin-5-yl)-β-glycopyranosylamines[4]. Herein, we report the synthesis and biological studies of novel polypyridyl Ru(II) and palladium(II) compounds containing N-phenanthroline glycosylamine ligands. Effect of the carbohydrate on the biological behaviour of the metalloglycoconjugates has been elucidated by comparison with corresponding metal-aglycones.

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New Cyclometalated Osmium(II) Complexes inhibit the Proliferation of Cancer Cells

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Keywords: osmium, anticancer, calcium homeostasis.

Osmium is a member of the platinum group of metals, but its complexes have been less studied as anticancer agents than complexes based on the other metals of the group as platinum and ruthenium. Recently, our research group has synhtesized new cyclometalated ruthenium complexes which are competent for hypoxic cancers via green light irradiation [1].

Herein, we present the synthesis of a new series of cyclometalated osmium(II) complexes of the type [Os(C^N)(N^N)$_2$]OTf where N^N is bipyridine or dipyrido[3,2-d:2',3'-f]quinoxaline and C^N is based on 2-arylbenzimidazole. The antiproliferative activity of complexes has been widely studied using a panel of human cancer cells under dark conditions and green light irradiation. Moreover, the mechanism has been investigated revealing that osmium complexes disrupt calcium homeostasis.

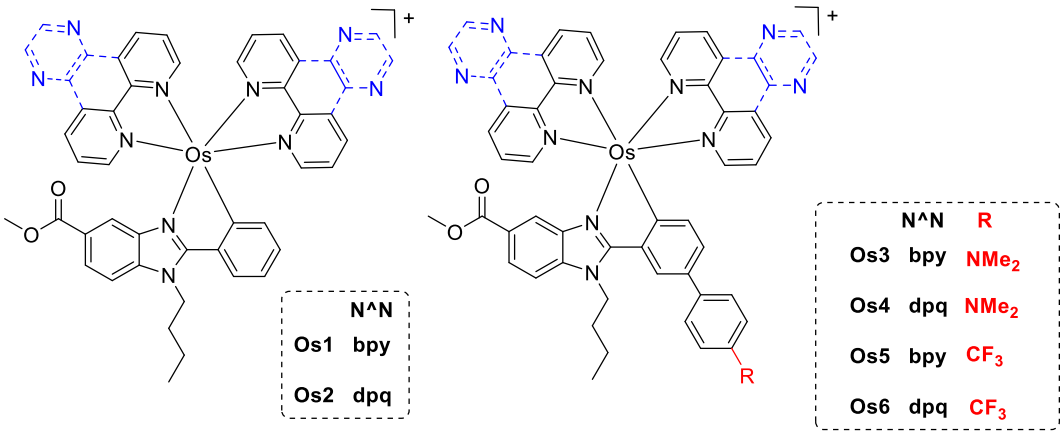

Figure 1. General structure of Os(II) complexes

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A Silver(I) complex with Probenecid: *in vitro* Antitumoral Activities and Development of a Cellulose-based device for the Sustained Release of the Complex

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Keywords: Probenecid, Silver complex, Antitumoral activity, Drug release, Bacterial cellulose

The increasing resistance of certain types of cancer to different classes of anticancer drugs constitutes a global case of concern [1]. Skin cancer, one of most diagnosed worldwide, results in high rates of morbidity and mortality [2]. In recent works, the *in vitro* antiproliferative activity of new silver complexes over a variety of cancer cells has been described [3,4]. *In vivo* studies developed by our research group using the silver(I)-nimesulide complex [3] demonstrated its noteworthy activity against squamous cell carcinoma in an animal model using a bacterial cellulose (BC) membrane as drug release system. Here, we describe the synthesis, spectroscopic characterization, and antitumoral activity of a silver(I) complex with probenecid (Ag-PROB), and the application of a BC membrane for the sustained release of the complex. The Ag-PROB complex was obtained by the reaction alkaline aqueous solution containing 1.0 mmol of probenecid and 1.0 mmol of $AgNO_3$. The synthesis was carried out under constant stirring for 2 hours at room temperature, and the solid obtained was collected by filtration, washed with water and dried. Elemental analysis indicated a 1:1 metal:ligand ratio. Infrared (IR), solid-state ^{13}C nuclear magnetic resonance (NMR) spectroscopies and Density Functional Theory (DFT) suggest that the ligand is coordinated to the silver ions by the oxygen atoms of the carboxylate group, forming a dimeric structure. The Ag-PROB complex showed antiproliferative activity over a panel of cancer cell lines (A549, HepG2, HeLa, MCF-7) and a low toxicity in normal eukaryotic cells (HUVEC and HaCat). Such results open a perspective for *in vivo* tests to evaluate the potential of BC-Ag-PROB device for the treatment of skin cancer.

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Enhancing Colon Cancer treatment: the potential of NSAIDS and Gold(I) complexes working in tandem

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Keywords: Cancer, metallodrugs, bioinorganic chemistry, gold(I), cyclooxygenase-2, multitarget therapy, NSAIDs, thioredoxin reductase

The use of non-steroidal anti-inflammatory drugs (NSAIDs) as chemopreventive agents for cancer, especially those related to the gastrointestinal tract, has become increasingly important in recent years [1]. One therapeutic target of NSAIDs is the enzyme cyclooxygenase COX-2, which is involved in inflammatory reactions that can lead to tumorigenesis [2]. Recent studies have shown that modifying the structure of NSAIDs and coordinating them with metal centers can improve their selectivity towards cyclooxygenases (COX-1/COX-2) and enable them to inhibit lipooxygenase (LOX) enzymes as well [3,4].

In this work, we have synthesized gold(I) complexes coordinated with new derivatives of NSAIDs that have a modified structure in the acid residue, thereby developing a multi-targeted therapy strategy. We conducted studies to determine the potential biological properties of these complexes against the colon cancer tumor line Caco-2/TC7 and to investigate their mechanism of action.

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Potencial Actividad Citotóxica de complejos de Rutenio(II) con Ligandos Tiosemicarbazona

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Palabras clave: Areno complejos de rutenio, tiosemicarbazona, citotoxicidad, difracción de raios X.

La aparición de mayores efectos secundarios y resitencia a fármacos llevó a desarrollar en la última década un conjunto de nuevos agentes antitumorales como alternatica al *cis*-platino y a sus derivados.[1] Dentro de estos nuevos agentes antitumorales, destacan los complejos de rutenio que han mostrado buena actividad y selectividad frente a tumores primarios y metastásicos.[2]

Por eso, en esta comunicación se presenta la síntesis, caracterización estructural y estudio de la actividad antitumoral *in vitro* frente a un conjunto de células tumorales de los complejos de rutenio con fórmula general [RuCl(κ^6-areno)(κ^{2}N3,S- TSC)]$^+$.

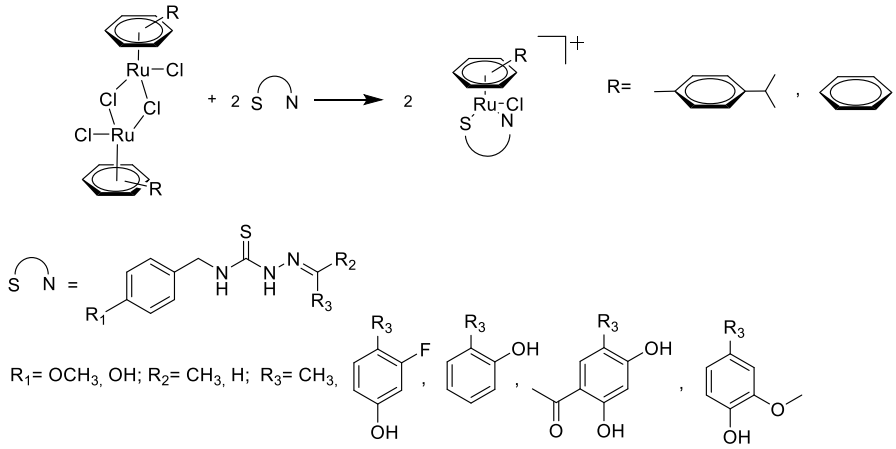

Figura 1. Esquema de síntesis de los complejos de rutenio(II) con ligandos tiosemicarbazona.

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Estudio de Complejos mono y polinucleares de Fe(II) Bioinspirados con Ligandos tipo Salen

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Palabras clave: Oxigenasas, ligandos tipo salen, cinética, Fe(II).

La oxidación selectiva de moléculas orgánicas es un proceso fundamental tanto en el laboratorio como en muchos procesos biológicos. En la naturaleza existen una serie de metaloenzimas que se encargan de realizar estos procesos. Algunas de estas metaloenzimas, como la metanomonoxigenasa, [1] contienen dos átomos de hierro en su estructura. Estas metaloenzimas catalizan la incorporación de átomos de oxígeno a un sustrato, realizando esta función en condiciones de reacción suaves además de presentar una gran regio- y estereoselectividad. Para la comprensión del modo de acción de estas enzimas es fundamental un conocimiento de la naturaleza de los intermedios que se forman en la reacción con oxidantes, así como la reactividad de esos intemedios frente a sustratos externos.

En esta comunicación se presentan los resultados preliminares obtenidos en el estudio de la formación de complejos de Fe(II) con ligandos de tipo salen, [2] bioinspirados en las metaloenzimas mencionadas y que contienen N y O como átomos donadores,. La estructura de los ligandos presenta dos o tres centros donadores que permiten la formación de complejos polinucleares con sitios de coordinación similares. Se discutirán tanto los aspectos termodinámicos como cinéticos de la formación de complejos, así como su reacción con distintos oxidantes.

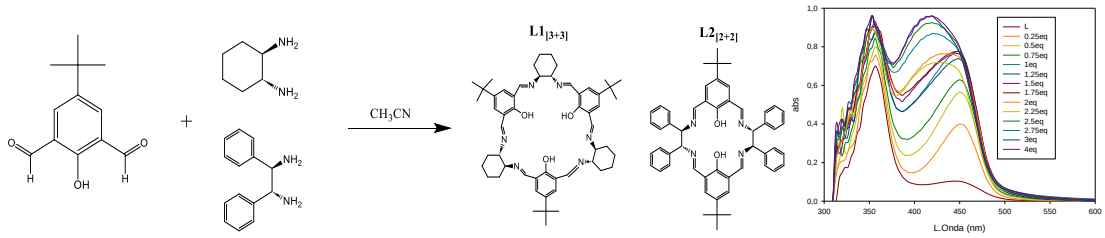

Figura 1. Ligandos utilizados y cambios espectrales observados tras la adición de distintas cantidades de Fe(II).

Agradecimientos: Se agradece la financiación del Ministerio de Ciencia, Innovación y Universidades a través del proyecto PID2019-107006GB-C22.

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Encapsulation and delivery of an immunogenic copper(II) complex using polymeric micelles

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Keywords: Metal complexes, Nanoformulation, Cancer Stem Cells

Cancer stem cells (CSCs) are tumour-initiating cells that can be responsible of metastasis and relapse [1]. In our group, metal complexes with promising anti-CSCs properties have been successfully synthesised and characterised [2-4]. However, their poor solubility in aqueous solutions can affect their internalisation by cells and their therapeutic effect. A well-established strategy to improve the solubility of lipophilic compounds is encapsulation into biodegradable nanoparticles (NPs). Elongated micelles (filomicelles) are less prone to be recognised by immune cells, leading to a longer circulating time in the blood and increased accumulation in the tumour. *In vivo* studies showed that filomicelles are able to effectively deliver anti-tumoral agents to tumours in murine models [5]. In this poster, we report the preparation and characterisation of spherical poly(lactic-*co*-glycolic acid)-polyethylene glycol (PLGA-PEG) NPs and poly(ethylene glycol)–poly(caprolactone) (PEG-PCL) filomicelles containing an immunogenic Cu(II) complex with anti-CSCs activity, and its delivery into breast CSCs. The Cu(II) complex was successfully encapsulated into PLGA-PEG NPs by nanoprecipitation and characterised by imaging and analytical methods. The polymeric envelope increased breast CSCs uptake and potency relative to the free Cu(II) complex. The encapsulated Cu(II) complex was able to induce reactive oxygen species and to activate endoplasmic reticulum stress and immunogenic cell death [6]. The same Cu(II) complex was encapsulated into PEG-PCL filomicelles using various self-assembly techniques: nanoprecipitation, film hydration and solvent evaporation. The morphology of the different formulations was characterised by transmission electron microscopy. The formulation obtained by solvent evaporation was employed for biophysical and biological studies and its potency towards breast CSCs was compared to the spherical NPs.

