Hybrid chemogenetic fluorescent pH probes to study protein trafficking and secretion

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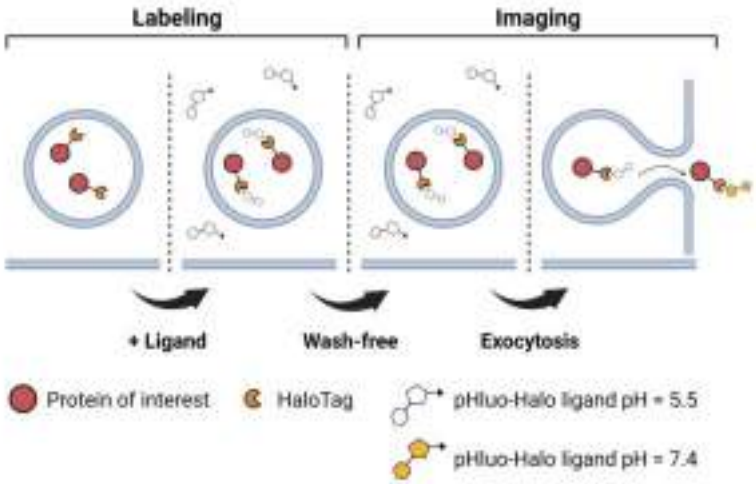
Live imaging of exocytosis dynamics is crucial for a precise spatiotemporal understanding of secretion phenomena. Thus, biologists use approaches that rely on pH sensitive fluorescent proteins[1] (SEP, pHuji) with a pKa around 7 that enables the study of protein secretion from acidic vesicles to neutral extracellular media. As an alternative, we set out to develop molecular fluorescent reporters with suitable spectral properties and pKa range as a more versatile toolkit[2]. The idea is to use a hybrid chemogenetic fluorescent platform based on HaloTag labelling activation[3,4] enabling the development of "dual-input" probes with a pH sensitive emission. By combining protein engineering of HaloTag[5] mutant and organic synthesis of red-shifted molecular pH probes analogue to GFP chromophore, we obtained a series of "dual-input" pH indicators with a pKa around 6 and an interesting specific dynamic both to pH and HaloTag protein. These obtained probes have been tested and characterized in cells to study the secretion of the protein CD63 which is a transmembrane protein. We will present then the characterizations and first biological results of these pH-probes during the oral communication.



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Diastereoselective Radical Cyclization Cascade of Ynamides Enabling Access to New Trifluoromethylated Tricyclic Structures

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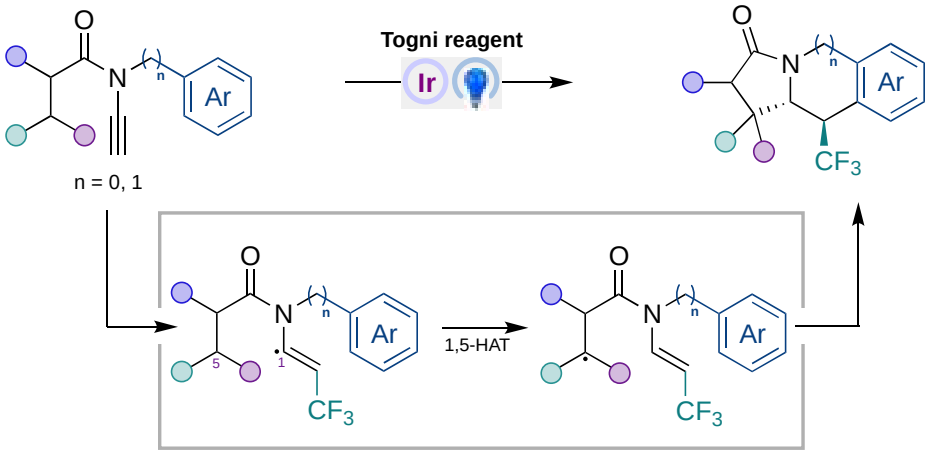
Despite significant advancements in radical cyclization cascades, [1] they are still attractive seeing how challenging and time consuming access to polycyclic scaffolds can be. Recently, our group reported a cyclization cascade employing terminal ynamides to access trifluoromethylated isoindolinones under photoredox conditions.[2] In light of our continued interest in the radical cyclization of ynamides, we have been motivated to further investigate their participation in more elaborate cyclization cascades. As shown in the scheme below, A novel multistep radical cyclization cascade of Ynamides has been developed, triggered by the addition of a trifluoromethyl radical under photocatalyzed conditions. the use of acetyl ynamides bearing an alkyl chain with an abstractable hydrogen in position 1,5 gives the product of 1,5 HAT, which after two cyclization steps leads to the formation of the tricyclic scaffolds in a diastereoselective manner



