YOUNG SYMPOSIUM

BOOK OF ABSTRACT

II Virtual Symposium on Pericyclic Reactions and Synthesis of Carbo- and Heterocyclic Systems

November 28th – 29th, 2024

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Università degli Studi di Messina

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SYMPOSIUM PROGRAMME

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Alastair Lennox

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The Lennox group is interested in fundamental reactivity and mechanism in organic chemistry, and how these insights can be used to create novel synthetic organic methods with sustainability and green chemistry as central drivers. Within this vein they are interested in the exploration of electrochemistry as a tool for performing selective redox transformations, because it has been shown to provide specific advantages over conventional redox reagents in terms of selectivity, scalability, safety and sustainability. The Lennox group research programme also have a strong emphasis on fluorine containing molecules, and in particular the synthesis of new selective fluorination reactions and the creation of new fluorinated building blocks.

Exploring Electrochemistry as a Tool for New Reactivity

Redox transformations and electron transfer reactions are essential for the incorporation and manipulation of functional groups in the synthesis of complex molecules. Traditionally, stoichiometric redox reagents are required for such transformations, which are typically not atom-economical, hazardous, use heavy metals and/or expensive reagents.

Although electrochemistry in organic synthesis has a long-standing history, it has only recently emerged as a viable alternative for wide-spread application in synthesis. This is due to the rapid development and introduction of myriad different transformations, and reactor types, including the ability to run large scale reactions in flow.

In this presentation, I will detail our recent efforts in the development of new reactions using electrochemistry. In the reductive sense we have been developing methods for the defluorination of trifluoromethyl groups, and in the oxidative sense, we have been undertaking C-H functionalisation reactions. Details of reaction optimisations and our mechanistic understanding will be provided.

Kevin Cariou

Chimie ParisTech-PSL University

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Dr. Kevin Cariou graduated from Chimie ParisTech in 2002, he received his PhD in 2006 from the University Pierre and Marie Curie (now Sorbonne University) in Paris (France) under the supervision of Prof. M. Malacria and L. Fensterbank, where he studied platinum- and gold-catalyzed transformations with a joint CNRS-Sanofi BDI fellowship.

From 2007 to 2009, including one-year as a Lavoisier fellowship holder, he worked as a postdoctoral researcher in the group of Prof. A. J. Frontier at the University of Rochester (NY, USA) in the field of total synthesis. He was appointed a Chargé de Recherche in 2009 at the CNRS at the ICSN in the team Synthesis and Methodology Applied to Research in Therapeutics (SMART) led by Dr R. H. Dodd. He obtained his Habilitation à Diriger les Recherches (HDR) in 2015. From 2017 to 2019, he was the leader of the SMART team before moving to Chimie ParisTech in 2020, when he officially joined the group of Gilles Gasser, and in 2021 he was appointed CNRS Research Director.

His research interest lie in the development of new synthetic methods, with a focus on iodine(III) reagents and nitrogen-rich building blocks, and their application toward the synthesis of biologically active molecules, in particular antibacterials.

Cycloadditions and Cyclization with Ynamides

Ynamides are particularly useful molecular bricks that can be activated in a variety of way to initiate all kinds of transformation. For our part we have been interested by the study of rather underexplored modes of activation such as basic or oxidative conditions.

During this talk, we will first present our latest results on the development of various transformations of ynamides to access original nitrogen-containing heterocycles, such as azetidinimines and amino-ferrocenophanes, through cycloadditions and cyclization process.

Gilles Gasser

Chimie ParisTech-PSL University

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Gilles Gasser was born, raised and educated in the French-speaking part of Switzerland. After a PhD thesis in supramolecular chemistry with Prof. Helen Stoeckli-Evans (University of Neuchâtel, Switzerland), Gilles undertook two post-docs, first with the late Prof. Leone Spiccia (Monash University, Australia) in bioinorganic chemisty and then as an Alexander von Humboldt fellow with Prof. Nils Metzler Nolte (Ruhr-University Bochum, Germany) in bioorganometallic chemistry. In 2010, Gilles started his independent scientific career at the University of Zurich as a Swiss National Science Foundation (SNSF) Ambizione Fellow before obtaining a SNSF Assistant Professorship in 2011. In 2016, Gilles moved to Chimie ParisTech, PSL University (Paris, France) to take a PSL Chair of Excellence. Gilles is a RSC Fellow recipient and received several fellowships and awards including the Alfred Werner Award from the Swiss Chemical Society, an ERC Consolidator Grant and Proof of Concept, the Thieme Chemistry Journal Award, the Jucker Award for his contribution to cancer research, the European BioInorganic Chemistry (EuroBIC) medal and recently the Pierre Fabre Award for therapeutic innovation from the Société de Chimie Thérapeutique (SCT). He was an Overseas Fellow of the Churchill College, University of Cambridge in 2022. Gilles' research interests lay in the use of metal complexes in different areas of medicinal and biological chemistry.

Metal Complexes as Therapeutics and Diagnostics

Metal complexes are currently playing a tremendous role in medicine. 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 based on iron, copper, rhenium, ruthenium, osmium as imaging and therapeutic agents against cancer and parasitic diseases. One of such has now entered clinical trial. During this talk, we will present our latest results, including *in vivo* results, on these topics, notably the use of metal complexes as photosensitizers for photodynamic therapy against cancer.

Jan Holub

University of Chemistry and Technology in Prague

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Jan Holub defended his PhD in 2016 under the tutelage of Prof. J.-M. Lehn at the Institut de Science et d'Ingénierie Supramoléculaires, Strasbourg, France studying metallosupramolecular self-assembly. He then joined the group of Prof. A. Llobet at Institut Català d'Investigació Química, Tarragona, Spain where he studied the use of molecular complexes for electrocatalytic activation of various small molecules. After a short period at the University of Cambridge, Cambridge, United Kingdom with Prof. G. Bernardes, he obtained a junior position at the University of Chemistry and Technology, Prague, Czech Republic focusing on guided metalo-driven self-assembly for the preparation of functional architectures and on electrocatalysis based on transition metals complexes.

Multivalency through self-assembly: supramolecular grids in bio-relevant interactions and material science

Such as bricks must be precisely organized to construct a wall, or a block of stone must be sculptured to serve a purpose. In the same way, the practical potential of a molecule can often be manifested only through its multiarrangement into "material" or through decoration with functional appendages. The supramolecular chemistry gives us a rich set of tools to build well-defined structures through designed self-assembly. Using orthogonal principles one can increase not only the complexity of the self-assembly but also alter the compound's use. In our group we implement these principles to build so-called supramolecular grids, a diverse yet underdeveloped group of coordination compounds with very regular structures. The relatively low number of their studies, compared to other supramolecular entities (e.g. cages, rotaxanes), is caused by the fact that the grids are mostly studied in their basic functionalised form as a single unit, thus greatly limiting their utility and applicability. However, in the spirit of the initial paragraph, we try to imbue our grids with a practical function through additional organisation or peripheral functionalisation and use them as platforms for catalysis or as multivalent ligands. In the lecture, we will talk about the basic conditions for the formation of grids, different supramolecular principles involved with grids, and how we implement these principles to prepare multivalent ligands for interactions with proteins or tailorable surface layers for (electro)catalysis

Eco-friendly innovative synthetic pathways for 1,3-polyheterocyclic ring systems

L. Molteni[1*], E.M. Beccalli[1]

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The development of sustainable processes using inexpensive, non-toxic, and readily available reagents for efficient organic synthesis remains a key objective in chemical research.[1] The ability to select alternative synthetic pathways that avoid hazardous reagents and minimize waste generation by using green precursors is an important goal for both academic and industrial research. In this context, methanol has emerged not only as solvent but also as a promising green and renewable carbon source for the formation of C-C, C-N, and C-O bonds, including its application in heterocycle synthesis,[2] representing and efficient alternative to formaldehyde and other methylation reagents.
Herein, we present the reaction of aliphatic substrates such as amino alcohols and aliphatic diamines with methanol under copper-catalysed oxidative conditions, providing an efficient one-pot approach to synthetise 1,3-oxaza- and 1,3-diazaheterocyclic systems in excellent yields. The synthetic utility of this transformation was demonstrated on gram-scale synthesis[3] and through the assessment of the Environmental Factor (*E*-factor) which further validated the sustainability of the proposed methodology.
Furthermore, a metal-free approach for the synthesis of oxazolidine scaffolds has recently been explored, further improving the atom economy of the reaction.

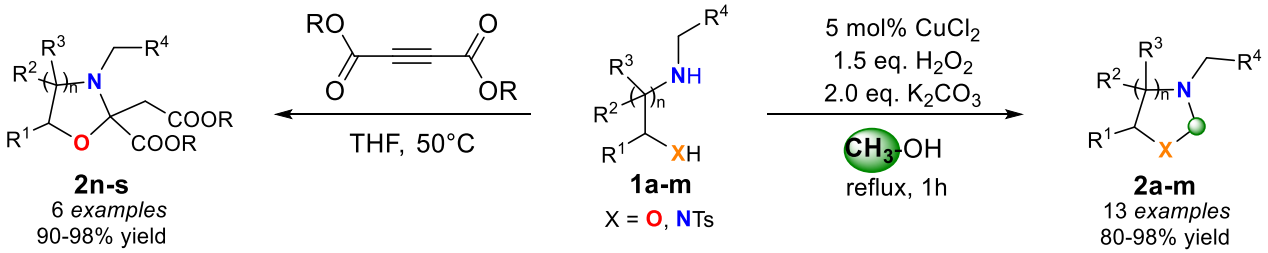

Figure 1: Synthesis of 1,3-polyheterocyclic systems.

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[1] P.J. Dunn *Chem. Soc. Rev.,* **2012**, *41*, 1452-1461.
[2] K. Natte, H. Neumann, M. Beller, R.V. Jagadeesh *Angew. Chem. Int. Ed.,* **2017**, *56*, 6384-6394.
[3] L. Molteni, E. M. Beccalli, L. Castoldi, G. Broggini, Camilla Loro *Eur. J. Org. Chem.,* **2023**, *26*, e202301106.