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Ferrozoles: Ferrocenyl derivatives of Letrozole with Dual Effect as Potent Aromatase Inhibitors and Cytostatic Activity

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Keywords: aromatase inhibitor, cytostatic, letrozole, docking, ferrocenyl

In the treatment of hormone-dependent cancers, aromatase inhibitors (AI) are receiving increased attention due to some undesirable effects of SERMs (selective estrogen receptor modulators). Letrozole is the most active AI with 99% aromatase inhibition. Unfortunately, this compound also exhibits some adverse effects. Therefore, there is an urgent need to explore new types of AIs that retain the same – or even increased – antitumor ability.

Inspired by the letrozole structure, a set of new derivatives has been synthesized replacing a benzonitrile fragment by a ferrocenyl moiety and including different heterocycles (Figure 1). The derivative that contains a benzimidazole ring, namely compound **6**, exhibits a higher aromatase inhibitory activity than letrozole and it also shows potent cytostatic behavior when compared to other well-established aromatase inhibitors, as it is deduced from dose-response, cell cycle, apoptosis and time course experiments. Furthermore, 6 promotes the inhibition of cell growth in both an aromatase-dependent and -independent fashion, as indicated by the study of A549 and MCF7 cell lines. Molecular docking and molecular dynamics calculations on the interaction of **6** or letrozole with the aromatase binding site revealed that the ferrocene moiety increases the binding affinity.

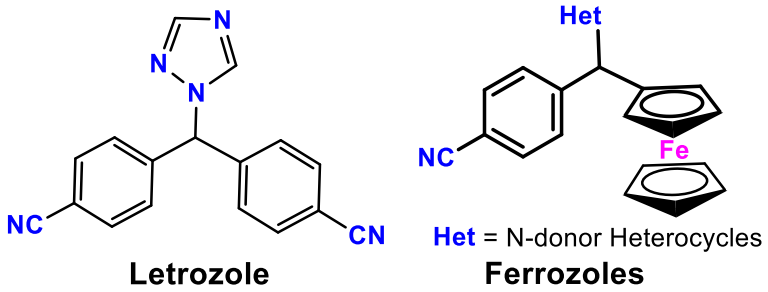

Figure 1. Structure of letrozole and the synthetized ferrozoles.

Acknowledgements: This work was supported by the MICINN, AEI and FEDER (Grants PID2021-127187OB-C21 and PID2021-122222OB-I00) and by JCCM (grants SBPLY/19/180501/000260, SBPLY/19/180501/000251 and SBPLY/19/180501/000191).

Gold complexes with NHC ligands: Tuning Luminescent and Biological properties

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Keywords: gold, luminescence, cancer, N-heterocyclic carbenes, theranostic

During the last decades, the interest in *N*-Heterocyclic Carbenes (NHC) has increased because their applications in different fields such as medicine, catalysis, and materials science [1]. This wide range of applications is a direct consequence of the great functionalization capacity of these compounds, being able to modify the substituents of both nitrogen atoms of the imidazole unit, and consequently, the electronic and steric properties of the final complexes.

The stability of these compounds with d^{10} cations such as Au(I) and Ag(I) has led to the development of new M-NHC species with applications in medicine (as antitumor or bactericidal agents) [2] or in catalysis (activation of multiple C-C bonds) [3].

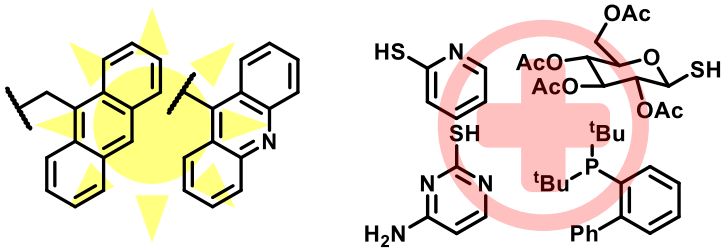

Figure 1. Fragments used in the design of the studied complexes.

The aim this work is the synthesis of Au(I) complexes with ligands that exhibit biological and/or luminescent properties, in order to study their potential use as theranostic drugs and imaging agents. For the synthesis of the luminescent ligand, two new imidazolium salts has been chosen, which contain anthracene and acridine fragments. The corresponding NHC-Au-Br complex has been functionalized with different ligands such as thiols, phosphines or nitrogen based derivatives, that provide the resulting complex with interesting biological properties.

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Complejos ciclometalados de Ru(II)

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Palabras clave: imidazol, ciclometalados, areno complejos de rutenio

Los ligandos que contienen anillos imidazol están presentes en una gran variedad de compuestos bioactivos con diferentes propiedades farmacológicas como anticancerígenos, antibacterianos, antivirales, antiepilépticos, antituberculosos y antifúngicos. Estos compuestos poseen propiedades únicas (elevada polaridad, así como capacidad para formar enlaces hidrógeno y compuestos de coordinación), que les permiten interactuar con una amplia variedad de biomoléculas [1]. Los complejos de rutenio son una alternativa como agentes antitumorales al cis-[PtCl2(NH3)2] y sus análogos, ya que presentan una mayor actividad frente a cánceres primarios y tumores metastásicos [2].

En esta comunicación presentamos la síntesis de los nuevos complejos de rutenio(II) C,N-ciclometalados del tipo [(η^6-p-cimeno)RuCl(κ^2-N,C-L)] donde HL = 1-(4 hidroxibencil)-2-(4-hidroxifenil)benzimidazol) y 4-[2,3-Dihidro-2-(4-hidroxifenil)-2-metil-1H-1,5-benzodiazepin-4-il]fenol. Para investigar la relación estructura-actividad, se evaluó la actividad citotoxíca *in vitro* de los ligandos benzoimidazol y los nuevos compuestos de rutenio (II) frente a un panel de líneas de celulas tumorales.

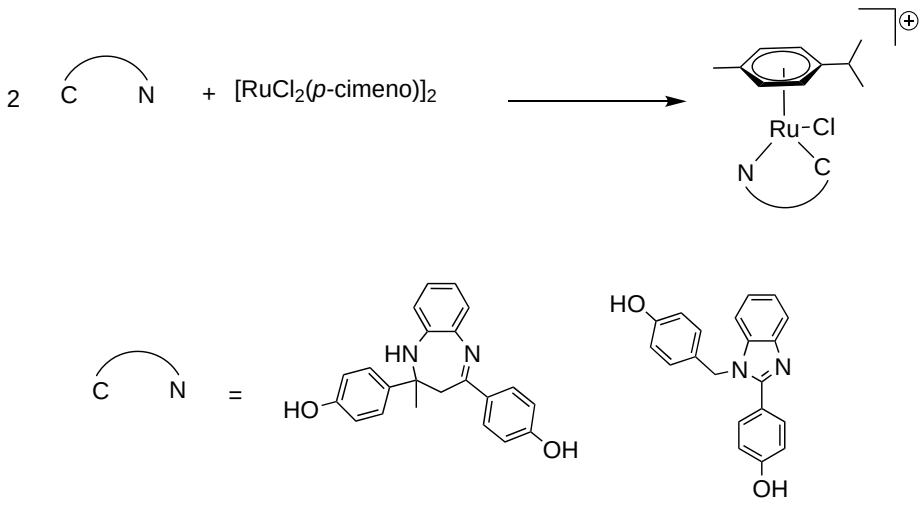

Figura 1. Esquema de síntesis

Agradecimientos: Ministerio de Ciencia e Innovación (PID2019-110218RB-I00).

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Organic/Inorganic Biomaterial composed of Hydroxyapatite and Collagen, Glycine or Sodium Formate

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Keywords: hydroxyapatite; bone, collagen; glycine, formic acid; carbonate substitution

Cremation provokes chemical and structural transformations in bones, whose study can be useful for forensic and archaelogical purposes [1]. The thermally induced changes affect to both the organic (mainly collagen protein) and inorganic (carbonate) contents in the hydroxyapatite (HAp) matrix. In bones and teeth, carbonate replaces up to a 6 % (w/w) of the hydroxyde and phosphate anions in the major $Ca_{10}(OH)_2(PO_4)_6$ phase (70 % of the weight of bone). The present work aims to establish a relationship between temperature ranges and the changes detected in bones, and to shed light into the origin of such changes and the chemical species involved in them. In order to achieve this, we have simplyfied the system by the preparation and characterization of a carbonate-substituted synthetic HAp derivative [2], together with synthetic HAp mixtures with organic molecules in increasing chemical complexity: HAp + (15, 40% NaHCOO), HAp + (15, 40% glycine, the most abundant amino acid in the collagen protein) and HAp + (15% collagen). All samples have been subjected to heat treatment in the RT-1100 °C range for 3 h. Finally, a comparison with chicken and pork bones has been performed.

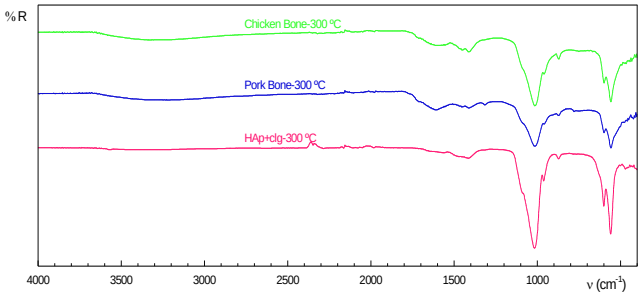

Figure 2. FTIR Hap + 15% collagen, Hap + pork and Hap + chicken bone at 300 ˚C.

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Multifunctional Nanomaterials towards Efficient and Sustainable Crop Production

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Keywords: calcium phosphate, antibacterial, nanofertilizer, sustainable, agriculture

In vivo biomineralization has long been used as a source of inspiration for the design of advanced biomaterials with high levels of performance and new functionalities [1]. Calcium phosphate nanoparticles (CaP-NPs) mimicking the bone mineral exhibit outstanding properties including: inherent biocompatibility and biodegradability, lack of toxicity, superior adsorption capacity of organic molecules, high capacity to host a large variety of ionic substitutions (*e.g.* K^+, Fe^{3+}, Zn^{2+}, CO_3^-, NO_3^-, etc.) and pH-dependent solubility providing a controlled and gradual release of the ionic constituents and adsorbed molecules upon dissolution.[2] Owing to the fact that they are intrinsically rich in Ca and P (important plant nutrients), their applications in precision agriculture for the controlled delivery of nutrients (*i.e.,* P, K, Ca, N) or bioactive molecules (*i.e.,* methyl jasmonate) is growing exponentially in the last years [2].

We will present an interesting strategy based on the internal doping of CaP-NPs to develop a mulifunctional nanomaterial with dual agricultural applicability: enriching crops with nutrients with important metabolic functions in humans and avoiding the development of important bacterial-based diseases, with considerable negative impact in crop production.[3] Results from field experiments in relevant crops will be presented to show the efficiency of the nanoparticles [3]. These all-in-one nano-platforms offer great opportunities to improve the safety and sustainability of agriculture while increasing crop yields and plant nutritional values.

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Multifunctional Nanomaterials against Microorganisms based on Silver Dopped Silica Nanoparticles

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Keywords: drug delivery, nanomaterial, metal complex, microorganisms

Silver nanoparticles (AgNPs) are one of the most widely nanomaterials used as antimicrobial agents. Despite they can be used in low concentration with great efectivity, they do not promote bacterial resistance, which is a remarkable advantage over other treatments [1]. In addition to this, the use of silver is not limited to metal nanoparticles, since a wide variety of metallorganic complexes with different organic ligands can be prepared, enhancing the expected biocide properties [2].

This work focuses on the synergistic effect provided by the combination of different silver triazolopyrimidine complexes with AgNP dopped mesoporous silica nanoparticles, taking into consideration the interaction between the complex and the carrier (covalent binding, adsorption or mix directly at the culture medium). Preliminary studies show a big dependence on this factor on the bactericide (*E. coli*, *S. aureus* and *P. aeruginosa*) and fungicide (*C. albicans*) efectiveness of these materials, even improving the reference drug values in some cases.

Aknowledgements: Ministerio de Universidades de España and Resilience Funds Next Generation of the European Union (Margarita Salas Grant for S.J.-F.)

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Optical and Magnetic Properties of Aerogels/Hydrogels with Biomedical Applications

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Keywords: aerogels, hydrogels, amyloid nanofibers, nanoparticles, biomedical applications.