In addition to providing a new utilization of ynamides in radical cyclization cascade, this reaction would afford an easy one step access to pyrroloindolinones from simple molecules. We report herein on the development of this reaction as well as its scope and limitations.

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Molecular tweezers for multifunctional switchable organogels

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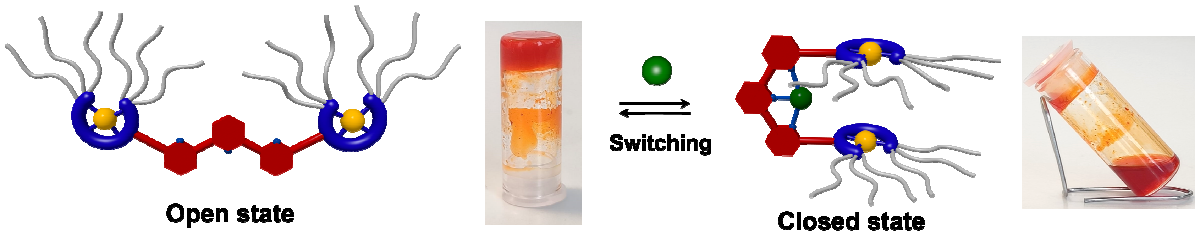
Organogels are a particular class of gels that result from the self-assembly of low molecular weight gelators (LMWG) into fibrous networks trapping solvent molecules. This new type of soft materials has attracted great interest due to their potential applications as smart materials.[i] The recent development of molecular machines and among them molecular switches has allowed the design of controlled dynamic multi-state molecular systems.[ii] We are currently interested in exploiting the mechanical motion of molecular switches to develop multifunctional switchable organogels.

In the past years, we have developed stimuli-responsive molecular tweezers composed of a terpyridine switching unit and of M-salen functional units with properties depending on the complexed metal ion. The coordination-induced closing-opening motion of the system has been used to modulate various physico-chemical properties (luminescence, catalysis, magnetism, …) with remarkable versatility.[iii-vi] Herein we report a new class of tweezers functionalized by long alkyl chains as gelling groups. The large structural reorganization driven by the motion results in reversible sol-gel transition by promoting inter- or intramolecular interactions between the tweezers depending on their conformation. The synthesis of these platinum-based molecular tweezers and the studies of their reversible gelation properties will be presented.



Acknowledgments: The authors thank G. Clodic and C. Przybylzki for the MALDI-TOF analysis, S. Casale, F. Ben Romdhane and D. Montero for the SEM and TEM imaging, Jean-Michel Guigner for the cryo-TEM experiments, Lise-Marie Chamoreau for the XRD analysis and the SWING Beamline for the SAXS experiments. This study was conducted with the financial support from the Initiave Sciences et Ingénierie Moléculaire funding.

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How to produce degradable polymers with iron/magnesium complexes?

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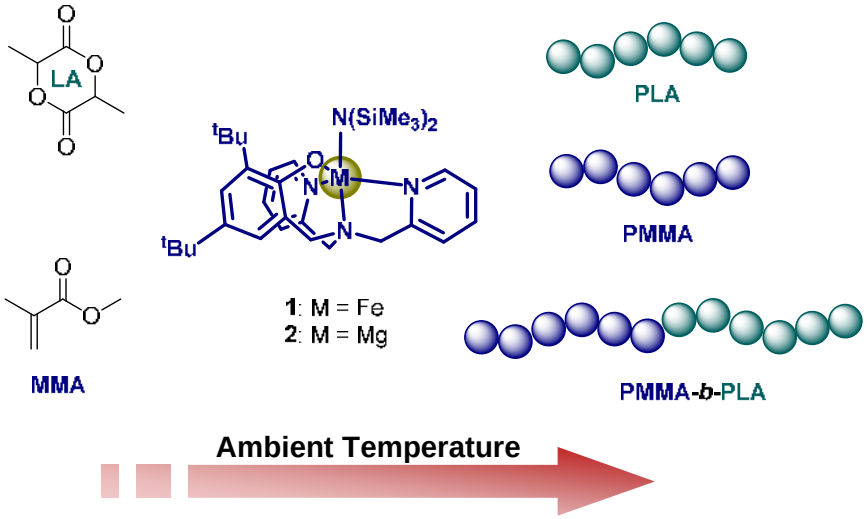