Cycloaddition of CO_2 to limonene diepoxide: kinetic and mass transfer analysis

Federica Orabona[1,2], Stefano Napolitano[2], Veronika D. Badazhkova[1], Wander Perez-Sena[1], Kari Eränen[1], Martino Di Serio[2], Dmitry Murzin[1], Vincenzo Russo[1,2], Tapio Salmi[1]

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Limonene is an abundant and cost-effective renewable chemical with a global annual production of approximately 70 kt (2017). Thanks to its particular chemical structure, it can be further functionalized to obtain different monomers for the production of biomaterials[1]. For instance, limonene diepoxide is a promising precursor for the synthesis of non-isocyanate polyurethanes (NIPU). The catalyzed cycloaddition of CO_2 to limonene diepoxide produces a bifunctional five-membered cyclic carbonate i.e., limonene dicarbonate which is particularly interesting as building block for the production of NIPU[2].
In this work, the carbonation of limonene diepoxide was performed in a stainless steel Parr reactor in solvent-free mode, at relatively high temperature and pressure of CO_2 and in the presence of a catalyst. Different quaternary ammonium salt halides were tested and precise kinetic studies were conducted with the best catalyst by varying different operating parameters. The reaction products were purified with column cromatography and identified by ^{1}H-NMR and GC-MS to unveil the reaction network. The solubility of CO_2 in the reaction media was measured at different temperatures and pressures and the gas-liquid mass transfer coefficients were evaluated.

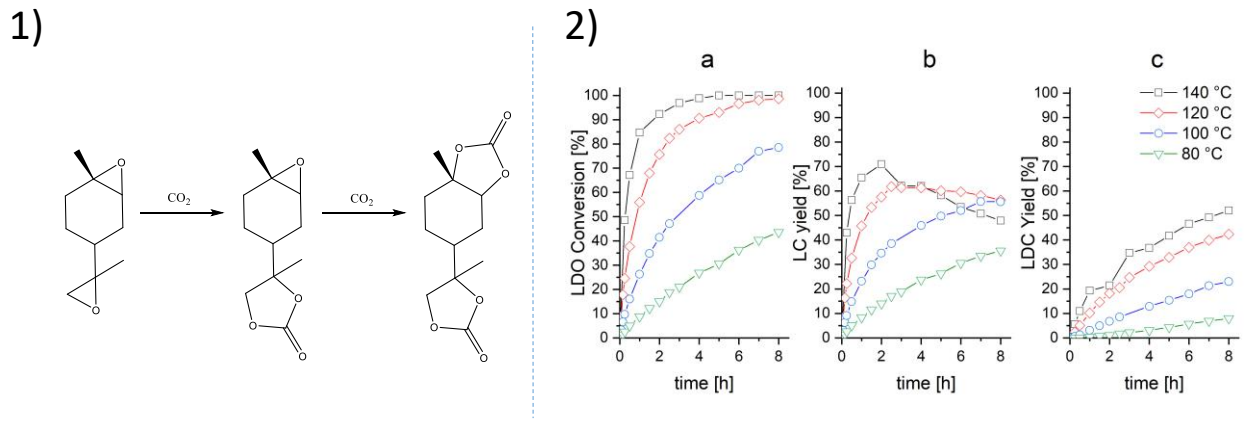

Figure 1: Reaction scheme of limonene dioxide carbonation (1). Temperature effect on the kinetics of limonene diepoxide carbonation (2).

References

[1] A. Mija, E. Louisy, S. Lachegur, V. Khodyrieva, P. Martinaux, S. Olivero, V. Michelet, *Green Chem.*, **2021**, 23, 9855.
[2] P. Mikšovsky, E. Horn, S. Naghdi, D. Eder, M. Schnurch, K. Bica-Schröder, *Org. Process Res. Dev.*, **2022**, 26, 10, 2799–2810

Waste-minimized C(sp3)-H activation for the preparation of fused N-heterocycles

Tian Sang[1,*], Tommaso Scarabottini[1], Francesco Minio[1], Luigi Vaccaro[1]

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One of the most effective strategies for reducing environmental pollution associated with chemical production is the use of efficient catalytic reactions. Transition-metal-catalyzed C–H functionalization technologies have emerged as a valid alternative to traditional cross-coupling reactions for the effective formation of carbon-carbon and carbon-heteroatom bonds. In particular, heterogeneous palladium catalysts have received widespread attention because they can be easily separated from the reaction mixture and reused.
N-containing heterocyclic compounds, such as oxindoles and pyrrole derivatives, are important structural motifs in many molecules of biological and pharmaceutical interest. In previous work, we present the development of a waste-minimized protocol for the synthesis of oxindoles using cyclopentyl methyl ether (CPME) as a safe and green reaction medium and palladium on carbon (Pd/C) as a reusable catalyst.[1] Then this work, we developed an effective waste-minimized approach for the intramolecular Pd-catalyzed C(sp3)-H activation of methyl pyrrole derivatives by using a heterogeneous recyclable palladium(II)-bis(N-heterocyclic carbene) catalyst and CPME, the heterogeneous catalytic system could be recovered and reused up to representative five runs without any loss in efficiency. The target products have been obtained selectively and with excellent isolated yields. Other green metrics have been calculated and the data collected demonstrate that our newly developed protocol is very promising in terms of its environmental impact profile.[2]

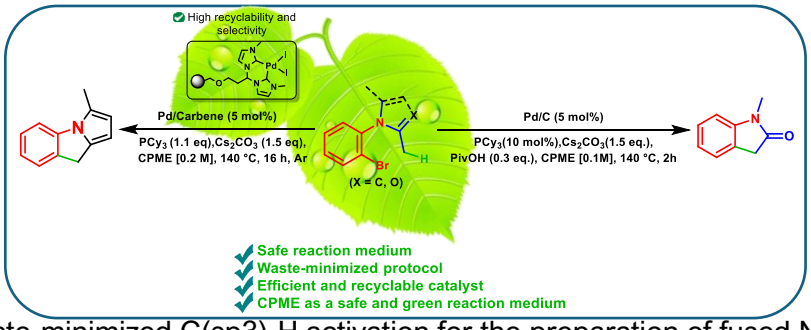

Figure 1: Waste-minimized C(sp3)-H activation for the preparation of fused N-heterocycles.

References

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[2] N. Salameh, F. Minio, G. Rossini, A. Marrocchi, L. Vaccaro *Green Synth. Catal.* **2023,** *4,* 240 – 245.

Selective C-H Functionalization at C3, C4 and C5 of furfural and HMF

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Furfural and 5-hydroxymethylfurfural (HMF) are renewable platform for sustainable production of high value-added chemicals derived from lignocellulosic biomass. Their selective functionalization is currently an emerging field, and a special quest for stabilizing substituents at C3 and/or C4 positions of furanic platforms is essential to improve chemical and thermal stability of the furanic core.[1] C3–H borylation was only reported on C5-substituted furfural derivatives to overpass the natural selectivity for the C–H bond α to the oxygen atom.[2] We developed a method to achieve a ligand-control selective borylation at C3 or C5 position of non-substituted furfural by transition metal-catalyzed C–H activation exploiting the aldehyde function to install an imine as directing/protecting group. This strategy provides an easy access to borylated reagents (**3** and **3'**), which can be used *in situ* as nucleophilic partners in Suzuki-Miyaura cross-coupling reactions, affording ortho-substituted heterobiaryl compounds (**4** and **4'**) after removal of the imine group. Finally, the installation of a second directing group *ortho* to the newly installed aryl moiety opens the way to transition-metal-catalyzed C4-H functionalizations, such as the Fujiwara-Moritani olefination, with the formation of **5** and **5'** in moderate to good yields.[3] This C3/C4-H functionalization strategy provides the first example of preparation of a tetrasubstituted furaldehyde.

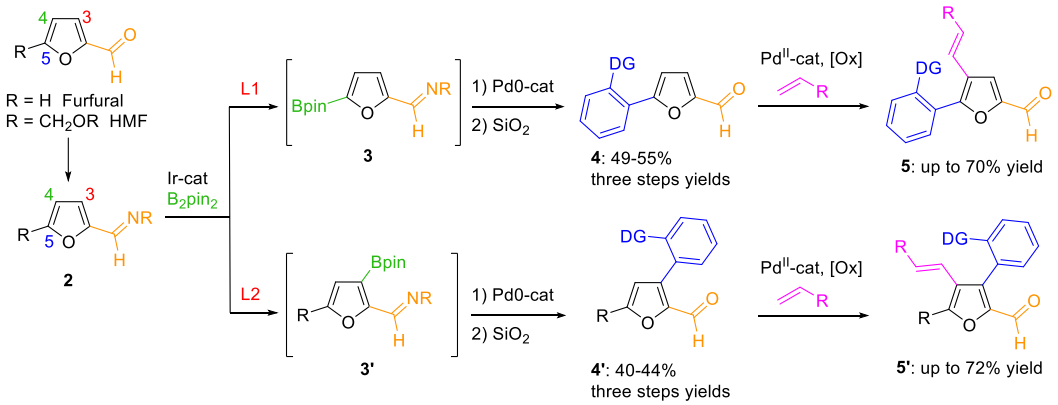

Figure 1: C5/C4-H or C3/C4-H functionalization of furfural and HMF

References

[1]A. Mori, S. Curpanen, C. Pezzetta, A. Perez-Luna, G. Poli, J. Oble. *Eur. J. Org. Chem.,* **2022**, e202200727.
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Synthesis of biheteroaromatic atropisomeric surfactants and their application in micellar Suzuki-Miyaura reactions

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The research for replacing classical organic solvents (which are unhealthy VOCs) with greener media represents an increasingly urgent scientific challenge. Water represents a safe and sustainable alternative, with the obvious problem that lipophilic organic reagents typically do not dissolve in it. Surfactants are amphiphilic molecules characterized by a hydrophilic and hydrophobic domain and give great opportunities to perform reactions in aqueous medium[1] making the process clean, fast and efficient with consequent remarkable overall benefits for sustainability.[2]

A new and innovative class of biheteroaromatic surfactants based on a 2,2'-biindole **1a-b** and a 3,3'-bibenzo[*b*]thiophene **2** scaffold, reported in Figure 1, was designed and synthetised. The introduction of bithienyl units on the biheteroaromatic core prevents the rotation around the interanular bond making them chiral, opening the possibility of employing them in enantioselective reactions as pure enantiomers.