Aerogels and hydrogels based on biopolymers such as polysaccharides and proteins are promising materials for biomedical applications due to their biodregradability, biocompatibility, abundance and non-toxicity. Furthermore, the are low-cost and renewable, making them suitable materials to address environmental issues. Biopolymers often have a high density of functional surface groups, thus providing convenient anchoring points for additional funtionality and opening up to new applications such as filtration, oil-water separation, catalysis and especially, in medicine (tissue engiereering, cell growth, disease diagnosis and treatment, drug delivery and bio-sensing) [1].

Recently, we have reported functionalized amyloid nanofibers for globular proteins [2-3]. Herein, we have used proteins as a template to from hydro- and aerogels and to incorporate different metallic nanoparticles (figure X) in order to obtain multifunctional materials with optical and magnetic propierties, thus creating new fascinating systems with new applications.

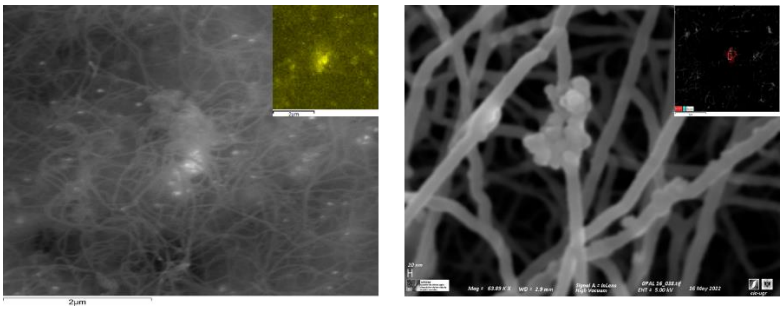

Figure 1. SEM image of fibrillar protein aerogel with gold nanoparticles (left) and maghemite nanoparticles (right).

Acknowledgements: proyecto P18-RT-1373 de la Junta de Andalucía y grupo FQM368 del departamento de Química Inorgánica.

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Intestinal crossing of Metal-Organic Frameworks

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Keywords: (Metal-organic frameworks, intestinal crossing, drug delivery)

Drug delivery systems (DDSs) are one of the most promising tools for human healthcare owing to the temporary and local control of drug release. The design of new and intelligent treatments has resulted in the development of a new class of nontoxic carriers, known as metal−organic frameworks (MOFs). MOFs represent an interesting class of synthetic crystalline materials consisting of organic ligands bonded to metal ions in such a way as to generate a porous network accessible to host molecules. Particularly, biocompatible nanoscaled metal−organic frameworks (nanoMOFs) have been widely studied as DDSs, through different administration routes, with rare examples in the convenient and commonly used oral administration.

So far, the main objective of nanoMOFs as oral DDSs was to increase the bioavailability of the cargo, without considering the advantages of the MOF intestinal crossing. In this work, we propose to address for the first time the direct quantification and visualization of MOFs' intestinal bypass [1]. The microporous nanoMOF, MIL-127, exhibiting interesting properties as a nanocarrier (biocompatibility, large porosity, green and multigram synthesis, stability along the gastrointestinal tract) was selected and its outer surface was engineered with the biopolymer chitosan (CS@MIL-127) to improve the nanoMOF intestinal permeation. The biocompatibility and intestinal crossing of nanoMOFs is confirmed using *Caenorhabditis elegans*; these worms are able to ingest enormous amounts of nanoMOFs (>35 g *per* kg). Finally, an *ex vivo* intestinal model (rat) is used to further support the nanoMOFs' bypass across the intestinal barrier, demonstrating a fast crossing (only 2 h). This work on the intestinal crossing of intact nanoMOFs sheds light on the safe and efficient application of MOFs as oral DDSs.

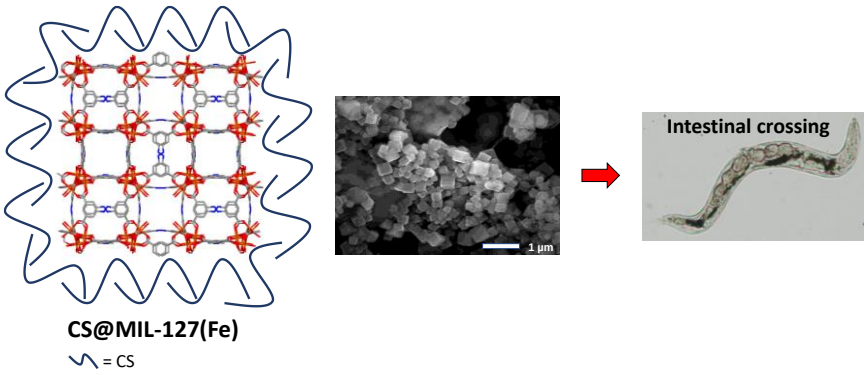

Figure 1. Schematic view of the structure of CS@MIL-127, SEM image, and direct observation of the bypass in the *C. elegans* model.

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Zeolitic Imidazole Frameworks as Nerve Agent Antidotes

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Keywords: drug delivery, acetylcholinestherase, organophosphate, metal-organic framework

Organophosphorus based pesticides and chemical warfare nerve agents are extremely toxic compounds, due to the central nervous system damage by irreversible inhibition of acetylcholinesterase (AChE) activity [1]. In this regard, much effort has been devoted to develop materials for protection against exposure to chemical warfare agents, particularly filters and detoxication catalysts [2,3]. However, disruptive antidots for poisoning treatment has been less explored. In this work, we have evaluated the effect of different zeolitic imidazolate frameworks as materials for organophosphate poisoning treatment: ZIF-L, ZIF-8, and ZIF-EC1. The sensitivity of the Zn-N(mIm) coordination bond to the G-type nerve agent model compound disisopropylfluorophosphate (DIFP) leads to both P-F bond hydrolysis, into nontoxic disisopropylphosphate (DIP) and framework structural degradation, with concomitant controlled release of nucleophilic mIm. The delivered mIm attacks AChE-organophosphate adduct leading to the recovery of the original enzymatic function and to reverse the organophosphate poisoning (**Figure 1**).

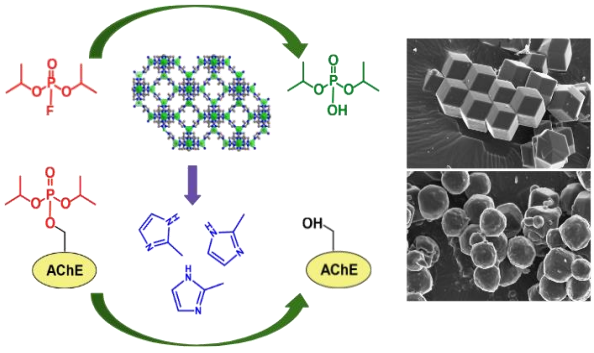

Figure 1. Dual behavior of ZIF-8 for DIFP degradation and inhibited AchE reactivation.

Acknowledgments: Spanish MCIN; AEI /10.13039/501100011033 (Project PID2020-113608RB-I00)

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RS69N@MOF-808: Un nuevo Antídoto para tratar la intoxicación por Agentes Fosforados

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Palabras clave: Sistema dual, oxima, reactivación acetilcolinesterasa, organofosforado.

Los compuestos organofosforados son altamente tóxicos debido a su capacidad para inhibir la enzima acetilcolinesterasa (AChE) provocando, aproximadamente, 110.000 muertes/año. El tratamiento actual tras la intoxicación por un agente organofosforado incluye la administración intravenosa, en pequeñas dosis, de moléculas reactivadoras de la AChE (ej. oximas). En este contexto, las redes metal-orgánicas porosas (MOFs) son sistemas idóneos para eliminar compuestos organofosforados presentes en los fluidos corporales, debido a su alta capacidad de adsorción y elevada densidad de sitios activos. Asimismo, pueden liberar de forma controlada y sostenida en el tiempo, diferentes moléculas bioactivas previamente adsorbidas en la matriz.

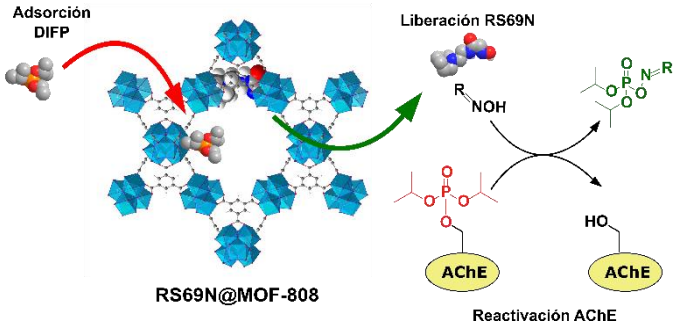

Figura 1. Adsorción de DIFP y liberación controlada de la oxima RS69N.

En este trabajo, se ha preparado un nuevo material híbrido basado en el MOF-808 ($[Zr_6O_4(OH)_4(trimesato)_2(HCOO)_8]$) y una oxima neutra, la RS69N, como tratamiento tras la intoxicación por un compuesto organofosforado (Figura 1) [1]. El material híbrido (RS69N@MOF-808) es capaz de liberar de forma controlada la oxima (37,5 % tras 24 h) conduciendo a una reactivación completa de la enzima AChE, en medios fisiológicos simulados. Al mismo tiempo, este sistema presenta una excelente capacidad de adsorción del compuesto organofosforado diisopropilfluoro fosfato (DIFP) (95 % de adsorción a las 24 h) reduciendo en un 78,4 % la inhibición de la enzima.

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Synthesis and characterization of Half-Sandwich Rhodium and Iridium Antimicrobials

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Keywords: multidrug-resistant, bacteria, iridium, rhodium, valproate.

The increasing global spread of multidrug-resistant (MDR) bacteria [1], which cause diseases that cannot be treated with conventional antibiotics, is threatening the world. Recent reports have highlighted the promising antibacterial properties of Rh and Ir half-sandwich complexes [2] and valproic acid (VPA) and derivatives [3]. Herein we report the synthesis and characterization of new half-sandwich Rh(III) and Ir(III) complexes containing benzimidazole ligands derivatized with valproic acid. We have also tested their biological activity against multidrug-resistant bacterias of clinical interest: vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* (Gram-positive) and *Acinetobacter baumanii* and *Pseudomonas aeruginosa* Gram-negative. The valproic acid conjugation seems to improve the stability and to switch on the antibacterial activity of the iridium and rhodium complexes.

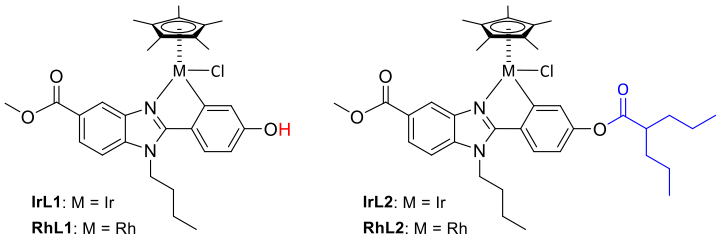

Figure 1. General structure of Ir(III) and Rh(III) half-sandwich complexes synthesized.

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NHC-Gold-Alkynyl Complexes derived from 3-Hydroxyflavones as potential Bactericide Agents

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Keywords: Alkynyl, N-heterocyclic carbene, gold complexes, hydroxyflavone, antibacterial, dihydrofolate reductase

N-heterocyclic carbenes gold complexes represent a promising class of metal based drugs for the treatment of infectious diseases or cancer, mainly due to their high stability under physiological conditions and towards blood thiols. The use of organometallic derivatives, including NHC complexes, as antibacterial agents [1] has received increasing interest mainly due to their specific modes of action that could hinder the development of mechanisms of bacterial resistance.