Iron and magnesium complexes supported by a tetradentate aminophenolate ligand were synthesized, and their reactivities for the homo- and copolymerization of *rac*-lactide, L-lactide and methyl methacrylate (MMA) were investigated. All complexes were active initiators for the ring-opening polymerization of LA and the anionic polymerization of MMA at ambient temperature. A metal-mediated addition copolymerization of lactide and methyl methacrylate was also reported. The homopolymers and block copolymers were characterized by size exclusion chromatography, differential scanning calorimetry and thermogravimetric analysis. The polymerization of all monomers was well controlled, resulting in predetermined molar masses and narrow dispersity values.

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Access to Enantioenriched α-Fluorinated and α-Trifluoromethyl Alcohols in Hetero- and Carbocycles Series via Transition Metal-Catalysed Asymmetric Transfer Hydrogenation

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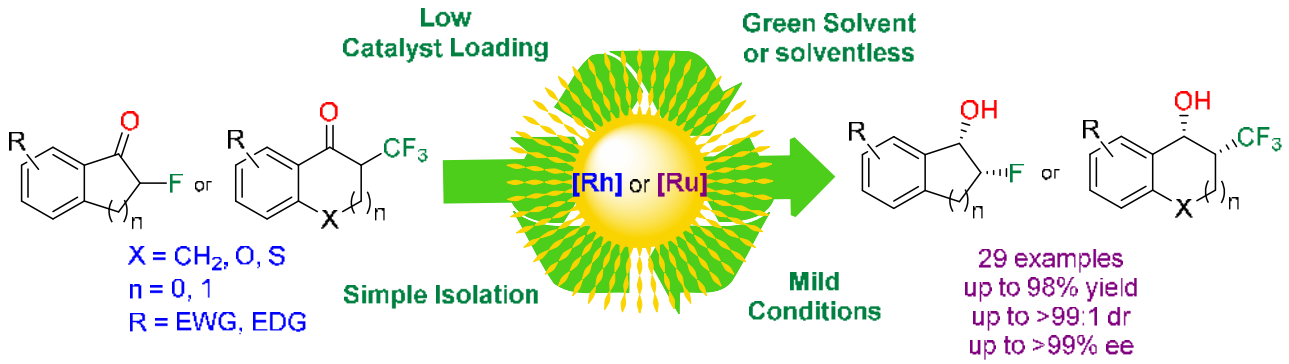
The effect of fluorine in the design and the synthesis of new bioactive compounds has been widely studied during the last two decades but still needs to be explored and understood into deeper levels.[1] Consequently, the potential of fluorine in organic and medicinal chemistry has prompted us to pursue our investigation[2] and develop an environmentally-sound way to access enantioenriched fluorinated or trifluoromethyl-containing building blocks. We report here a Rh(III)[3]- and Ru(II)-catalyzed asymmetric transfer hydrogenation[4] of α-trifluoromethyl and α-fluorinated ketones under mild conditions to access a series of enantioenriched *cis*-trifluoromethyl and *cis*-monofluorinated alcohols via a dynamic kinetic resolution process[5]. The reaction was efficiently performed in the green solvent 2-MeTHF or solventless with HCO_2H/Et_3N as the hydrogen donor. Good yields up to 98% alongside high diastereo- and enantioselectivities (up to >99 :1 dr and >99% ee) were obtained for the synthesis of CF_3-chromanol, CF_3-indanol, CF_3-tetralol derivatives[6] as well as for the monofluorinated carbocyclic alcohols[7].