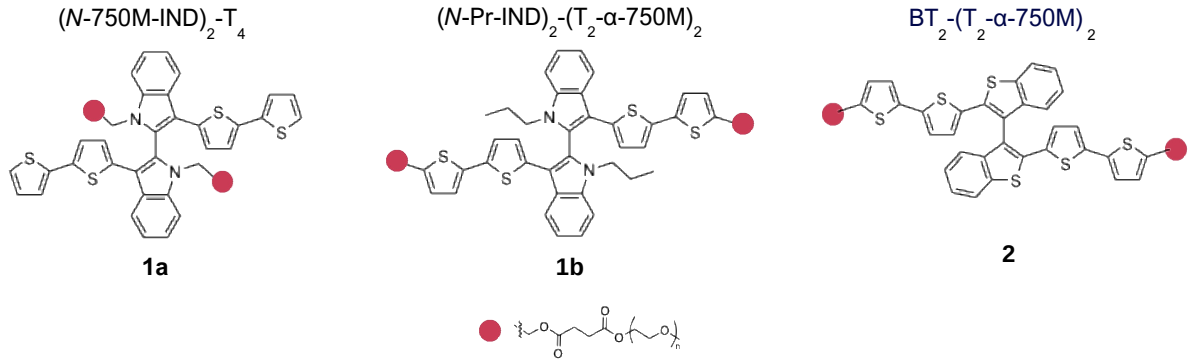

Figure 1: Surfactants based on a 2,2'-biindole **1a-b** and a 3,3'-bibenzo[*b*]thiophene **2** scaffold.

The performances of the racemic surfactants in Suzuki-Miyaura micellar reactions will be discussed.

References

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Asymmetric Synthesis of γ-Amino Alcohols Featuring Tertiary Carbon Stereocenters

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Triazoles, including 1,2,3- and 1,2,4-isomers, are highly exploited scaffold in drug design due to their ability to mimic different functional groups, making them suitable for bioisosteric substitutions.[1] In last decades, 1,2,3-triazole-bearing compounds have attracted researchers interest due to their polyhedral bioactivity and accessible chemical synthesis via both the Huisgen 1,3-dipolar cycloaddition and other green chemistry protocols.[2] Moreover, FDA approved several drugs containing 1,2,3-triazole ring as anticancer, antiviral or antidiabetic agents. Likewise, 1,2,4-triazole-containing compounds have found wide range of medical applications, such as the anticancer drugs Vorozole, Letrozole, and Anastrozole. However, all these compounds are N1-substituted.[3] Conversely, preparation of 3,5-disubstituted-1,2,4-triazoles is not trivial and only a limited number of synthetic strategies have been reported (Figure 1A). Despite the numerous synthetic challenges, we have recently synthesized a library of 3,5-substituted-1,2,4-triazoles, by reacting the appropriate hydrazide derivatives and carbonitriles under basic conditions (Figure1B). These compounds showed promising activity with an antiproliferative effect in in vitro cell models of lung epithelial fibrosis targeting Rho-associated protein kinase (ROCK), a key protein involved in pulmonary fibrosis development.[4]

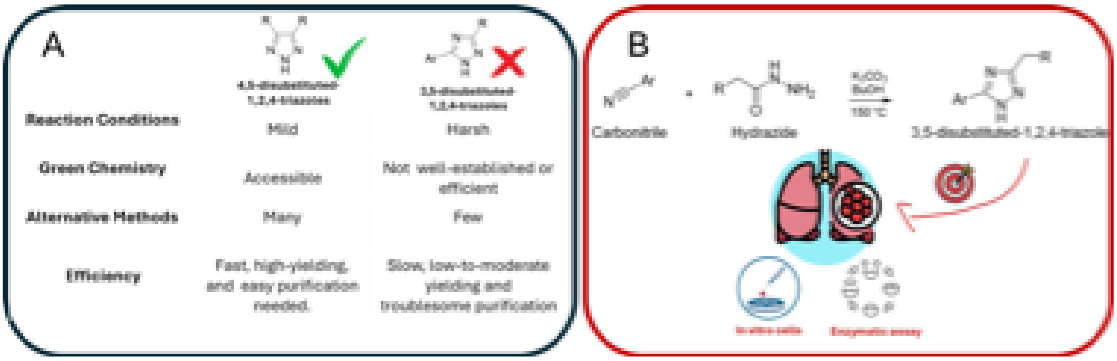

Figure 1: Overview of the study.

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Imidazo[1,2-a]pyridines as ALDH1A3 inhibitors: Is it really true that reaction yield does not matter in MedChem?

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Imidazopyridines are widely employed scaffolds in Medicinal Chemistry due to their high synthetic accessibility and versatility in terms of chemical functionalization. Among the different isomers, imidazo[1,2-a]pyridines have long been exploited for several biomedical applications, including antimicrobial, antidiabetes, and anticancer purposes.[1]

In this context, in recent years, we reported a library of derivatives as inhibitors of Aldehyde Dehydrogenase (ALDH) 1A3, an enzyme involved in the detoxification of aldehydes to carboxylic acids, the conversion of retinal in retinoic acid, and a recognized biomarker for cancer stem cells (CSCs).[2] Interestingly, the inhibitory potency along with the isoform-selectivity profile was found to be addressed by the substitution pattern on the imidazopyridine nucleus, with the 2,6-diphenyl substitution emerging as highly promising.[3]

The growing interest in this field led us to extend the series by resorting to a two-step synthetic scheme, involving a cycle condensation and a Suzuki-Miyaura cross-coupling reaction.[3] Aimed to compare the isolation feasibility and the overall yield of a case study compound, we tried a basic modification of the approach, by switching the two reactions and/or employing a microwave-assisted protocol. The results helped us to gain a deeper understanding of the yield issue in MedChem along with speeding up the library development process.

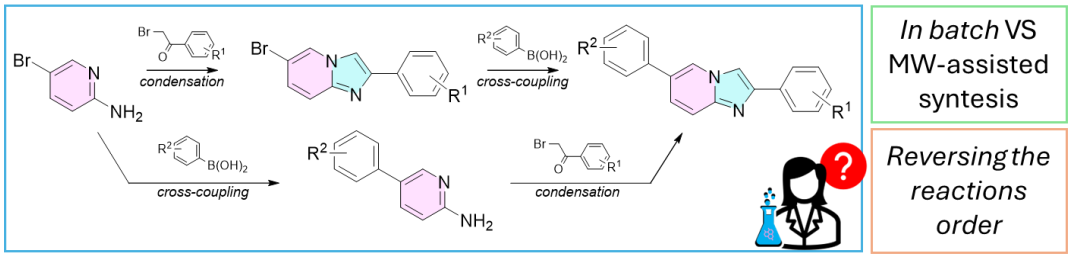

Figure 1: Synthetic schemes for imidazo[1,2-*a*]pyridines explored in this study.

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Donor-acceptor dyads containing thia-bridged triarylamine hetero[4]helicene units

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The project is focused on the synthesis, resolution, and characterization of chiral donor-acceptor dyads, to explore their Chiral Induced Spin Selectivity (CISS) effect.[1] A perylene diimide acceptor is covalently linked through bridges of various structure and length, to a chiral donor unit: *i.e.* a thia-bridged triarylamine hetero[4]helicene (Figure 1).[2] Each donor-acceptor dyad has been resolved by chiral HPLC, and the interaction with circularly polarized light, as well as the electronic properties of all single enantiomers investigated.

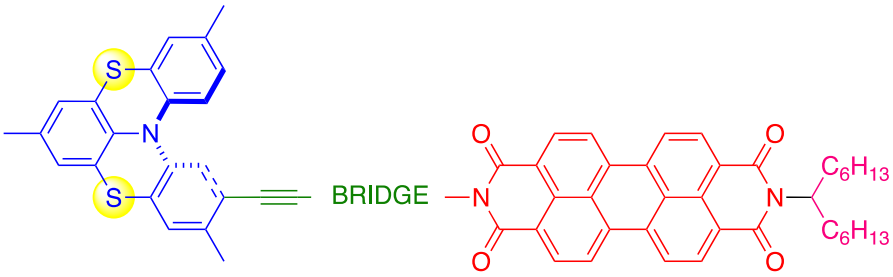

Figure 1: General structure of our chiral donor-acceptor dyads.

The final aim of this research is the direct spectroscopic detection of an intramolecular CISS effect, studying the photoinduced electron transfer after photoexcitation of our dyads, through time-resolved optical and magnetic resonance spectroscopies.[3]

We acknowledge the support of the European Union by the Next Generation EU project B12B23000300006 "Progettazione, sintesi e studio di sistemi chirali a selettività di spin nel trasferimento elettronico per il controllo di spin qubit molecolari". We also acknowledge the support from the Horizon Europe Programme through ERC-Synergy project CASTLE (proj. n. 101071533).

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Synthesis of functionalized 2-cyclopentenones by the gold(I)-catalyzed Rautenstrauch reaction

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A one-pot synthesis of ring-fused, α-hydrazino-2-cyclopentenone derivatives **4** is achieved from suitable propargyl esters **1** through a gold(I)-catalyzed Rautenstrauch/hetero-Diels-Alder/ring opening cascade process. By mixing the propargyl esters with a dialkylazodicarboxylate in the presence of a gold(I) catalyst, in particular 2 mol % of t-$Bu_3PAuNTf_2$, the 1,2-acyloxy migration/cyclization process (Rautenstrauch reaction)[1] leads to 2-acyloxycyclopentadiene intermediates **2** which are stereoselectively trapped by the heterodienophile present in situ. This provides strained, heterocyclic intermediates **3** which quickly undergo highly regioselective ring opening by a retro aza-Michael reaction in the presence of traces of water and promoted by the gold(I) catalyst, eventually yielding the target compounds.[2,3] Six- and seven-membered ring-fused cyclopentenones bearing a pendant α-hydrazino moiety can be obtained in moderate to excellent yield (50-98%) by this approach.[4] When the reaction is carried out on a chiral enantiopure propargyl ester it occurs with a minimal erosion of the initial optical purity providing the final product in excellent ee.