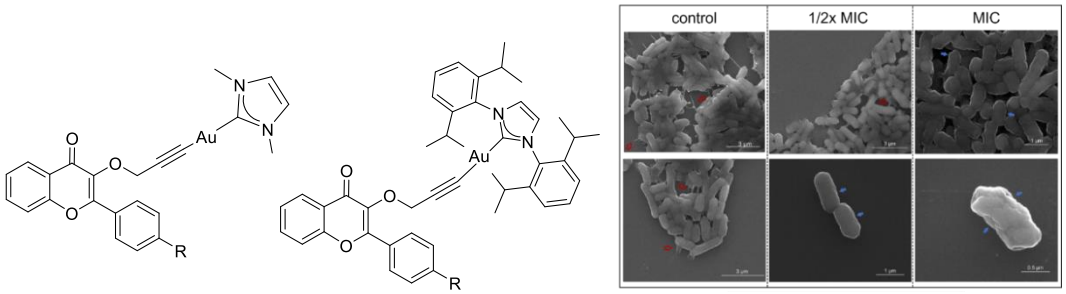

Figure 1. Gold complexes and SEM images

Here we report on the synthesis of new gold(I) N-heterocyclic carbene derivatives with flavone-based ligands functionalized with a propargyl ether group. The study of their biological effect reveals that the introduction of NHC ligands induces antibacterial activity, even against Gram-negative bacteria, which points to a different mechanism than that based on enzyme thioredoxin reductase interaction. In fact, significant decreased of the dihydrofolate reductase activity was detected instead of reduction of TrxR activity of E. coli cell lysates. Besides, destabilization of the bacterial membrane causing loss of structural integrity is observed by SEM in the bacteria E. coli envelope after treatment with gold complexes (Figure 1).

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Two Zn-MOFs based on a tricarboxylate linker that promote antibacterial activity

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Keywords: metal-organic framework, zinc, antibacterial activity

Metal-organic frameworks (MOFs) are compounds with high porosity, flexibility, and stability. This makes MOFs good candidates for a wide variety of applications. Nowadays, drug-resistance bacteria has turned into a global health problem, and one strategy to control this problem is the development of novel antibacterial agents. Since zinc is an essential element in human body, we have obtained two novel Zn-MOFs based on a tricarboxylate ligand, named GR-MOF-8 and GR-MOF-9. The structures were elucidated by single-crystal X-ray diffraction and compounds were fully characterized by physicochemical techniques. In addition, their antibacterial properties against *S. aureus* and *E. coli* were studied. The results show two open 3D MOFs with channels along the *a* axis. Finally, both materials show antibacterial activity, highlighting GR-MOF-8, which is likely due to the progressive release of Zn^{2+}.

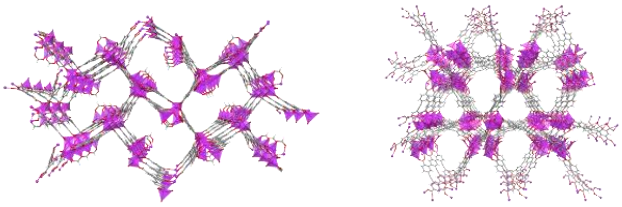

Figure 1. 3D structures of GR-MOF-8 and 9, respectively.

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Bisphenols Adsorption on Activated Carbon Clothes improved by the presence of Bacteria

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Keywords: BPA, BPS, E. coli, Activated carbon clothes, bioadsorption, water purification.

This study investigated the adsorption of two endocrine-disrupting chemicals, bisphenol A (BPA) and S (BPS), from water using activated carbon clothes (ACCs) in the absence and presence of bacteria *E. coli*. The experiment results indicate that ACC is a much better adsorbent of *E. coli* compared to commercial granular activated carbons, which is attributable to the differences in macrostructure or morphology between these adsorbents. Thus, ACCs comprise yarns formed by multitude of activated carbon fibers, whose interweaving produces a net in which the bacteria become trapped (Fig. 1). Kinetic study showed that the adsorption rates of the BPA and the BPS are reduced by the presence of bacteria due to obstruction of the macroporosity by adsorbed bacteria [1]. The presence of bacteria increases the adsorption capacity of ACC by around 33% for BPA and 24% for BPS (Fig. 2). This different behaviour is due to the fact that the relative affinity was more pronounced for BPA, due to its higher hydrophobicity. Bacteria outer walls formed by phospholipids increase the surface hydrophobicity of ACC. These results are of interest in the ACC applications for the bioremediation and biofiltration of water.

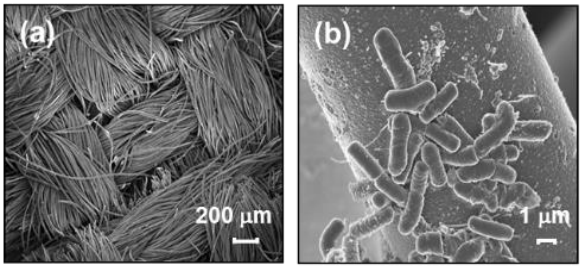

Fig. 1. SEM images of ACC before (a) and after bioadsorption (b).

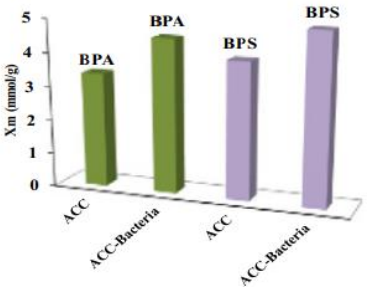

Fig.2. Adsorption capacity of bisphenols on ACCs in the presence and absence of bacteria.

Acknowledgements: The authors acknowledge financial support from the Junta de Andalucía (Projects FEDER-UJA-1380629 y FEDER-UJA-1381652).

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Recognition of Analytes of Environmental interest and Antioxidant Activity of a Pyridoxal-Polyamine

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Keywords: Pyridoxal, pollutants, SOD activity, coordination.

One of the biggest problems facing chemistry arises from the everyday increasing pollution of the environment. Pollutants range from toxic or radioactive metal ions and anions to chemical products like herbicides, pesticides or drugs. Supramolecular complexes offer a new and efficient way for the monitoring and removal of many pollutant substances [1]. Here, the synthesis, acid base behaviour and heavy metal (Hg^{2+}, Cd^{2+}, Pb^{2+} and $UO2^{2+}$) coordination chemistry of the polyamine TAL3px have been studied by potentiometric, NMR and UV Vis techniques. Furthermore, the antioxidant properties of the pyridoxal moiety have allow us to investigate the possible use of TAL3px and its metal complexes as mimics of defence enzymes against reactive oxygen species.

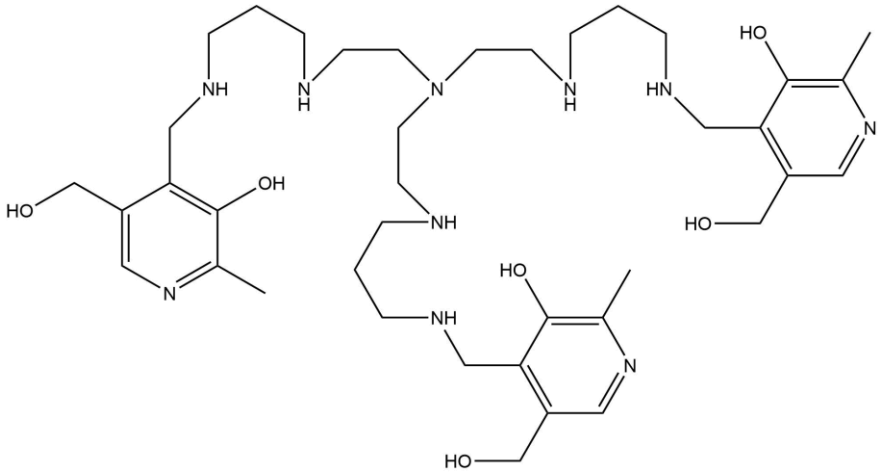

Figure 1. Structure of TAL3px.

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1*H*-pyrazole azamacrocyclic compounds as an antioxidant mimetics

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A class of metalloprotein mimetic is constituted by simple metal complex able to reproduce, at least in part, the structure, properties, or function of the active centre of given enzymes. The superoxide dismutase (SOD) [1,2] family of enzymes is the first biological line of defence against reactive oxygen species (ROS) produced as result of imbalances in oxygen metabolism but it's the familly of catalase enzymes the ones that finish the cell detoxyfication process. ROS species are related to neuronal death processes in neurodegenerative disorders as Alzheimer, Parkinson, and Huntington diseases.

In this work, we purpose the design, synthesis, and characterization of metal complexes of azamacrocyclic ligands with 1*H*-pyrazole aromatic spacers as SOD and catalase mimetics. We study their coordination with Cu(II) at different molar ratios and their applications as SOD and catalase mimetics [2].

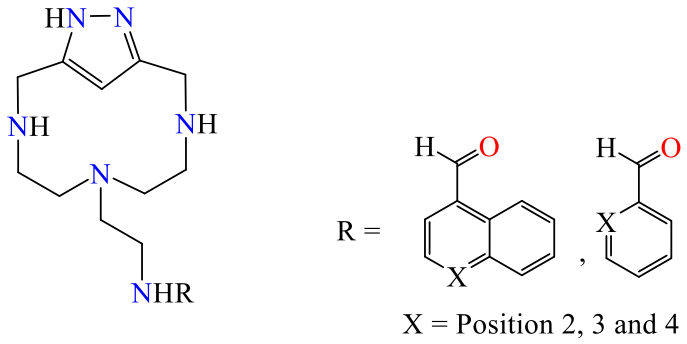

Figure 1. Azamacrocyclic ligands constituted by polyamine tris 2-(aminomethyl)amine linked to an 1*H*-pyrazole spacer; R= pyridine, quinoline.

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Biomimetic Nanoelicitors: a new strategy towards more efficient and sustainable viticulture

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Keywords: nanotechnology, calcium phosphate, elicitor, precision agriculture, viticulture

Currently, climate change alowg with increasing populations and declining soil quality are challenging global food security triggering to the dire need of developing much more sustainable agriculture alternatives. In this line, the application of nanotechnology in agriculture provides multiple benefits over conventional agrochemicals such as controlled release kinetics, enhanced permeability and solubility, and prevention of premature degradation under harsh conditions [1,2].

In this context, calcium phosphate nanoparticles (CaP NPs) as biomimetic apatite (Ap) and its precursor phase, amorphous calcium phosphate (ACP), are exposed as ideal nanocarriers towards more efficient and sustainable agrochemical practices due to their main composition is rich in plant nutrient (Ca and P), bioactivity, biocompatibility and biodegradability properties, together with the capacity to incorporate anionic or cationic species in their structure, providing them a slow release of the species [3-5].

In the last years, our group has prepared multi-nutrient nanofertilizers that allows a gradual release of macronutrients (NPK) [3]. In addition, we have developed a novel nanoelicitor (nano-MeJ) by functionalization of CaP NPs with the elicitor methyl jasmonate (MeJ), which stimulates the production of secondary plant metabolites (anthocyanins, stilbenes and flavonoids) in grapes. This nano-MeJ provided a protective effect against thermal degradation and offered a gradual release. These improvements allow reduce 10-fold the amount of elicitor in Monastrell vineyards *in vivo*, maintaining grape quality [4].

In this communication, two types of NPs (ACP and Ap) were functionalizated with MeJ and some important features such as size, morphology, surface charge and structure were discussed. Furthermore, the adsorption capacity, release kinetics and thermal stability were studied and tested by foliar application in Monastrell (*Vitis vinifera L*) vineyards. Field experiment showed the use of ACP-MeJ and Ap-MeJ as nanocarriers of elicitors, improving wine quality in a more sustainable way [5].

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Desulfurization reactions of Thiosemicarbazone-copper(II) complexes in acid and basic media

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Keywords: copper, crystal structure, DFT, desulfurization, thiosemicarbazone

Antitumor studies on thiosemicarbazones (TSCs) have found that reactions of free TSCs with intracellular copper could be pivotal to understand the biological activity [1]. Phase I-III clinical trials have reported glucuronide formation and an increase in sulfate contents in plasma, which suggest possible transformations of TSCs in physiological media [2]. The present work on pyridine-2-carbaldehyde thiosemicarbazone (HL), the common fragment to all the TSCs checked in clinical trials up to date, shows that Cu(II)-HL compounds are prone to undergo desulfurization reactions in acid and basic media. Ancillary ligands with relatively low coordinating ability, as nitrato or perchlorato, allow to synthesize and crystallize species involved in these processes. Spectral evidences for the formation of $[Cu_2L_3]^+$ entities, as those present in $[Cu_2L_3](ClO_4)\cdot 2H_2O$ (**1**), in desulfurization processes at biological pH values are supported by DFT theoretical calculations that identify a highly exergonic (ΔG = –146.1 kcal·mol^{-1}) nucleophilic attack of a hydroxide anion to the thioamide carbon that triggers the process (Figure 1).