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Functionalization of a glassy carbon electrode with carboxyl groups as a support for the development of a thyroxine electrochemical biosensor

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Thyroid hormones (THs) regulate vital biological processes such as growth and metabolic homeostasis. Chemically, THs are iodinated amino acids, including tetraiodothyronine (T4) also known as thyroxine, and 3,3'5-triiodothyronine (T3).[1] Recording the levels of THs in the body in real time could dramatically expand the understanding of hormonal modulation in health and disease. Seeking to enable this ability, the present work focuses on the development of electrochemical, aptamer-based sensors (E-Abs) against thyroid hormones, a technology that can support continuous molecular sensing in the body. Specifically, given that carbon electrodes are known to be cheap materials, chemically inert and non-toxic in biological environments.[2] The work seeks to demonstrate carbon-supported E-Abs, focusing on the aptamer/target affinity evaluation in solution and on immobilization ways of aptamers on electrode surface. By the functionalization of carbon electrodes enabling the bioconjugation of aptamers to the carbon surface.[3] We specifically explore the modification of glassy carbon electrodes *via* electrochemical polymerization, by using several oxidizable monomers: aminobenzoic acid, and aminohexanoic acid with hexylamine and electropolymerisation conditions were optimized. The resulting layers contain carboxylic groups that can be coupled to amine-terminated aptamer *via* amide coupling reactions.

Each step of GCE surface modification was characterized by electrochemistry (cyclic voltammetry, differential pulse voltammetry, impedance).

Aminoferrocene (AmFc), new methylene blue (NMB) and para-nitroaniline (p-NA) have been used as model of electroactive molecules to be immobilized before testing an aptamer sequence. After coupling, electrochemistry, contact angle and FTIR have been used to characterize the electrode surface.

Other techniques are being studied to characterize the electrode surface, such as contact angle and FTIR.

Regarding the aptamer/target affinity evaluation, ITC (Isothermal Titration Calorimetry) assays were performed to determine the affinity between the proposed aptamer and the T4.

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Light-Driven Hydrogen Evolution Reaction Catalyzed by a Molybdenum-Copper Artificial Hydrogenase.

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Orange Protein (Orp) is a small bacterial metalloprotein of unknown function that harbors a unique molybdenum/copper (Mo/Cu) heterometallic cluster, $[S_2MoS_2CuS_2MoS_2]^{3-}$ [1]. In this study, the performance of Orp as a catalyst for the photocatalytic reduction of protons into H_2 has been investigated under visible light irradiation. We report the complete biochemical and spectroscopic characterization of *holo*-Orp containing the $[S_2MoS_2CuS_2MoS_2]^{3-}$ cluster, with docking and molecular dynamics simulations suggesting a positively charged Arg, Lys-containing pocket as the binding site. *Holo*-Orp exhibits an excellent photocatalytic activity, in the presence of ascorbate as the sacrificial electron donor and $[Ru(bpy)_3]Cl_2$ as the photosensitizer, for hydrogen evolution with a maximum turnover number of 890 after 4 hours irradiation. DFT calculations were used to propose a consistent reaction mechanism in which the terminal sulfur atoms are playing a key role in promoting H_2 formation. A series of dinuclear $[S_2MS_2M'S_2MS_2]^{(4n)-}$ clusters, with M = Mo^{VI}, W^{VI} and $M'^{(n+)}$ = Cu^{I}, Fe^{I}, Ni^{I}, Co^{I} , Zn^{II}, Cd^{II} were assembled in Orp, leading to different M/M'-Orp versions which are shown to display catalytic activity, with the Mo/Fe-Orp catalyst giving a remarkable TON of 1150 after 2.5 hours reaction and an initial turnover frequency (TOF°) of 800 h^{-1} establishing a record among previously reported artificial hydrogenases.ChemDraw schemes: ACS Document 1996 settings

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Synthesis of benzo[*c*]naphthyridinone and *5H*-chromeno[*c*]pyridine derivatives through ruthenium-catalyzed [2 + 2 + 2] cycloaddition