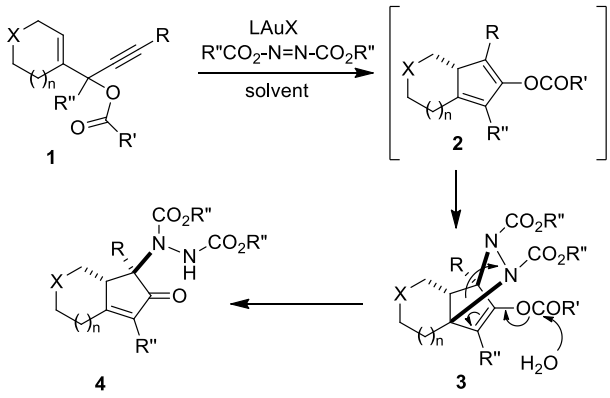

Figure 1: Reaction process object of the study.

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Flexible dithienyls: novel chiroptical probes for determining the absolute configuration of chiral molecules.

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The determination of absolute configuration is a crucial task when dealing with chiral molecules. Among the available methods, chiroptical spectroscopy stands out as an attractive option, offering fast results, the ability to analyze samples in solution, and requiring only sub-milligram quantities. There features are particular appealing for studying natural products, which are often non-crystalline compounds and available in very small amount. In recent years, the use of chiroptical probes has gained attention as an innovative alternative to computational methods for chiroptical analysis, particularly for conformationally flexible or UV-transparent molecules. Our research group has contributed to this field by applying flexible biphenyl-based chiroptical probes for the determination of absolute configuration in various chiral compounds, including diols,[1] carboxylic acids,[2] and amines.[3] In this communication, a novel flexible dithienyl probe is introduced and applied to determine the absolute configuration of chiral amines, acids, and amino acids. When a chiral amine is converted into its corresponding dithienyl azepine derivative (Figure 1a), the interaction with the chiral substrate induces a preferred *M* or *P* twist, depending on the amine absolute configuration. This twist can be identified through a characteristic band in the electronic circular dichroism (ECD) spectrum, enabling the determination of the amine absolute configuration from the ECD spectrum of the azepine derivative. A similar process occurs when a chiral carboxylic acid is transformed into its corresponding dithienyl amide (Figure 1b). Compared to biphenyl probes, the dithienyl probe offers the advantage of producing a more distinct diagnostic ECD signal and also has the potential to determine absolute configuration using Optical Rotation measurements.

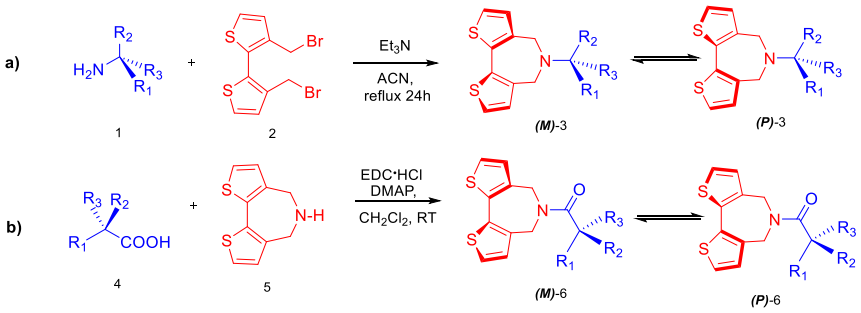

Figure 1: Dithienyl probes used for absolute configuration determination of chiral amines and acids.

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Symmetry Breaking and Chirality: A Journey Through Molecular Crystals

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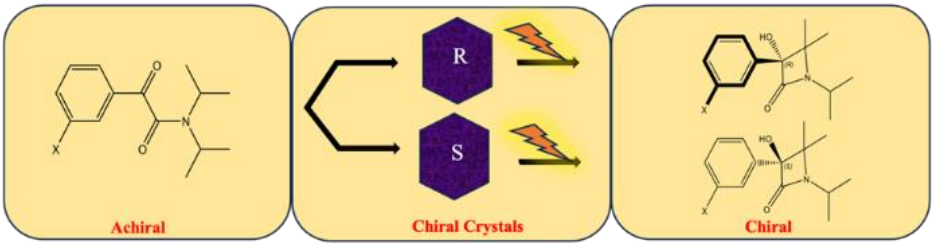
Chirality has become increasingly significant across a spectrum of disciplines, such as chemistry and materials science1. Chiral crystals have garnered significant attention due to their potential applications in enantioselective catalysis, chiral sensing devices, and as fundamental components for functional materials. The study of chiral symmetry breaking in molecular crystals presents an engaging interdisciplinary research area2. Under non-equilibrium conditions, the symmetric state becomes unstable and the spontaneous emergence of a non-zero enantiomeric excess arises from an achiral state through a chiral symmetry breaking transition3. This study focuses on a series of achiral X-oxoamide molecules that crystallize as chiral crystals, exhibiting an uncommon similarity in their crystal structure. Utilizing UV light, we can freeze the chirality in the solid-state and fix the stereo genic centres into a preferred configuration, which enables the separation of enantiomers. This transition from the supramolecular chirality to molecular chirality is significant, as it enhances the ability to control and manipulate chiral properties of materials at a molecular level. Characterization techniques such as X-ray diffraction, HPLC, spectroscopy, and computational modelling are employed to investigate chiral symmetry breaking. These methods offer insights into the three-dimensional arrangement of molecules within the crystal lattice, elucidating the origins of chirality and the critical intermolecular interactions, including hydrogen bonding, van der Waals forces, and electrostatic interactions.



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Asymmetric Synthesis of γ-Amino Alcohols Featuring Tertiary Carbon Stereocenters

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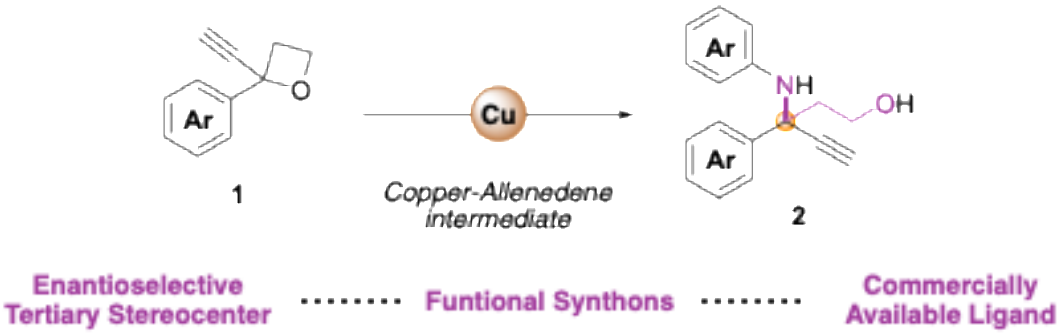
Enantioselective synthesis of γ-amino alcohols featuring a tetrasubstituted tertiary carbon center remain a current challenge in organic synthesis. Here, we present a Cu-catalyzed propargylic amination reaction of alkynyl-oxetanes, a versatile substrates for the synthesis of structurally diverse γ-amino alcohols.[1,2] The protocol developed offers user-friendly reaction conditions and demonstrates a reasonable scope for both alkynyl oxetanes and functional aromatic amines. Post-synthetic modifications of selected γ-amino alcohols further showcase the synthetic potential of these chiral building blocks, offering access to advanced synthons that may prove valuable in future drug discovery and development efforts.



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In-situ synthesis of peptidomimetics bearing (hetero)cyclic moieties using a photocatalytic approach

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Recently, peptidomimetics have been widely studied in drug discovery and medicinal chemistry. Peptidomimetics present enhanced properties compared to peptides (i.e. selectivity, affinity, conformational and proteolytic stability), thanks to their structural modification.[1]

Herein, we studied an innovative metal-free organo-photocatalytic carbamoylation of imines for the synthesis of peptidomimetics, by forming a new C-C bond using Hantzsch ester (HE) derivatives as radical precursors (**Figure 1**).[2]

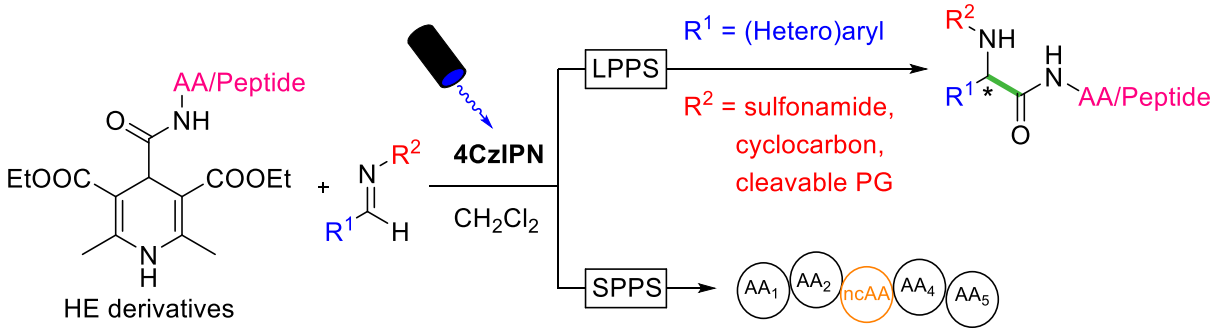

Figure 1: Photocatalytic carbamoylation of imines to form peptidomimetics.

By varying the starting imine and the amino acid (or peptide sequence) linked to the HE, we developed this novel approach to form peptidomimetics, where the non-natural portion of the sequence is obtained as a result of the newly formed C-C bond. Moreover, we successfully employed this methodology on solid phase peptide synthesis (SPPS) testing few peptides with different lengths and secondary structures proving the feasibility of the method, independently from the hinderance of the system.

Finally, we reported one example using the solid phase where the non-coded amino acid was successfully inserted within the peptide backbone.