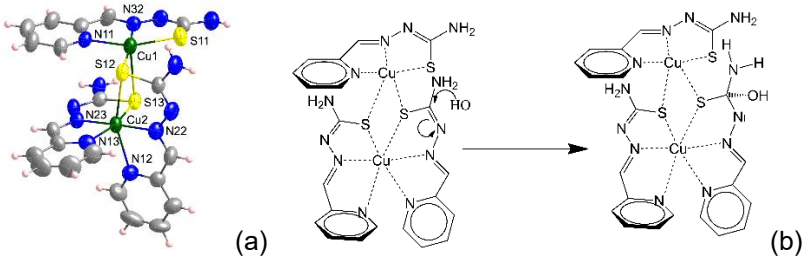

Figure 1. The $[Cu_2L_3]^+$ cation in 1 (a), together with the most exergonic step in the process (b).

Acknowledgements: European Union H2020-LC-SC3-2020-NZE-RES-CC, NMBP-16-2020-GA 953152 and DT-NMBP-04-2020 Projects and Ministerio de and Ministerio de Ciencia, Innovación y Universidades CTQ(QMC) RED2018-102471-T MultiMetDrugs Network (Spain).

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New Desulfurization process with Biological significance: Transformation of Thiocarbohydrazone in Azine

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Keywords: desulfurization, biological activity, thiocarbohydrazone

Thiosemicarbazones and its analogous thiocarbohydrazone are promising compounds regarding its antitumoral activity. The mechanism of action of this type of molecules at biological leve is barely known even if some metabolic reaction products in wich they are involved have been identify, including the oxidative desulfurization [1]. Our research group [2] has a broad experience in the study of oxidative desulfurization process of thiosemicarbazones, in some cases induced by metal ions.

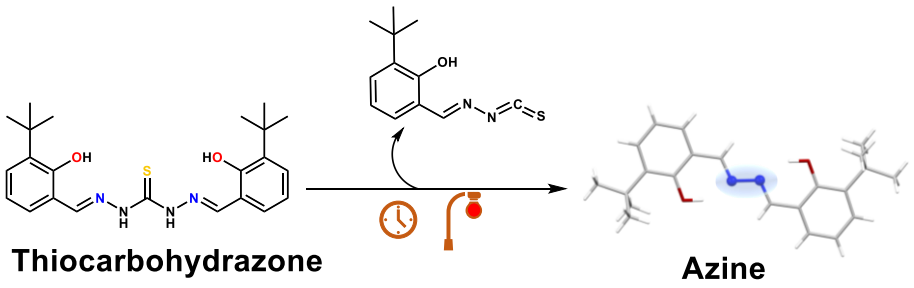

Figure 1. Obtention of azine through thiocarbohydrazona via desulfurization.

In this commmunication we present the results of the study of the influence of some factors as the reaction time and the light in the formation of azine skeltons from thiocarbohydrazone through oxidative desulfurization (Figure 1). To do this some techniches like X-Ray difraction, ^{1}H NMR and mass spectrometry have been used, this allows us to propose a possible mechanism for this process.

Acknowledgements: Ministerio de Ciencia e Innovación (MCIN), MultiMetDRUGS (RED2018-102471-T) y PID2021-127531NB-I00 (AEI/10.13039/501100011033/FEDER, UE).

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Érase una vez el hierro. EL COMIC

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Palabras clave: metabolismo de hierro, proteínas de hierro

En este póster se presenta el metabolismo del hierro en el cuerpo humano en forma de cómic. Las diferentes proteínas involucradas en la captación, transporte, almacenamiento y aprovechamiento del hierro son representadas en forma de personajes de comic que se comunican entre ellos para explicar todos los procesos que tienen lugar desde que el hierro es adquirido en la dieta, hasta la síntesis de hemoglobina y su posterior recirculación.

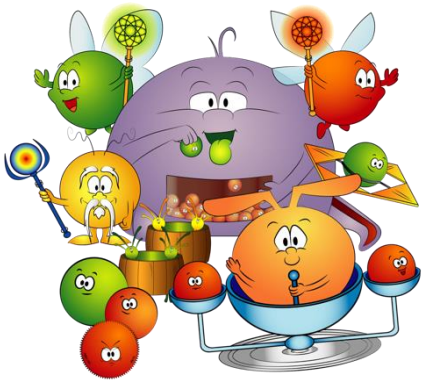

Figura 1. Personajes del cómic Erase una vez el hierro

Copper(II) Complex with Hydrazone derived of B_6 Vitamin: Crystal Structure and Non-covalent interactions

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Keywords: Crystal structure, Hydrazone, Copper(II) complex, Noncovalent interactions.

Hydrazones are Schiff bases that have broad biological properties and pharmacological applications and due to their variety of coordination sites have great relevance in bioinorganic chemistry [1,2]. The present work reports the synthesis, crystal structure, and noncovalent interactions investigation of a new copper(II) complex [$CuBr_2(B_6Bh)$], where B_6Bh = pyridoxal-benzoyl hydrazone. The crystals were investigated by single crystal X-ray analysis, Hirshfeld surface, and physicochemical and spectroscopic methods. The single-crystal X-ray study reveals the metal center coordinated with a tridentate Schiff base molecule through the *ONO*-donor atoms and two bromide ions, resulting in distorted square pyramid geometry with the copper atom. The fingerprint plots show the most intermolecular contacts attributed to the H•••H and Br•••H bonds with 34.6% and 33.1% respectively. The full interaction maps of the copper(II) complex show the hydrogen bond acceptors and donor regions, as shown in Figure 1.

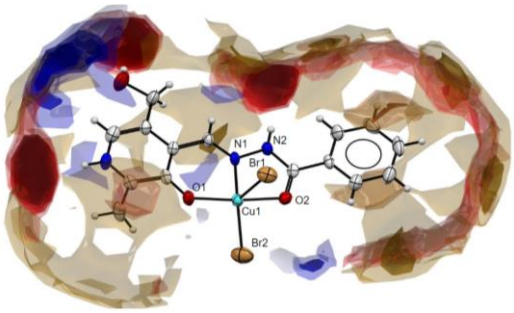

Figure 1. Full interaction maps are shown around the molecular conformation of [$CuBr_2(B_6Bh)$].

Acknowledgments: *FAPDF, CAPES, CNPq, and UnB.*

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Photocatalytic Detoxification of Fenamiphos by hybrid salts based on Metalorganic polyhedra and Phosphopolyoxometalates

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Keywords: Organophosphate, acetilcholinesterase, metal-organic polyhedra, polyoxometalate.

One of the greatest challenges nowadays is to increase the production of crops to satisfy the high demand of food of the ever-increasing world population. This challenge involves an increment of crops production which is dependant in the use of agrochemicals. One of the most common classes of pesticides are organophosphates; they are highly toxic to humans and ecosystems due to their acetylcholinesterase (AchE) inhibition activity [1]. Metal-organic frameworks have attracted great attention for detoxification of organophosphorus compounds. Metal-organic polyhedra, which can be considered downsized MOFs, possess improved processability and solubility. In a previous work, we have shown that Zr-MOPs can be used as vehicles for controlled release of bioactive molecules involved in the reactivation of AchE [2].

In this context, we have integrated cationic Zr-MOPs with different phosphopolyoxometalates (POMs) to obtain hybrid salts which combine the functional properties of MOPs with the functional properties of POMs. The results show a synergistic interplay between the photooxidative activity of the MOP with the hydrolytic activity of the POM which is useful for the degradation of toxic organophosphorus fenamiphos under UV irradiation (**Figure 1**).

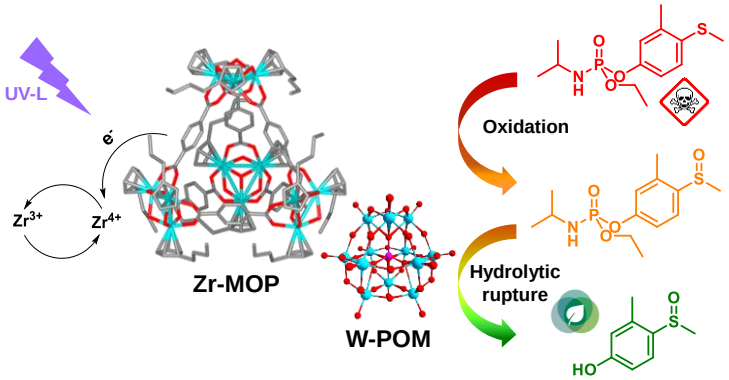

Figure 1. Scheme of the mechanism of fenamiphos photodegradation by the hybrid salt.

Acknowledgements: Spanish MICIN; AEI /10.13039/501100011033 (Project PID2020-113608RB-I00

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Exploring the Metal-Coordination-triggered Carbamate Self Immolative Hydrolysis Process

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Keywords: Carbamates, hydrolysis, metal, coordination

Carbamates are compounds of great interest due to their potential applications in different fields such as new materials [1] or nanomedicine [2]. To date, it should be highlighted that some examples of platinum(IV) carbamate derivatives have been described as prodrugs with the aim of minimise side effects of platinum(II) drugs used to treat cancer disease [3]. Herein, we were focused on the conditions under which carbamate ligands can be hydrolyzed. We have studied the coordination behaviour of a carbamate ligand in its neutral form with different metal chloride salts. Surprisingly, we observed a self-immolative hydrolysis process of the ligand, yielding the release of dihydrazone mononuclear complexes, carbon dioxide and an alcohol species corresponding to the pendant groups of the carbamate (Figure 1). A plausible mechanism for this process has been proposed, which has been supported by ^{1}HNMR and MS studies as well as by X-ray diffraction studies.

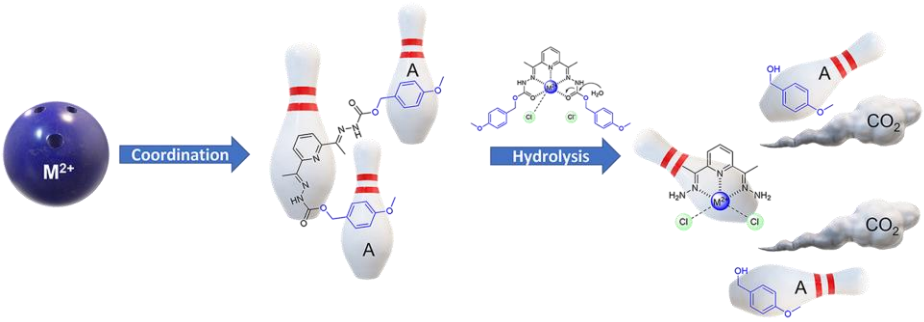

Figure 1. Hydrolysis of the carbamate H_2L release the dihydrazone L' derived metal complexes and the pendant groups.

Acknowledgements: Ministerio de Ciencia e Innovación (MCIN), MultiMetDRUGS (RED2018-102471-T) and Project PID2021-127531NB-I00 (AEI/10.13039/501100011033/FEDER, UE).

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Development of bis-phenantroline metal complexes for targeting G-Quadruplex DNA

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Keywords: G4-binders, bis-phenanthroline, metal complexes.

Non-canonical nucleic acid structures have attracted considerable attention in many science fields, including chemistry, biology, physics, materials and nanotechnology. They include triplexes, *i*-motifs, three/four-way junctions or G-quadruplexes (G4). G4 structures are formed in guanine-rich sequences, in which four guanine bases are held together by Hoogsteen hydrogen bonds to form a coplanar G-quartet, and then two or more G-quartets stack to form the G-quadruplex structure retaining sodium or potassium ions in a central core channel [1,2]. Strikingly, a large number of putative G-quadruplex forming sequences have been identified in the genomes of human and viruses, and evidences suggest their pivotal role in key biological processes such as ageing, neurodegenerative diseases and cancer [1]. Therefore, these G4 structures have been proposed as potential targets by small molecules for therapeutic intervention.

Herein, we show the synthesis of several metal complexes containing a bis-phenahtroline moiety, which allows an efficient binding to G-quadruplex structures [3]. We are planning to investigate the interaction with a panel of G4s by means of FRET melting and gel electrophoresis assays.