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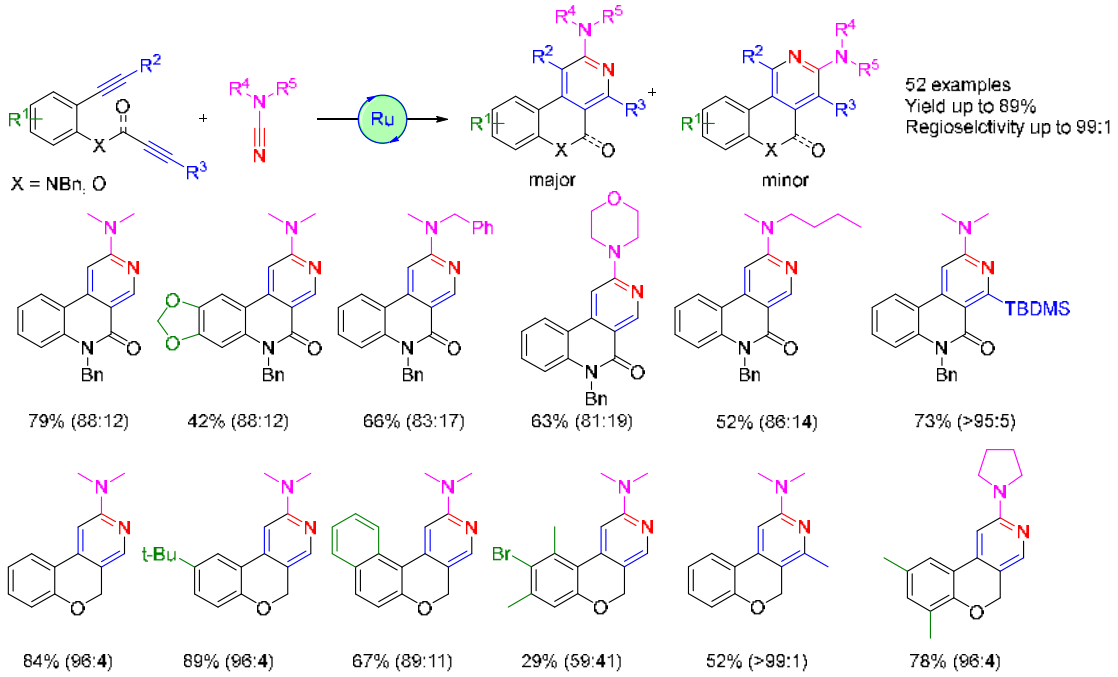
Benzo[*c*]naphthyridinones and *5H*-chromeno[*c*]pyridines are privileged tricyclic motifs in various natural molecules and diverse organic chemicals.[1] These scaffolds exhibit great interest as biologically active molecules and several inhibitors of kinase-1 containing this framework were depicted.[2] Because of the increasing importance of these scaffolds, several synthetic strategies have been developed over the last decades (e.g: Cascade Suzuki cyclization, Knoevenagel condensations). Alternatively [2 + 2 +2] cyclization between alkynes and nitriles is a powerful method for the preparation of heterocyclic structures.[3,4]



A convenient method for the synthesis of benzo[c]naphthyridinones and 5H-chromeno[c]pyridine derivatives was described. The [2+2+2] cycloaddition of various mono- or di-substituted 1,7-diynes and cyanamides in the presence of 2 mol % of ruthenium catalyst provided the corresponding cycloadducts with yields up to 89% and regioselectivities up to 99%. The versatility and the robustness of the reaction have been demonstrated by achieving gram scale synthesis and post-functionalizations.[5,6]

Acknowledgments: The authors thank the CNRS and the MESRI for financial support. G. Gontard for X-ray structure determination, Dr. C. Fosse and the MS3U platform for HRMS analysis and Dr M.-N. Rager for NMR analysis.

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A Facile Route to the Synthesis of Poly(silylether)s from Renewable Resources in the Presence of a Commercial Catalyst