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1,3-Azaprotio Cyclotransfer Reaction for the Synthesis of New 3-Methylindolizidines

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Polyhydroxylated indolizidines, such as Castanospermine **1** (Figure 1a), represent a deeply investigated class of iminosugars known for their biological activity (i.e. anticancer, antimetastatic, and antiviral ones).[1] In addition, naturally occurring polyhydroxylated pyrrolizidines with a methyl substituent adjacent to the bridge-head nitrogen atom, such as hyacinthacines A_3 **2** and B_3 **3**, can inhibit intestinal lactase displaying antidiabetic activity.[1,2] However, the only example of 5-methylindolizidine found in nature, namely Steviamine **4**, did not show interesting inhibitory activity.[3] Nonetheless, the synthesis and the biological activity of polyhydroxylated indolizidines bearing a methyl substituent adjacent to nitrogen in the pyrrolidine moiety have never been reported.

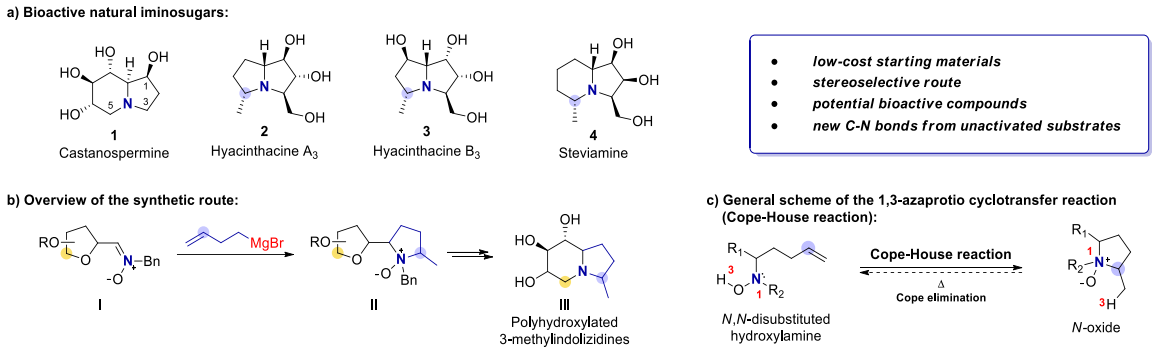

Figure 1: General scheme of the work.

Herein we report the first synthesis of polyhydroxylated 3-methylindolizidines **III** exploiting enantiomerically pure nitrones **I** derived from low-cost sugars (Figure 1b); the key methyl pyrrolidine moiety has been assembled with a stereoselective, timesaving, and 100% atom economical method using a 1,3-azaprotio cyclotransfer reaction[4] (Cope-House reaction,[5] Figure 1c) on the intermediate alkenyl-hydroxylamines.

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Biaryl Synthesis Through Biobased Palladium Catalyst

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The Suzuki-Miyaura cross-coupling reaction is a widely used method in organic synthesis for constructing biaryl compounds (Figure 1), and it is appreciated for its mild conditions and compatibility with various functional groups.[1] Despite the remarkable reactivity of homogeneous palladium (Pd) catalysts, their environmental drawbacks, such as Pd leaching and toxic solvents, present significant sustainability challenges. To address these issues, we developed an innovative macroporous biopolymeric catalyst (C-PhebPd), synthesised from modified phenylalanine complexed with palladium ions, offering a greener catalytic alternative.[2,3] The catalyst was synthesized *via* radical polymerization at subzero temperatures and thoroughly characterized using SEM, FTIR, and XPS analysis. This eco-friendly catalyst features high porosity and exceptional stability and operates efficiently in non-toxic solvents.[4] In Suzuki-Miyaura reactions, C-PhebPd demonstrated excellent activity, yielding even quantitative results across various substrates. Moreover, the catalyst is fully recyclable, maintaining its high catalytic efficiency over multiple cycles, making it a practical and sustainable alternative for these reactions. With its fast reaction times, superior atom economy, and reduced environmental impact, this innovative approach offers promising applications in various catalytic processes, enhancing performance and sustainability.

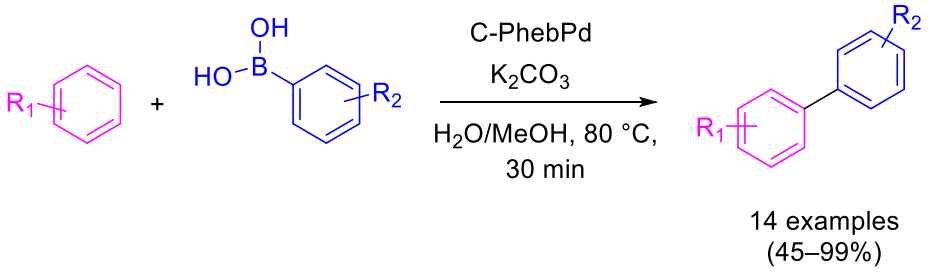

Figure 1: General scheme of Suzuki-Miyaura reactions catalysed by C-PhebPd.

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Radical addition approach for dihydrobenzofuran synthesis

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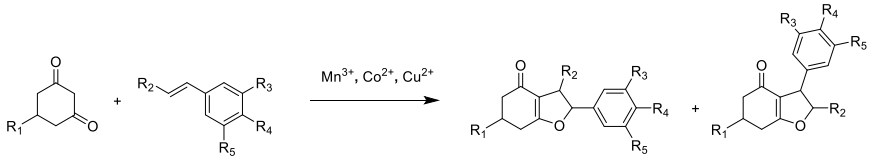
Benzofurans and 2,3-dihydrobenzofurans are known for their important biological properties like anticancer, antioxidant and anti-inflammatory.[1] A key reaction to synthesize them could be a [3+2] radical addition of a cyclic 1,3-dicarbonyl to different substituted internal olefin, using metal ions as promoters,[2-3] but also electrochemical methods have been recently reported.[4] Since now only examples of α-alkylstyrenes are reported, in which the *trans*-diastereoisomers have been obtained.[5] Currently we are involved in the cycloaddition of cyclic 1,3-dicarbonyls with more complex internal olefins as showed in the scheme 1, and the regio- and diasteroselectivity of the reaction will be studied.



1. R_1 = Me; R_2 = COOMe; R_3 = H; R_4 = OH; R_5 = OMe;
2. R_1 = Me; R_2 = COOMe; R_3 = H; R_4 = OH; R_5 = H;
3. R_1 = Me; R_2 = 4-OMe-phenyl; R_3 = OMe; R_4 = H; R_5 = OMe;
4. R_1 = ;R_2 = 4-OMe-phenyl; R_3 = OMe; R_4 = H; R_5 = OMe;

Scheme 1: [3+2] cycloaddition of 1-3 dicarbonyls with internal olefins induced my metal ions.

Then the aromatization of the cyclohexane ring would furnish the dihydrobenzofurans. Following these pathways we could obtain for example the gnetin c, an important dimer of resveratrol for which no synthesis has been reported yet.

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Use of o-alkyl substituted benzaldehydes in the photoenolization/Diels-Alder reaction sequence

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Photochemistry is the elective tool for the generation of highly reactive intermediates under mild conditions and their application in the formation of C–C bonds.[1] From a synthetic point of view, an intriguing possibility is the photoenolization/Diels-Alder (PEDA) strategy. In this work, we demonstrate the possibility to efficiently employ o-alkyl substituted benzaldehydes in the named reactivity, differently from the previous reports, where mainly ketones were investigated.[2-4] Mechanistically, light absorption by the carbonyl in A, followed by intersystem crossing (ISC), generates a triplet excited state T1. A 1,5-hydrogen atom transfer (HAT) leads to the diradical (*Z*)-C and then the reactive intermediate of interest (*E*)-A (Figure 1a). Such species, called hydroxy-o-quinodimethane, can act as diene and be conveniently trapped in a thermal Diels-Alder reaction with electron-poor alkenes or alkynes (Figure 1b).[2] The resulting carbocyclic adducts are common motifs in naturally occurring substances and are also important building blocks for the synthesis of drugs. Our approach gives access to a variety of products: both 1,4-dihydronaphthalenes and naphthalenes are obtained in the reaction with alkynes, while 1,2,3,4-tetrahydronaphthalenes are formed with alkenes as reaction partners. The latter derivatives can be additionally elaborated through an acidic treatment to afford 1,2-dihydronaphthalenes via water elimination. The versatility of the process is further demonstrated by the possibility to implement a continuous flow protocol.

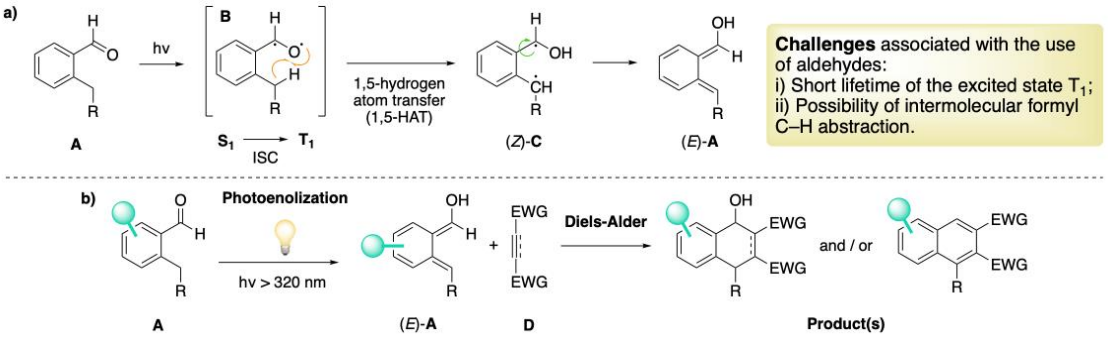

Figure 1: **a)** Photoenolization mechanism and **b)** photoenolization/Diels-Alder sequence.