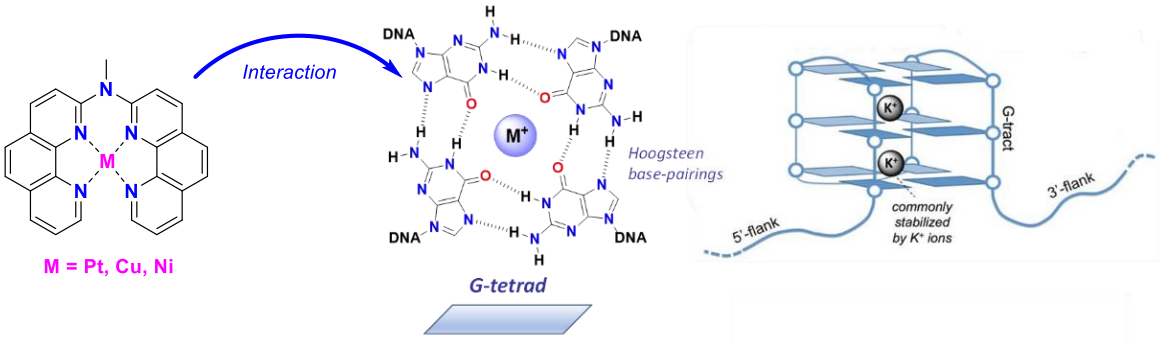

Figure 1. Metal complexes (left panel) and G-quadruplex structure (right panel).

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Synthesis and biological activity of glycoconjugated Pd(II) and Pt(II) complexes based on extended planar aromatic ligands

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Keywords: Palladium, anticancer, glycoconjugates.

The development of more efficient anticancer drugs has been a topic of intense research over the past few decades [1]. The anticancer activities of palladium compounds were firstly studied due to their structural analogies with platinum complexes [2]. However, Pd(II) compounds are more labile and suffer from aquation and ligand-exchange rates much faster than those of Pt(II) analogues. It was soon demonstrated that using chelating and bulky ligands reduces the reactivity and renders Pd(II) derivatives suitable as anticancer drugs [3].

On the other hand, carbohydrates play an important role in anticancer medical chemistry [5]. The Warburg effect has led to the hypothesis that glycoconjugation could enhance the targetting efficiency of potential anticancer metallodrugs.

Herein, we report the synthesis, characterization and biological studies of palladium and platinum complexes based on *N*-4-(1*H*-imidazo[4,5-f][1,10]phenanthrolin-2-yl)phenyl-β- glycopyranosylamine ligands.The extended planar aromatic imidazophenanthroline and the extra π-conjugation given by the aryl group improves π-stacking interactions leading to an efficient binding and selectivity towards G-quadruplexes DNA structures, in which the carbohydrate scaffolds have an important role [4].

Acknowledgements: Funding from Spanish MICINN (PID2019-108251RB-I00) and UAH (CCG20/CC-026, PIUAH22/CC-028) is gratefully acknowledged. YMP is grateful to Comunidad de Madrid and SEPE for a research contract within the Investigo Program, (NextGeneration Funds).

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Cathecol Oxidase Activity of Dinuclear Copper(II) Complexes derived from Bisthiosemicarbazones

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Keywords: metalloenzyme, copper, bisthiosemicarbazone

In recent years, the design and synthesis of metallo-supramolecular structures that simulate the active sites of metalloenzymes has become of great interest, as these artificial models can allow us to understand the function and mechanism of action of these enzymes [1].

In nature, there are several metal ion-derived enzymes that can catalyse a wide variety of reactions with high selectivity under mild conditions [2]. In this work, we present dinuclear copper(II) complexes as potential models of natural redox metalloenzymes such as cathecol oxidases. To this end, we have developed a family of pentadentate [N_2S_2O] bisthiosemicarbazone H_3L^n ligands capable of stabilising copper(II) complexes. Dinuclear neutral copper(II) compounds [$Cu_2L^n(OH)$] (Figure 1, left) have been obtained by an electrochemical synthesis methodology. Their catalytic activity has been studied following the biomimetic oxidation of 3,5-DTBC into 3,5-DTBQ by UV-Vis (Figure 1, right).

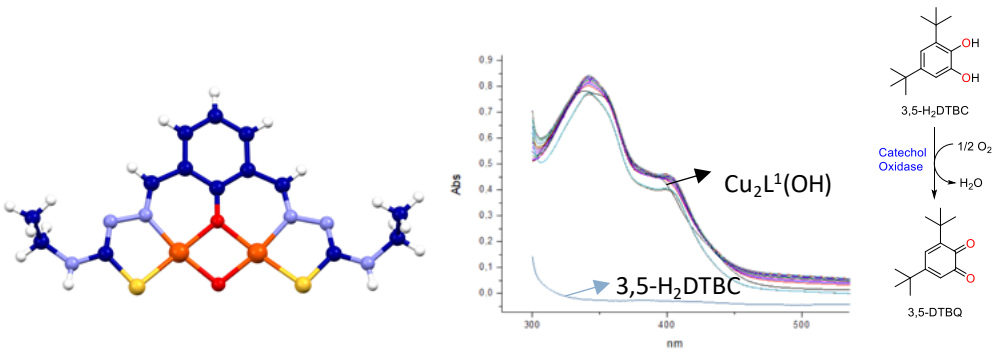

Figure 1. Structure of the dinuclear copper(II) complex [$Cu_2L^1(OH)$] (left) and the UV-vis spectra of the biomimetic oxidation of 3,5-H_2DTBC (right).

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Platinum and Palladium complexes of tetraazapyridinacyclophanes and their interaction with mono and polynucleotides

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In recent years, research on platinum coordination chemistry has aroused great interest due to their potential biological applications [1,2]. Thus, one of the most important platinum complexes is *cis*-platin, which contains two chloride leaving groups in *cis* positions allowing itsanchoring to DNA, being used effectively for the treatment of different cancer types. In fact, this complex has served as a starting point for the development of a large number of derivatives with similar properties [3,4,5].

Herein, we report the interaction of $PtCl_4^{2-}$ and $PdCl_4^{2-}$ with different small tetraazapyridinacyclophane ligands (**Figure 1**), by UV-Vis, NMR spectroscopy and X-ray diffraction analysis. For Pt(II) and Pt(IV), different coordination modes have been observed as function of the macrocyclic cavity size. The interaction of the platinum and palladium complexes with different mononucleotides and polynucleotides poly A/U and Calf thymus DNA has been analyzed.

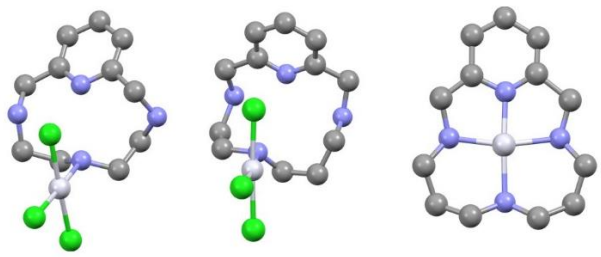

Figure 1. Structures of the studied Pt(II) tetraazapyridinacyclophanes complexes solved by X-ray diffraction.

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Synthesis, DNA interaction and cytotoxic activity of Pt(II) complexes based on 3,5,6,8-tetraphenyl-1,10-phenanthroline

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Key words: DNA, G-quadruplex, 1,10-phenanthroline, metal complexes, cytotoxicity

Since the discovery of cisplatin as an anticancer drug in 1965, new metal complexes have been pursued and developed to be used as chemotherapeutic analogues, with a focus on reducing toxicity and undesired side-effects [1]. One strategy widely accepted is the incorporation of bioactive ligands of different nature and structural features to the coordination sphere of the platinum center.

The use of ligands of extended flat surface area, such as polyaromatic systems derived from polysubstituted 1,10-phenanthroline, can be used to facilitate effective π-stacking interactions with nucleic acids and, more specifically, with quadruplex structures (G4s) [2,3]. This is particularly relevant because these ligands, among other actions, have the potential to indirectly inhibit telomerase and exert important biological effects, by binding and stabilizing the telomeric DNA quadruplexes.

We are currently involved in the synthesis novel metallo-organic G4 ligands based on Pt(II) complexes that contain the 1,10-phenantroline heterocycle tetrasubstituted in positions 3-, 5-, 6- and 8- with aryl groups. Several structures, incorporating additional inert nitrogen-based ligands or maintaining the two chloro labile ligands have been prepared and studied. In this communication, the synthetic procedures will be reported, along with preliminary DNA interaction data and cytotoxic activities determined in cultured cells. These results will be used to establish useful structure-activity relationships with the purpose of designing and developing novel metallodrugs with improved antitumor activity.

Acknowledgements: Funding from Spanish MICINN (PID2019-108251RB-I00) and UAH (CCG20/CC-026, PIUAH22/CC-028) is gratefully acknowledged. LB is grateful to Comunidad de Madrid and SEPE for a research contract within the Investigo Program, (NextGeneration Funds).

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XIII Reunión Científica de Bioinorgánica

Granada, June 5-7th 2023

Complejos de Fe(II) con ligandos Tiosemicarbazonas con Piridinas sustituidas como transportadores de oxígeno para oxidaciones con peróxido de hidrógeno

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Palabras clave: Catálisis,Complejos Tiosemicarbazonas, cinética, Mecanismos de Reacción

La reacción de los complejos $[Fe^{II}(TSC)_2]$, donde TSC es un ligando tiosemicarbazona con una piridina sustituida de las familias de DpT o BpT, con H_2O_2 en acetonitrilo, ocurre sin la acumulación de los complejos $[Fe^{III}(TSC)_2]^+$. Se produce una mezcla de intermedios diamagnéticos de especies de Fe^{II} de bajo espín, generadas por la adición de uno o más átomos de oxígeno a las tiosemicarbazonas coordinadas. Dado que la adición de átomos de oxígeno sugiere que puede ser posible la transferencia de éstos a sustratos externos, se probaron estos complejos en la oxidación de tioanisol y estireno con H_2O_2; y efectivamente, son activos en la oxidación de tioanisol a sulfóxido y de estireno a benzaldehído, con escalas de tiempo que indican la participación de espedies intermedias que contienen ligandos con oxígenos añadidos. Es sorprendente que los tres ligandos también catalicen la oxidación de tioanisol, pero sean inactivos para la oxidación de estireno. El conjunto de los resultados sugiere que las tiosemicarbazonas coordinadas juegan un papel activo en la transferencia de oxígenos en las oxidaciones catalíticas, y abre nuevos caminos para la catálisis y la oxidación de ROS en sistemas biológicos.

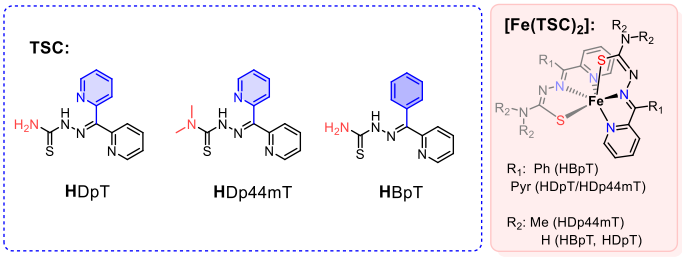

Figura 1. Ligandos y Complejos Tiosemicarbazonas empleados

Agradecimientos: This work has been co-financed by Ministry of Science, Innovation and Universities (PID2019-107006GB-C22, PID2019-107006GB-C21) and the 2014-2020 ERDF Operational Programme and by the Department of Economy, Knowledge, Business and University of the Regional Government of Andalusia *(FEDER-UCA18-106753)*

Síntesis y caracterización de Complejos de Galio(III) con Ligados tipo Hidrazona y Tiosemicarbazona

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Palabras clave: Galio(III), hidrazona, tiosemicarbazona

El galio está considerado uno de los metales con mayor actividad antitumoral después del platino [1]. Además, existen dos isótopos (^{67}Ga y ^{68}Ga) que permiten su incorporación en fármacos para la obtención de radioimágenes. Desde el descubrimiento de ambos tipos de propiedades, existe un creciente interés en el diseño de complejos de galio(III) con ligandos orgánicos que eviten los procesos de hidrólisis en medios acuosos y mejoren sus propiedades farmacocinéticas [2].

En la presente comunicación se muestra la síntesis y caracterización estructural de diferentes complejos de galio(III) con ligandos hidrazona y tiosemicarbazona. Se han estudiado las diferentes posibilidades coordinativas del centro metálico mediante la combinación de los ligandos, empleando para ello una ruta sintética basada en ligandos de intercambio (Figura 1). Así mismo, se han realizado estudios de reactividad y estabilidad de los complejos aislados con el fin de optimizar su obtención y establecer posibles modificaciones que mejoren su estabilidad en medios biológicos.