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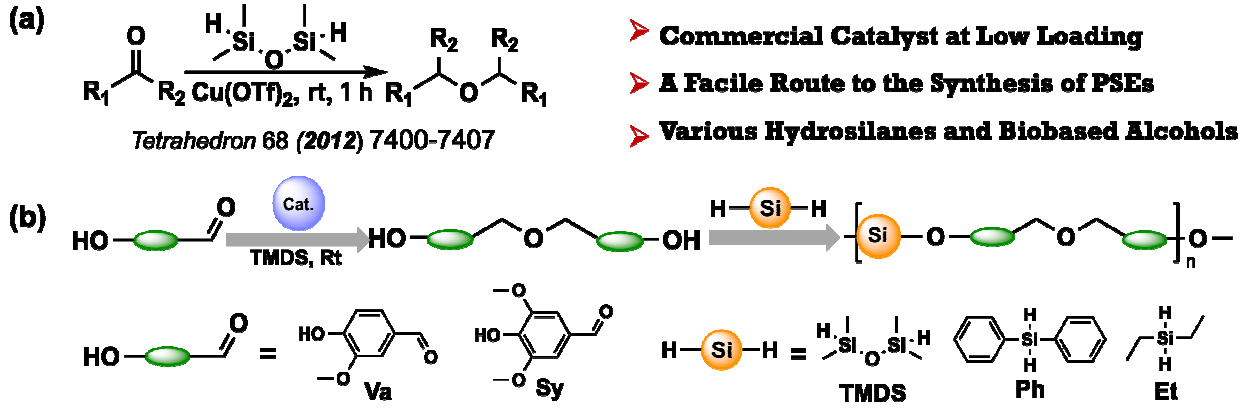
Poly(silyl ether)s (PSEs) are an important class of polymers due to the presence of Si-O-C bonds, which make them readily degradable by acid- or base-catalyzed hydrolysis. A series of PSEs have been synthesized from renewable feedstocks, such as vanillin and syringaldehyde coupled to different dihydrosilanes. The one-pot synthesis of the polymers was carried out using the Karstedt precatalyst, and the resulting PSEs were characterized by IR and NMR spectroscopies, as well as GPC, DSC and TGA analyses.[i]



Scheme 1. (a) Silane-reductive etherification (b) One-pot synthesis of Poly(silylether)s from biobased alcohols.

Acknowledgments:
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Oxaliplatin-induced peripheral neuropathy and redox modulation: evaluation of SOD mimics for enhanced anticancer activity and neuroprotection

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Oxaliplatin-induced peripheral neuropathy (OIPN) is the main dose-limiting side effect of oxaliplatin, a Pt(II)-based anticancer agent used for metastatic colorectal cancer (Figure 1). Despite the origins of this condition being intricate and unclear, it is accepted that a burst in oxidative stress, neuroinflammation and mitochondrial damage are commonly present in patients suffering from this condition. Therefore, oxidative stress might not only play an essential role in the mechanism of action of Pt(II) drugs (through glutathione depletion) but also in the generation of toxicity mechanisms and side effects, being a double-edged sword. Some strategies for reducing and/or preventing this side effect include combination treatments with antioxidants, anti-inflammatory agents or ion-channel targets.[i]

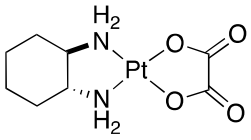

Figure 1. Chemical structure of oxaliplatin.

Superoxide dismutases are one of the front-line antioxidant enzymes in our body, protecting cells against oxidative stress. They catalyze the dismutation reaction of superoxide anions into hydrogen peroxide and dioxygen. Small bioinspired metal complexes mimicking these natural enzymes are largely studied for therapeutic applications.[ii] In our group, Mn1 (Figure 2), a Mn(II) complex mimicking the active site of MnSOD, and its derivatives are studied in the context of IBD (inflammatory bowel disease) for its antioxidant and anti-inflammatory properties.[iii] Interestingly, Mn1 also showed, while combined with oxaliplatin, encouraging neuroprotective *in vivo* results on balb/C mice.[iv] The regulation of superoxide/hydrogen peroxide balance in cancer cells has also been shown to be relevant for tumor proliferation and progression.[v] Therefore, SOD mimics could, potentially, both enhance the anticancer activity and reduce oxaliplatin's toxicity.

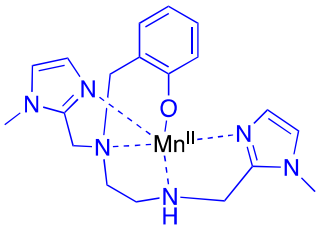

Figure 2. Chemical structure of Mn1.

From these results, we work on the development of new combination treatments between SOD mimics as redox modulators and oxaliplatin, but also on the possible use of Pt(IV) prodrugs and nanomedicine approaches to improve the therapeutic index of oxaliplatin.[vi] Synthesis, *in vitro* and *in vivo* results will be presented.

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