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Photo-cycloaddition-selective ligands to covalently stabilize dimeric G-quadruplex forming aptamers

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High mobility group box 1 (HMGB1) is a nonhistone chromatin-associated protein present in the cellular nucleus. In response to various biological mechanisms, it can be secreted into the cytoplasm and in the extracellular environment where it plays a pivotal role in inflammation and tumour metastasis[1]. As a DNA binding protein, HMGB1 is able to recognize non-canonical DNA conformations, including the G-Quadruplex (G4) structure adopted by the 26-mer tract of the human telomeric DNA sequence (tel_{26})[1,2]. Considering that this protein is involved in the pathogenesis of several diseases, it would be clinically interesting to modulate the cytokine activity of HMGB1 by identifying appropriate inhibitors. In this scenario, we recently identified the G4-forming aptamer L12 as the best HMGB1 inhibitor within a partially randomized library of sequences based on tel_{26}[3]. The biophysical characterization of L12 showed that it exists both in monomeric and dimeric form, the latter one having the highest ability to inhibit the HMGB1-induced cell migration[3]. With the aim of identifying even more effective L12 analogues, several strategies are being pursued to covalently stabilize the dimeric species of L12. Xanthotoxin[4], which is able to react with thymines in a well-described photo-cycloaddition reaction, and is known as an effective DNA intercalator, upon UV irradiation, could form covalent bonds with the thymine residues of the termini of L12 monomeric units forming the dimer. This approach was here tested as a proof of concept in a wider program of in situ stabilization of G4-forming aptamers. Our preliminary experiments provided the desired covalent dimer of L12, whose identity was confirmed by ESI-MS experiments. Future studies will regard the evaluation of the interaction with HMGB1 of the xanthotoxin-aptamer adduct as well as its ability to inhibit the biological processes induced by the protein.

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Condensation of Primary Nitro Compounds with Functionalised Alkynes in Deuterated Water§

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Activated primary nitro compounds condense in water with alkynes to selectively form the corresponding 3,5-disubstituted isoxazole cycloadducts; the process is modulated by the presence of an acid-base catalytic system.[1,2]
In this work, such cycloaddition was applied to various alkynes using ethyl nitroacetate as the nitro compound, in order to develop an efficient synthetic methodology for incorporating of deuterium at position 4 of the isoxazole ring. These reactions were first carried out in water to develop a reliable experimental procedure and then repeated in deuterated water, optimising the variables and experimental conditions to achieve an optimum degree of deuteration for all substrates used. Achieving a high level of deuteration relies on controlling the exchange of the deuterium for the acetylenic proton.

§ § D. Cappuccini, part of the Master's thesis in Advanced Molecular Sciences at the University of Florence, 2023.

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Caerulomycin K: first total synthesis exploiting selective, multiple C-H functionalization of pyridines

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Caerulomycins, natural pyridine-based alkaloids, have been previously synthesized starting with highly pre-functionalized starting materials or requiring many functional group interconverions.[1–3] In this work,[4] we exploit recent C-H activation methodologies of N-heterocycles for the first total synthesis of Caerulomycin K, a diversely tri-functionalized pyridine readily assembled in three steps. Starting from mono-functionalized pyridines, the first strategy looked at a double C-H activation by means of phosphonium chemistry.[5] However, this strategy revealed unsuccessful. A better alternative was represented by a radical approach, achieved via Minisci chemistry. Firstly, an ortho-arylation on 4-chloro pyridine occurred, followed by an ortho-alkylation using trioxane.[6] In conclusion, a one pot SNAr, trioxane deprotection and oxime formation occurred to obtain the desired final product. Compared to already reported Caerulomycin syntheses, this novel approach requires only three step and a mono-functionalized starting material

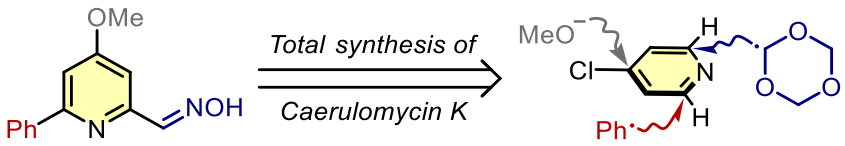

Figure 1: The first total synthesis of Caerulomycin K has been reported exploiting Minisci-type chemistry. Compared to previously reported Caerulomycin syntheses, this novel approach does not require highly pre-functionalized starting materials.

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C(sp^3)–H activation, a powerful sustainable tool to access N-containing heterocycles.

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C–H activation reactions have recently emerged as an efficient and sustainable tool to access valuable classes of heterocyclic relevant molecules whose interest ranges from medicinal chemistry to biology, including anti-tumoral, anti-inflammatory, anti-bacterial activities.[1,2] In the last two decades, several reports have shown that, despite the challenging reactivity compared to C(sp^2)–H bonds, intriguing target moieties can be synthesized through C(sp^3)–H bonds.[3] Additionally, the increasing attention toward environmental issues has led to a shift toward the development of processes that employ safer and recoverable solvents, and exploit reusable heterogeneous catalytic systems.[4] This is particularly crucial for the pharmaceutical production, where API synthesis can lead to a massive waste generation. This contribution outlines our research group's effort to assess a viable methodology for synthesizing oxindole moiety, found in numerous APIs,[5] through an intramolecular C(sp^3)–H activation. The developed protocol presents features that make it a sustainable alternative for accessing Nitrogen-containing heterocycle structures to the ones existing.

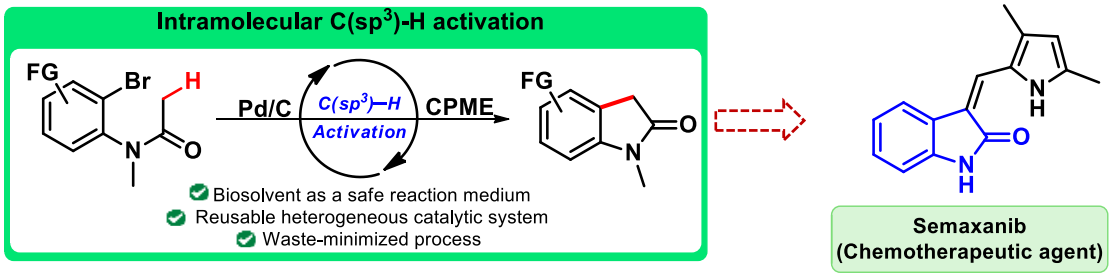

Figure 1: Sustainable alternative to access oxindole structure.

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Cyclopropane pipecolic acid derivatives for targeted interaction with the enzyme β-glucocerebrosidase.

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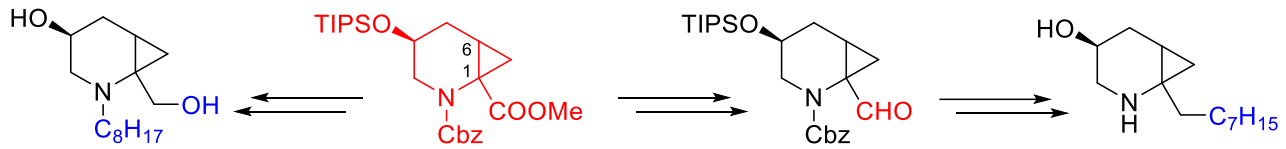
Pipecolic acids and their derivatives, known for their structural similarity to proline, have been widely used in peptidomimetics to enhance interactions with protein receptors and enzyme binding sites.[1] The structural rigidity of these compounds can be further improved by incorporating a fused cyclopropane ring, which may increase their interactions and affinity with biological targets. Cyclopropane pipecolic acids, derived from common aldose sugars,[2] feature functional groups that provide an ideal platform for introducing substituents (compounds **1**-**4**; Fig.1), such as aliphatic chains, which have been shown in the literature to enhance interactions with the enzyme β-glucocerebrosidase (GCase).[3] Deficiencies in GCase activity are linked to Gaucher's disease and Parkinson's disease.[4] Therefore, compounds capable of binding and restoring the activity of this enzyme, known as pharmacological chaperones, have become promising therapeutic agents for addressing both pathologies. Iminosugars with long aliphatic chains have shown potential as effective GCase inhibitors and chaperones.[3] We report our synthetic efforts to obtain these new cyclopropane pipecolic acid derivatives bearing aliphatic chains (compounds **5**-**8**; Fig.1) to evaluate how the conformational rigidity resulting from the fusion of a cyclopropane system onto a well-established piperidine scaffold influences their biological activity towards GCase.



7: 1*S*, 6*R*
8: 1*R*, 6*S*

1: 1*S*, 6*R*
2: 1*R*, 6*S*

3: 1*S*, 6*R*
4: 1*R*, 6*S*

5: 1*S*, 6*R*
6: 1*R*, 6*S*

Figure 1: New cyclopropane pipecolic acid derivatives (**5**-**8**) synthesized from functionalized precursors (**1**-**2**), derived from common aldose sugars.

Acknowledgement

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Synthesis of Functionalized Trivalent Iron Chelators for Biocompatible Materials

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Infections caused by resistant microorganisms pose a significant challenge, as they often withstand conventional treatments, underscoring the urgent need for new antimicrobial agents. This study addressed this challenge by developing two new antimicrobial compounds, **2** and **3**, that disrupt microbial metal metabolism through metal-chelating agents. The first step involved functionalising an alginate matrix with an ionic liquid, resulting in compound **1**, which displayed enhanced antibacterial efficacy. Further functionalisation with tris(hydroxypyridinone) (THP)[1] produced compound **2**, further improving antibacterial activity and reducing the minimum inhibitory concentration from 6 to 3 mg/mL while maintaining non-cytotoxicity toward healthy cells.[2] Compound **3** was synthesised by functionalising alginic acid with kojic acid via chlorokojic acid. This resulted in a biocompatible, sustainable material that exhibited broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria without toxicity to human cells.[3] All three compounds demonstrated significant potential for safe and effective antibacterial applications.