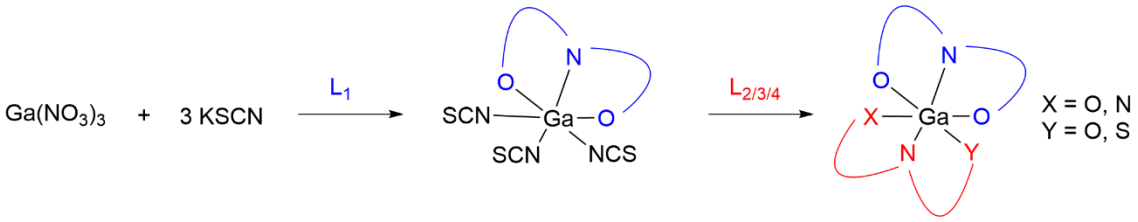

Figura 1. Ruta sintética de los complejos de galio(III) con diferentes ligandos.

Agradecimientos: Ministerio de Ciencia e Innovación (PID2019-110218RB-I00)

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Crystal design and Hirshfeld surface investigation of a new Ni(II) complex with carbazate ligand

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Keywords: Crystal structure, Carbazate, Ni(II) complex, Hirshfeld surface.

Carbazates are interesting Schiff bases due to their coordinative ability to form stable metal complexes and ability to inhibit cancer cell lines or bacteria and fungi strains, making them valuable resources in the research of new pharmaceutical metal complexes.[1,2] This present work reports the synthesis, crystal structure, and investigation of noncovalent interactions of the new nickel(II) complex [Ni(L_2)] with the isatinmethylcarbazate ligand (HL). Both compounds have been characterized by spectral measurements (IR, UV-Vis, ^{1}H, and ^{13}C NMR). The crystal structure was evaluated by single-crystal X-ray analysis and their interactions were investigated by Hirshfeld surface. The Ni(II) atom is coordinated by two deprotonated carbazate molecules through the *ONO*-donor atoms and resulting in a distorted octahedral geometry, Figure 1. The π···π stacking interactions are observed in the complex with two different distances 3.614 Å and 3.651 Å between the aromatic rings of the ligand.

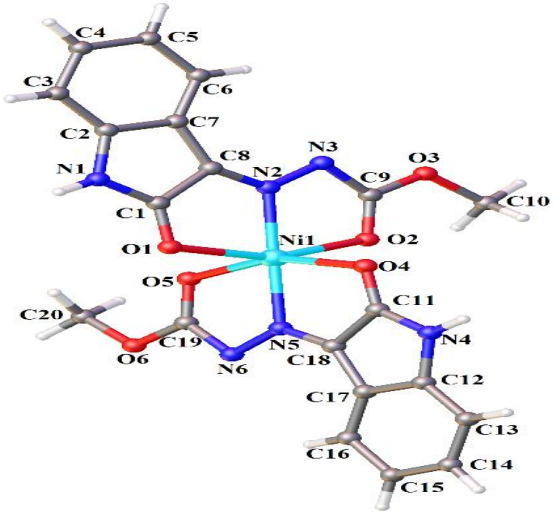

Figure 1. Molecular structure of [Ni(L_2)] with crystallographic labeling (30% probability displacement).

Acknowledgments: *FAPDF, CAPES, CNPq and UnB.*

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Molecular Recognition between the copper(II)-oxydiacetate chelate and N9-(2-hydroxyethyl)adenine

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Keywords: copper(II), oxydiacetate, N9-(2-hydroxyethyl)adenine, interligand interactions, molecular recognition, crystal structure

As a part of our works on molecular recognition between metal chelates and synthetic nucleosides (acyclovir [1] and N9-(2-hydroxyethyl)adenine [2], hereafter 9heade) herein we report the tedious syntesis, molecular and crystal structures as well as theoretical calculations on the mixed-ligand Cu(II) complex $[Cu(oda)(9heade)(H_2O)_2]\cdot H_2O$ (compound **1**- Figure 1). An asymmetric elongated O_h coordination, type 4+1+1* (*refers to the Cu···O(2a) contact) is assumed for the Cu(II) centre. Theoretical calculations, thermal, espectral and magnetic results are available.

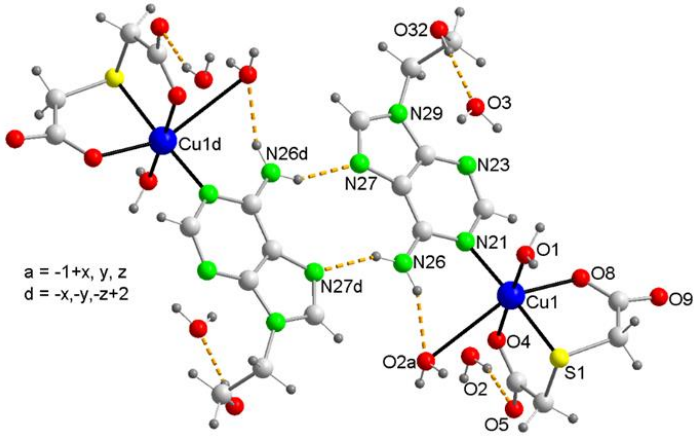

Figure 1. Two asymmetric units of compound **1** showing the molecular recognition 'metal chelate-nucleoside' consisting on the cooperation of the Cu1-N21 coordination bond and the 'long term' O2-aqua mediated interaction (N26-H···O2a H-bond + O2a···Cu1 weak contact). Adenine-moieties base pairing (by symmetry related N26-H···N27d H-bonds) is also shown.

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Molecular Recognition between the copper(II)-(pyridine-2,6-dicarboxylate) chelate and the Bio-ligand Creatinine

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Keywords: copper(II), 2,6-pyridine-dicarboxylate, creatinine, molecular recognition, crystal structure

The interest of creatinine (crea) as bioligand was claimed by M. Mitewa [1]. Nevertheless, only eight structures for Cu(II)-crea compounds are known, six of them being mixed-ligand complex molecules [2]. In this work, we focus on molecular recognition between the Cu^{II}(pdc) chelate (pdc = pyridine-2,6-dicarboxylate) and crea, on the basis of the crystal structure of *trans*-[Cu(pdc)(crea)$(H_2O)_2$]·H_2O (**1**, Figure 1).

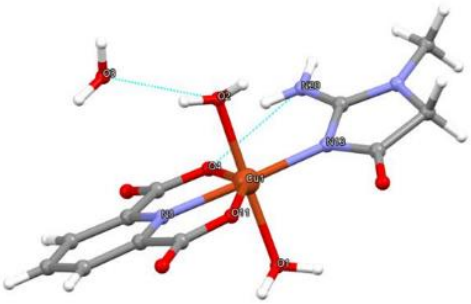

Figure 1. Asymmetric unit in the crystal of *trans*-[Cu(pdc)(crea)$(H_2O)_2$]·H_2O (**1**).

In **1**, (a) the Cu(II) centre exhibits an elongated O_h coordination, type ~4+2, (b) both *trans*-aqua ligands occupies proximal coordination sites, (c) pdc provides a proximal Cu-N bond, including the two longest Cu-O(distal) bonds, and (d) N-crea occupies the remaining proximal site. The Cu-N(crea) bond (1.996 Å) falls in the range of previously reported Cu-N(crea) bonds, 1.955-2.014 Å [2]. The molecular recognition Cu(pdc) chelate-crea consists in the cooperation of the Cu-N(crea) bond and the (crea)N-H···O4(carboxylate distal, pdc) interligand interaction. That leads to a dihedral angle crea-pdc of 21.02°. Despite the referred tridentate mode for pdc ligand, it seems clear that the Cu(pdc) chelate is a good receptor for crea.

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Synthesis and Structural Evaluation of a new Copper(II) complex with Dithiocarbazate

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Keywords: Cu(II) complex, Dithiocarbazate, Crystal Structure.

The dithiocarbazates are Schiff bases that present huge versatility, their chemical properties can be modified with the introduction of different substituent groups in their structure, allowing the formation of metal complexes with different coordination polyhedra.[1] In addition, dithiocarbazates and their complexes are reported in the literature showing biological properties such as antifungal, antibacterial, and antitumoral.[2,3] The current work reports the synthesis and structural evaluation of a new dithiocarbazate ligand HL (2-acetylpiridine-S-p-clorobenzyl-dithiocarbazate) and its Cu(II) complex, [CuCl(L)], as shown in Figure 1.

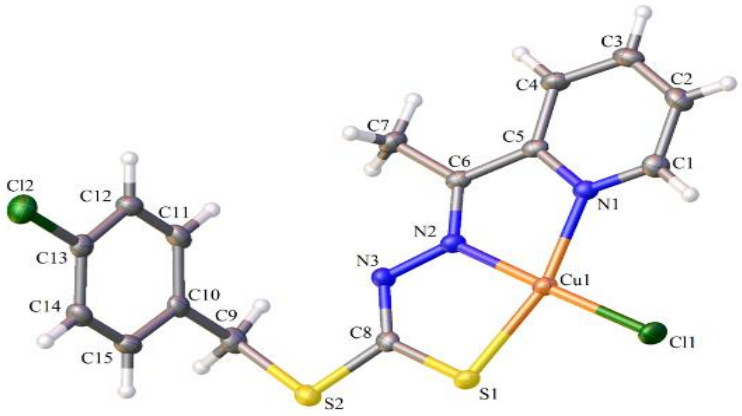

Figure 1. Molecular structure of [CuCl(L)] with crystallographic labeling (30% probability displacement).

The complex [CuCl(L)] was investigated by single crystal X-ray analysis, Hirshfeld surface, physicochemical and spectroscopic methods. The single-crystal X-ray study reveals the dithiocarbazate in its anionic form and the thiol tautomer and the metal center show a square geometry where the copper(II) is coordinated by *NNS*-system and a chloride ion. Intermolecular interactions were found between S1····H14 and Cl1····H2, those interactions contribute to the formation of the supramolecular arrangement of the crystal.

Acknowledgments: FAPDF, CAPES, CNPq and UnB.

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Crystal Structure and Investigation of Noncovalent Interactions of New Ni(II) Complex with a Dithiocarbazate Ligand

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Keywords: Crystal structure, Ni(II) complex, noncovalent interactions, dithiocarbazate.

Dithiocarbazates ligands are an important class of biologically active organic compounds that have attracted great interest due to their wide range of pharmacological properties. They have been studied as promising ligands in the formation of metal complexes with biological applications as antibacterial, antimicrobial, and antifungal, among others[1,2]. The present work reports the structural elucidation and investigation of noncovalent interactions of new nickel(II) complex [Ni(L)Py] with pyridine and dithiocarbazate ligand (H_2L = thenoyltrifluoracetone-S-benzyldithiocarbazate). The metal center is coordinated with the dithiocarbazate by the tridentate *ONS* chelating system and completes the distorted square planar geometry with a pyridine ligand. The crystal structure was evaluated by single-crystal X-ray analysis, and intra- and intermolecular interactions were investigated by the Hirshfeld Surface. The fingerprint plots revealed intermolecular contacts attributed to the H···H and C···H bonds with 27.2% and 22.3%, respectively. The full interaction maps (Figure 1) show the hydrogen bond acceptors, donor regions, and the possibility for hydrophobic interactions.

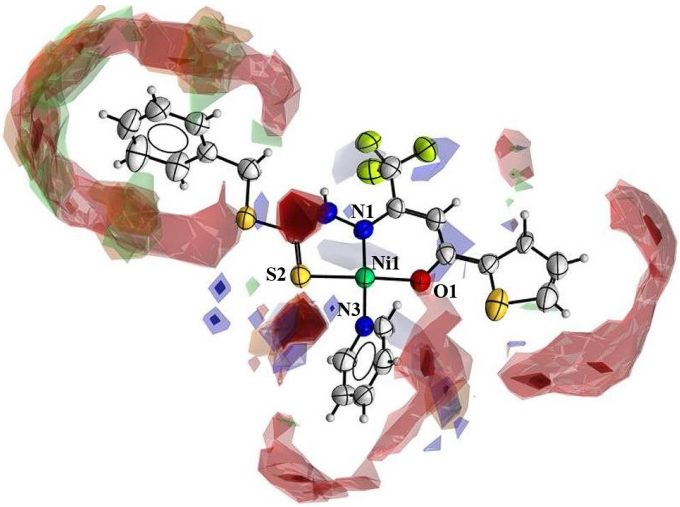

Figure 1. Full interaction maps are shown around the molecular conformation of [Ni(L)Py] with contour levels.

Acknowledgments: *FAPDF, CAPES, CNPq and UnB.*

[1] C. C. Gatto, et. al, J. Inorg. Biochem., **224**, 111559 (2021).

[2] M. A. Ali, et. al, Transition Met. Chem., **36**, 471-479 (2011).

XIII Reunión Científica de Bioinorgánica

Granada, June 5-7th 2023

Interligand interactions in two copper(Ii) complexes having flexible N-(alkyl-phenyl)-iminodiacetate chelators and creatinine

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Keywords: copper(II), N-(phenyl-alkyl)-iminodiacetate, molecular and crystal structure, interligand interactions

In a rather clasisc papper on ternary Cu(II) complexes with adenine (Hade) and N-substituted iminodiacetate chelators (N-R-IDA) we emphasithe that the binding pattern of Hade differs in funtion of the nature of the non-coodinating (alkyl, benzyl or phenetyl)-R pendant arm. Now we becomes interested in related complexes where Hade is replaced by the also bioligand creatinine (crea) [1]. Here we report the crystal structures of compounds [Cu(NBzIDA)(crea)(H_2O)]·H_2O (**1**) and [Cu(pheida)(crea)(H_2O)]·3H_2O (2) –see figure.

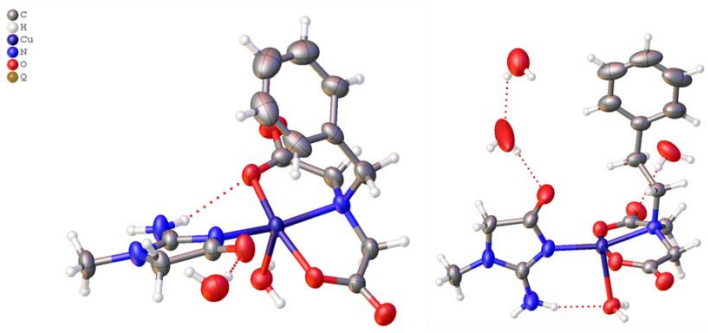

Figure 1. Asymmetric units in the crystals of **1** (left) and **2** (wright), showing the cooperation between the Cu-N(crea) bond with an interligand H-bond, being (crea)N-H···(O- carboxyl) for **1** or (crea)N-H···(O-aqua, distal) for **2**, respectively .

We conclude that, in the here reported molecular complexes, the methylene or ethylene alkyl chain of the used chelators determines the distinct nature of the interligand H-bonding interaction.

[1] E. Bugella Altamirano, D. Choquesillo Lazarte, J.M. González Pérez, M.J. Sánchez Moreno, R. Marín Sánchez, J.D. Martín Ramos, B. Covelo, R. Carballo, A. Castiñeiras, J. Niclós Gutiérrez. Inorg. Chim. Acta. 2002, 339, 160-170. doi.org/10.1016/S0020-1693(02)00920-9

[2] M. Mitewa. Coord. Chem. Rev. 1995, 140, 1-25. doi.org/10.1016/0010-8545(94)01122-R

The copper(II) complex with N-(1-naphtyl)methyl-iminodiacetate and purine coligands. Molecular and supra-molecular recognition

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Keywords: copper(II), N-(1-naphthyl-methyl)iminodiacetate, molecular and crystal structure, interligand interactions

The main aim of this work is to deep in the molecular recognition in copper(II) complexes with N-benzyl-iminodiacetate (NBzIDA) and adenine (Hade) [1,2]. Whit this purpose, the N-benzyl group of NBzIDA was replaced by a 1-nathtylmetyl arm in 1-NamIDA. In addition purine (Hpur) is used instead of adenine as coligand. That results in the novel molecular compound [Cu(NamIDA)(H(N9)pur)(H_2O)]·3H_2O (**1**)**.** Its crystal revealed π-stacked interactions inside and between molecules and purine links the metal by its N7 donor atom (Figure 1). In clear contrast the molecular compound [Cu(NBzIDA)(H(N9)ade)(H_2O)]·H_2O (**2**) [1] adenine binds the copper(II) center by is less basic N3-heterocyclic donor, because that enables the cooperation of the Cu-N3(Hade) bond with a N(9)-H···O(carboxylate) interligand interaction. Compounds **1** and **2** uses the most stables tautomers of H(N9)pur and H(N9)ade.

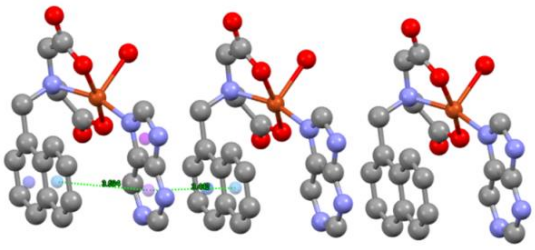

Figure 1. Intra- and inter-molecular NamIDA/Hpur π-stacking interactions generates chains of complex molecules, parallel to an axis of the crystal of **1**.

[1] E. Bugella Altamirano, D. Choquesillo Lazarte, J.M. González Pérez, M.J. Sánchez Moreno, R. Marín Sánchez, J.D. Martín Ramos, B. Covelo, R. Carballo, A. Castiñeiras, J. Niclós Gutiérrez. Inorg. Chim. Acta 2002, 339, 160-170.

[2] P.X. Rojas González, A. Castiñeiras, J.M. González Pérez, D. Choquesillo-Lazarte, J. Niclós-Gutiérrez. Inorg. Chem. 2002, 41, 6190-6192.

C-H···F, F···π, N-H···O and O-H···O interligand interactions in the crystal of (p-F_3C-benzyl-iminodiacetate)(purine)(aqua)copper(II), [Cu(p-F_3C-BzIDA)(H(N9)pur)(H_2O)]

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Keywords: trifluorometyl group, interligand interactions, molecular recognition, purine,copper(II)

To elucidate the weak interligand interactions related to a *p*-trifluoromethyl substituent in the aryl moiety of the N-bencyliminodiacetate ligand (NBzIDA) [1], now we report the molecular and crystal structure of [Cu(p-F_3C-BzIDA)(H(N9)purine)(H_2O)] (**1**) where there is an absence of π,π-interligand interactions, in contrast to those existing in the related compound [Cu(NBzIDA)(adenine)(H_2O)]·H_2O (**2**) [2]. In **1**, there are C-H···F, C-F···π and N-H···O interactions (Figure 1) in addition to (aqua)O-H···O(carboxylate) ones (not shown for clarity). We conclude that the insertion of the p-F_3C-substituent in NBzIDA does not modify the molecular nature of **1** and **2**, but markedly alters the nature of the interligand interactions in their respective crystals.

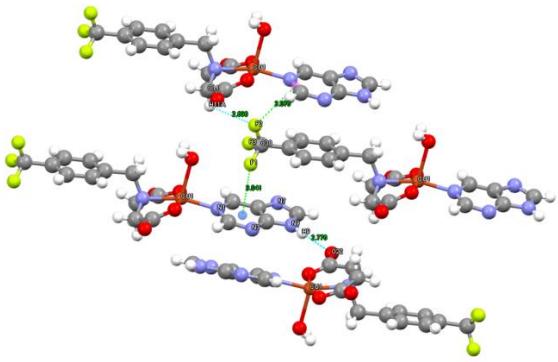

Figure 1. C-F···π , C-H···F and N-H···O interactions in compound **1**.

[1] M. Serrano-Braceras et al. J. Coord. Chem. 2015, 68, 2739-2759.

[2] E. Bugella Altamirano et al. Inorg. Chim. Acta. 2002, 339, 160-170.

Enhanced photocatalytic degradation of ciprofloxacin via Silver doped zinc oxide (Ag-ZnO) under solar irradiation

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Keywords: Photocatalytic degradation, Silver doped ZnO, Ciprofloxacin, Solar irridiation.

This investigation aimed to study the enhancement of photocatalytic degradation of ciprofloxacin by sliver-doped zinc oxide (Ag-ZnO) under solar irradiation. Ciprofloxacin (CIP) is an antibiotic commonly used to treat bacterial infections but can have a negative impact on the ecosystem if not used or managed well due to its high rate of antibiotic resistance [1]. The zinc oxide and silver-doped zinc oxide nano-photocatalysts were successfully synthesized through a simple and low-cost chemical route. Fourier Transform Infrared Spectroscopy (ART-FTIR), X-ray Diffraction (XRD), and Scanning Electron Microscopy (SEM) were employed to investigate the functional groups, structural, and morphological properties, respectively. The resultant nanomaterials were then examined to determine the influence of various parameters such as pH, photocatalyst dosage, initial concentration of CIP, and time of irradiation. Ag-ZnO exhibited exceptional degradation efficiency, with 95% degradation after 90min of exposure to solar light.

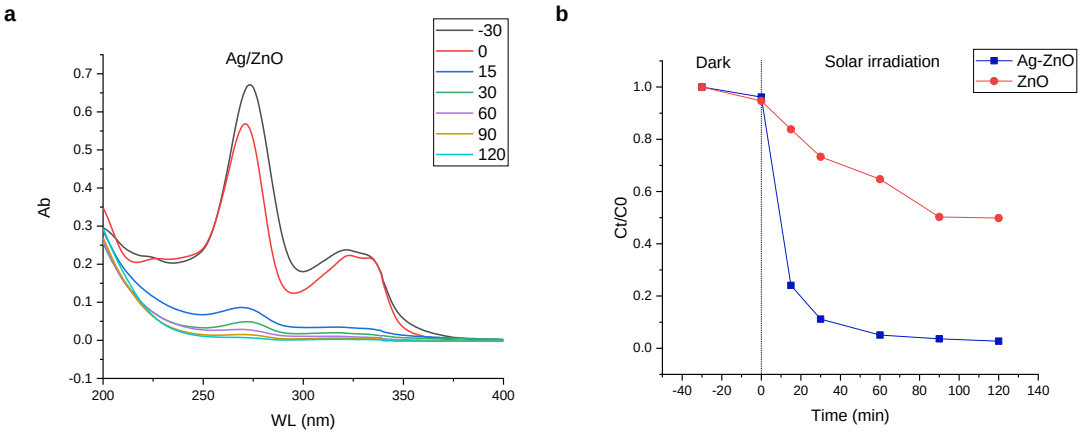

Figure1. **a**.Uv-vis spectra of CIP photodegradation by Ag-ZnO **b**. photocatalytic activity of Ag-ZnO and ZnO nano-materiels under optimum condtions

[1] D. Van Thuan *et al.*, "Photodegradation of ciprofloxacin antibiotic in water by using ZnO-doped g-C3N4 photocatalyst," *Chemosphere*, vol. 308, no. P2, p. 136408, 2022

Novel Photosensitizers based on Ru-Coumarin Complexes for combating Hypoxic Tumors

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Keywords: metallodrug, coumarin, PDT, photosensitizer, hypoxia

Although photodynamic therapy (PDT) is a well-established technique for the treatment of cancer, its efficacy is usually compromised by the hypoxic conditions commonly found in deep-seated and large tumors. To overcome this challenge, we have developed a new family of photosensitizers (PSs) based on ruthenium(II) complexes incorporating coumarin fluorophores and that can be easily obtained with high purity through straightforward syntheses [1]. The new PSs have the advantage of being non-toxic in the absence of light but exhibit high phototoxicity upon irradiation within the phototherapeutic window. Indeed, Ru-coumarin PSs exhibited exceptional photoactivities towards different cancer cell lines with IC_{50} values in the low nM range (e.g., 7.4 nM at 645 nm) and impressive PI values (PI > 34000). Importantly, the PSs retained good photoactivities with highly-penetrating NIR light (e.g., IC_{50} = 0.26 μM at 770 nm), and remained highly phototoxic under hypoxic conditions, particularly in the 540-670 nm light window (PI values around 2900-3300), which can be attributed to the generation of both type-I and type-II ROS upon light irradiation. Besides being able to inhibit the growth of 3D tumor spheroids, pharmacokinetic (PK) and toxicological maximum tolerated dose (MTD) studies in albino swiss adult CD1 mice have demonstrated a good biodistribution profile and the absence of toxicity at the investigated doses for one of the best lead compounds.

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[1] V. Marchán, A. Gandioso, G. Gasser, S. Chumillas, D. Castaño, M. López, D. Abad. Patent title: Metal complex compounds as photosensitizers for photodynamic therapy. Application number: EP23382155, Registration date: 20/02/2023.

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