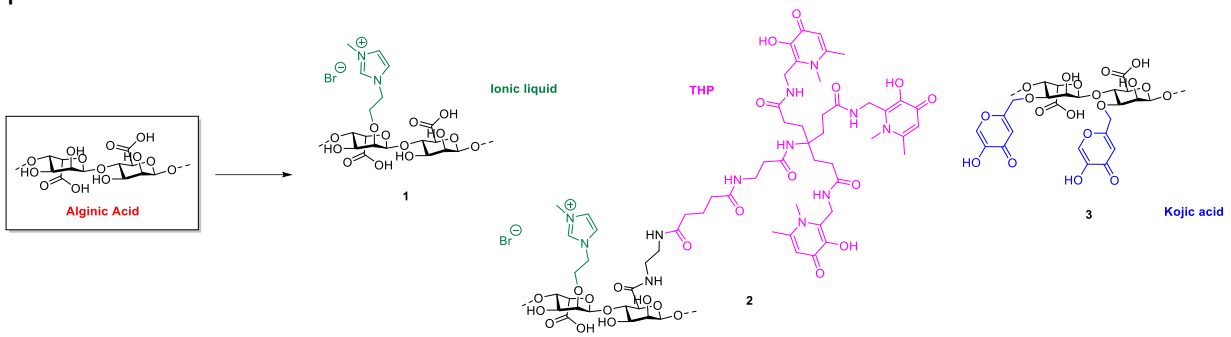

Figure 1: Synthesis of new materials based on alginic acid.

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DESIGN AND SYNTHESIS OF PEPTIDOMIMETICS TARGETING hIAPP PROTEIN

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Diabetes is a disease characterized by the presence of amyloid deposits, which arise from the hyperproduction and gradual aggregation of a specific protein known as human Islet Amyloid Polypeptide (hIAPP). The formation of hIAPP aggregates leads to extracellular amyloid deposition near pancreatic β-cells.
The initial step of the aggregation process involves the conformational change of hIAPP monomers: from a helical structure to a transition in β-strands which start to interact between each other forming β-sheets, fibrils and then insoluble amyloid plaques[1].
Recently, we focused on the design and synthesis of two distinct peptidomimetics with the aim to interact with the monomeric helical hIAPP. The goal is to stabilize the α-helical secondary structure, thus preventing the conformational switch that leads to the aggregate formation.
In order to increase their stability, the two synthetized peptidomimetic chains contain the non-natural cyclic β-Morph depicted in figure. Based on previous experience[2], this β-AA is able to stabilize γ-turns in ultra-short sequences and helical conformations in longer ones.
To prepare these sequences using Solid Phase Peptide Synthesis, a new synthetic strategy to obtain the (2*S*, 6*S*)-*N*-Fmoc-β-Morph was developed.

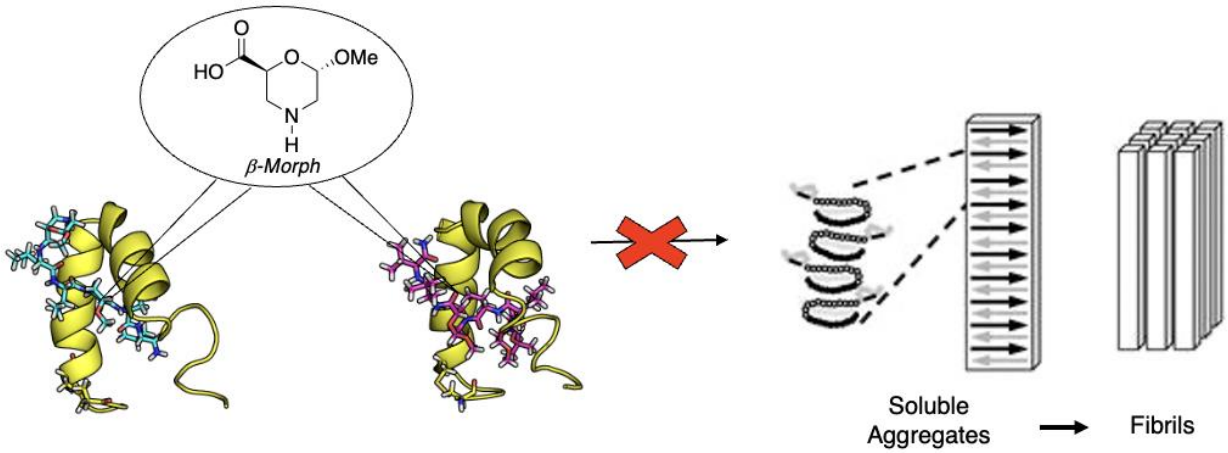

Figure 1: the use of the two peptidomimetics to inhibit hIAPP aggregation

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Synthesis and characterization of noncovalent nanohybrids of a β-η^1-Pd(II)-thioethyl porphyrazine complex and graphene nanoflakes

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Tetrapyrrole macrocycles are organic molecules of significant interest in organic photovoltaics (OPV) due to their thermal and chemical stability, as well as their peculiar spectroscopic properties. These features allow the development of devices capable of converting solar energy into electricity. Recent studies have shown that non-symmetrically substituted porphyrazine-type tetrapyrroles at the periphery of the macrocycle with π- extended aromatics are very promising dyes for photovoltaic cells. In particular, nanohybrids capable of current photogeneration have been obtained by using a thioethyl porphyrazine substituted with pyrene moiety, which can non-covalently interact with carbon nanostructures such as graphene nanoflakes or single walls nanotubes.[1] In our search for novel tetrapyrrole structures suitable for OPV applications, we report herein the synthesis of the β-η^1-Pd(II)-thioethyl porphyrazine complex **1** (Figure 1), the first example of isolable *beta*-ring-metalated tetrapyrrole. Additionally, we present its application in forming hybrids with graphene nanoflakes.[2] In this case, non-covalent π-π interactions with graphene are facilitated by both macrocycle core and the six benzene rings linked to the two phosphorus atoms.

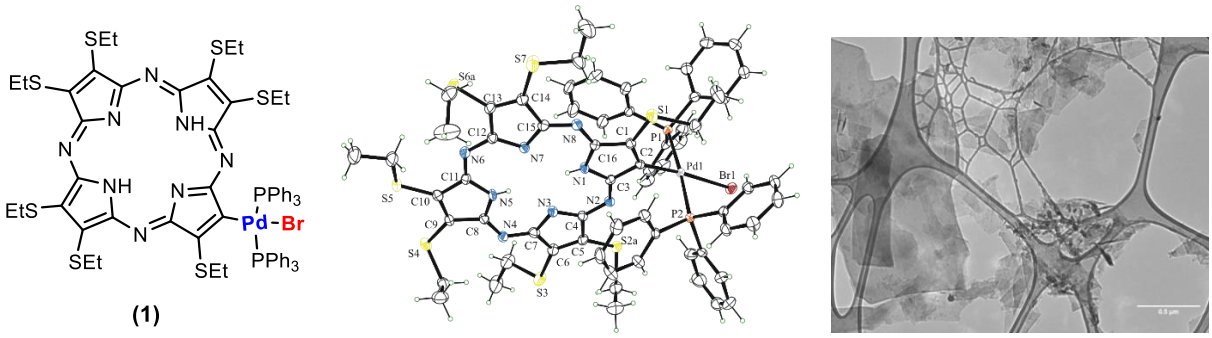

Figure 1: Schematic (*left*) and crystallographic (*center*) structure of compound **1**; TEM images of graphene nanoflakes (*right)*.

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Multimeric pyrrolidine iminosugars as levansucrase inhibitors to fight kiwifruit canker

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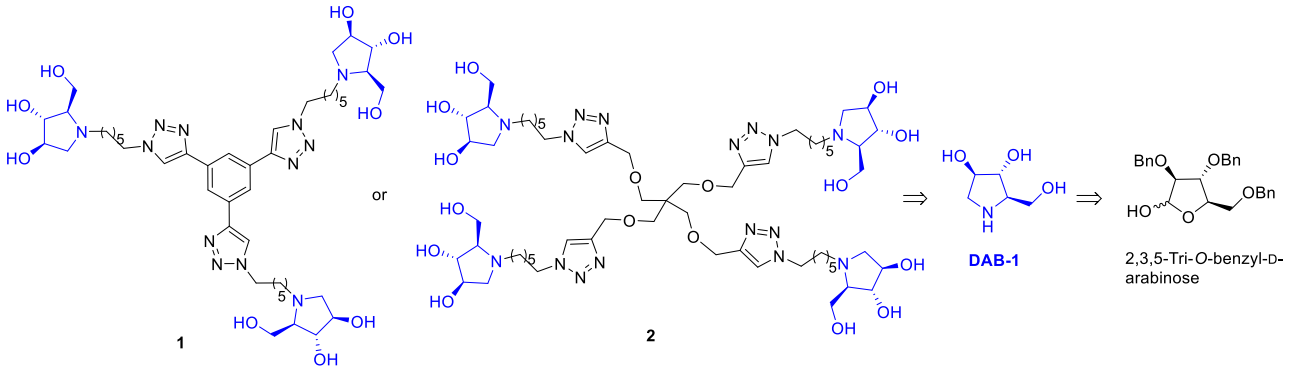
In recent years, Italian kiwifruit crops have been severely impacted by a bacterial canker disease caused by *Pseudomonas syringae pv. actinidiae* (*Psa*), with significant environmental consequences[1]. Mechanistic investigations highlighted the potential role of a polysaccharide called levan in masking and protecting the pathogen from the detection and defence mechanisms of the host[2]. Since levan's synthesis is catalyzed by an enzyme known as levansucrase, the discovery of new levansucrase inhibitors is a key objective. This project aims to develop new molecules derived from natural compounds that are non-toxic for humans and plants and able to specifically target the levansucrase enzyme. To date, no levansucrase inhibitors have been identified. Due to their well-known activity as glycosidase inhibitors, iminosugars (carbohydrate analogues with a nitrogen atom replacing the endocyclic oxygen of sugars) have attracted our attention as ideal candidates. Initial screenings revealed a trimeric (**1**) and a tetrameric (**2**)[3] polyhydroxypyrrolidine based on natural 1,4-deoxy-1,4-imine-D-arabinitol (**DAB-1**), as the most effective inhibitors.



These compounds are derived from the inexpensive sugar D-arabinose, which undergoes a five-step transformation to obtain **DAB-1**[4]. The multimeric compounds are obtained using the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) method[5].

We thank #NEXTGENERATIONEU (NGEU) and the Ministry of University and Research (MUR), National Recovery and Resilience Plan (PNRR), DM 352/2022, for a PhD fellowship.

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Design, synthesis and biological evaluation of novel antiviral agents for the treatment of Dengue and Zika virus infections

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Neglected Tropical Diseases (NTDs) includes 20 different infections that are prevalent mainly in tropical areas, where they affect poor communities, women and children. Two NTDs are those caused by the Dengue (DENV) and Zika (ZIKV) viruses. DENV can lead to fatal haemorrhagic fever while ZIKV causes Guillain-Barré syndrome in adults. Unfortunately, no vaccines are available yet to treat DENV and ZIKV infections. In the present scenario, NS2B/NS3, the main serine protease of DENV and ZIKV is considered a promising target for the development of specific anti-flavivirus therapies.[1]

Our research is focused into the development of novel antiviral agents targeting NS2B/NS3 serine protease; currently, our work involves the batch synthesis of allosteric inhibitors starting from the lead compound **1** (Figure 1)[2] which inhibits the serine protease of DENV and ZIKV with IC_{50} values of 8.58 μM and 0.93 μM, respectively. An extensive study of the structure-activity relationship (SAR) has been carried out concerning the variation of the three critical portions of the molecule, i.e. the benzothiazole nucleus, that bears two hydroxyl groups, the proline residue and the aromatic region anchored to the sulfonyl group. The role of the benzothiazole ring has been evaluated through its replacement with other nuclei such as the benzimidazole. We investigated the role of the proline residue stereochemistry on the inhibitory properties by synthesizing both the *R* and *S* enantiomers for the most promising inhibitors. The sulphonyl has been replaced also with a carbonyl group to investigate its role, while the nitro group present in *para* position of the aromatic ring has been replaced with different electron-withdrawing substituents in *ortho*, *meta* or *para* position, to evaluate the impact on antiviral activity. All the synthesized inhibitors have been tested against NS2B/NS3 of DENV and ZIKV and the results will be presented.

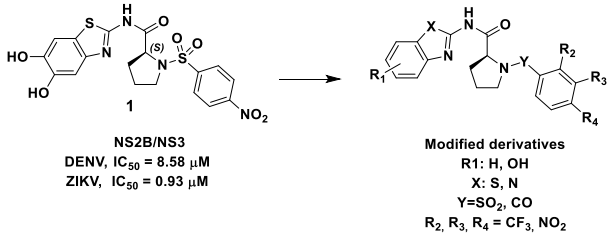

Figure 1. Design of novel inhibitors of NS2B/NS3 serine protease of DENV and ZIKV.

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Taking advantage of ferrocene-based *N*-substituted thiazolidinone chemistry in anti-protozoan drug discovery

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With approximately one third of the world's population infected, toxoplasmosis is a serious health concern for the major sequels of infection.[1] Thiazolidinone-based compounds have been considered promising new anti-*Toxoplasma* agents for their wide-spectrum biological activity. Indeed due to the presence of heteroatoms like nitrogen, and the chalcogens oxygen and sulfur, this cycle has unique electronic and chemical properties, useful in medicinal chemistry.[2] Furthermore, ferrocene is a particular complex with two cyclopentadienyl rings sandwiching an iron atom, with a remarkable stability, low toxicity, similarities in aromaticity and chemical versatility.[3]

Firstly, acetylferrocene was converted in its thiosemicarbazone derivative. Then, this moiety was cyclized into a thiazolidinone ring by using ethyl bromoacetate. Lastly, two series of compounds were synthesized through a nucleophilic substitution, characterized by alkyl, saturated or unsaturated, chains at the lactam nitrogen or presenting differently substituted benzyl counterparts (Figure 1A).

Lastly, this library of compounds was assayed against *T. gondii* highlighting good pharmacological behaviour and high therapeutic index. Moreover, the crystal structure of *n*-propyl derivative (**4**) was analysed as well (Figure 1B).

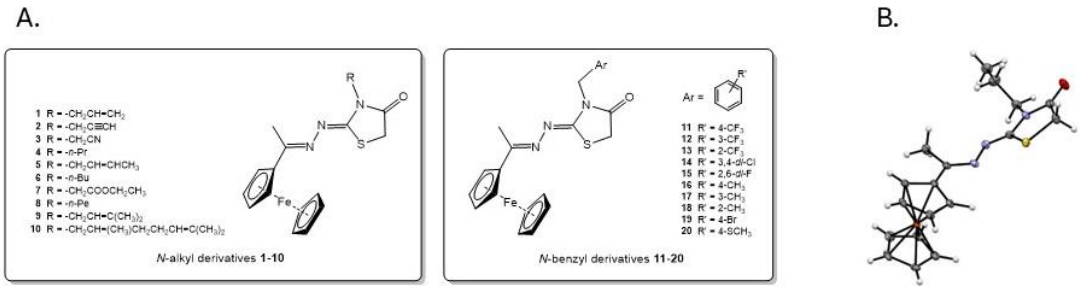

Figure 1: A. Ferrocene-based *N*-substituted thiazolidinone derivatives. B. Crystal structure of compound **4**.

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Synthesis of Biologically Active Heterocyclic Compounds and their Applications in Sensor Technology

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The object of this research is to synthesize new receptors for the development of a detection platform for the FKBP12 protein in biological fluids. FKBP12, a peptidyl-prolyl *cis-trans* isomerase, plays a well-established role in cancer, neurodegenerative processes and anti-rejection therapy.[1] The synthesized receptors are designed with two key components: an inhibitory portion capable of binding to the protein and an anchoring unit for attachment to sensor chips, enabling analysis via QCM, SERS and SPR.[2] The proposed detection platform is constructed on a Gold or ITO coated support for QCM measures, functionalised with the specific synthetic receptors. It has been demonstrated that the optimal binders for FKBPs expose the two contiguous carbonyl oxygens in the proline-mimetic chain and are characterized by a rigid quasi-cyclic structure mimicking the macrolide structure of the natural inhibitors FK506 and Rapamycin.[3] Based on the above knowledge, we have designed and synthesized the GPS-SH1 and GPS-Si receptors with a selective FKBP12 binding group and a linear chain ending with the thiol or the Silane groups. These termini allow for chemisorption onto the QCM sensor surface, forming a self-assembled monolayer (SAM) ensuring the FKBP12 detection. The prepared sensor platforms can be stored for up six months and regenerated with ethanol, allowing several analyses from different samples.

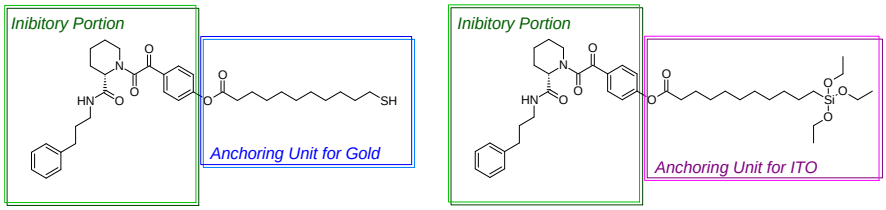

Figure 1: GPS-SH1 and GPS-Si receptors.

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Acknowledgements

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Inhibition of the SARS-CoV-2 Non-structural Protein 5 (NSP5) Protease by Nitrosocarbonyl-Based Small Molecules

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The research line based on the chemistry of nitrosocarbonyl intermediates, generated from nitrile oxides, has been active in Pavia since 1997. Through the use of computational methods we investigated which molecules potentially active as antivirals could be accessed via this synthetic route.[1,2,3] We have designed and synthesized potential NSP5 protease allosteric inhibitors exploiting both docking and molecular dynamic data on SARS-CoV-2. The chemical protocols were developed on the basis of 1,3-dipolar cycloaddition reactions as well as the chemistry of nitrosocarbonyl intermediates while the computational studies were first conducted for determining the best candidate for SARS-CoV-2 NSP5 inhibition. Selected compounds were submitted to biological tests, showing low cytotoxicity and moderate activity. Binding affinity measurements and experiments for the determination of the compounds' influence on the Kd value of protein dimerization are ongoing, and some preliminary results available.

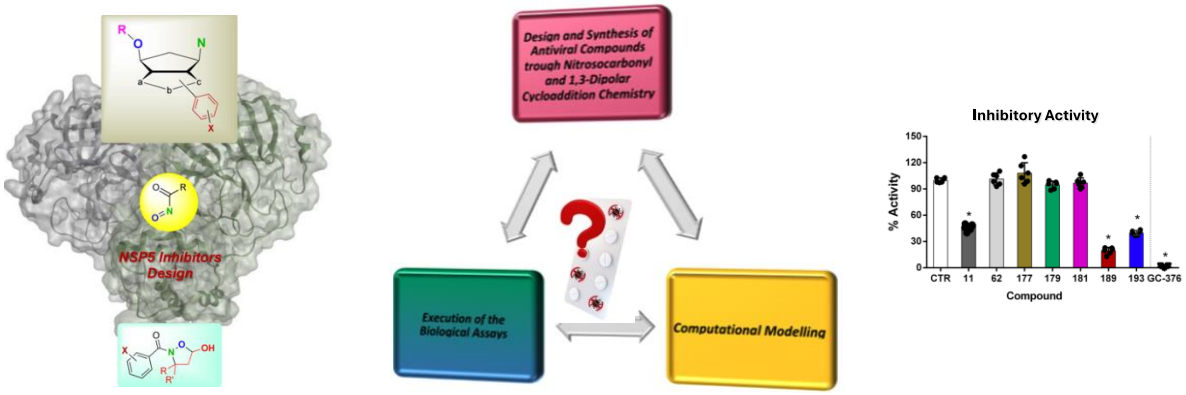

Figure 1: Overview of the design, synthesis, and evaluation process for allosteric inhibitors of the SARS-CoV-2 NSP5 protease. The bar graph on the right shows the inhibitory activity of the selected compounds.

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BODIPY-based compounds targeting tyrosinase enzyme

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BODIPYs (derivatives of 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene) represent an important class of heterocyclic molecules with strong absorption and emission profiles in the visible region, high photostability, small stokes shift and chemical versatility. BODIPYs have received attention for a variety of applications such as chemosensors, laser dyes, drug delivery, photodynamic therapy and fluorescent labels.[1] In the present study, we designed and synthetized some BODIPY dies targeting tyrosinase (TYR, EC 1.14.18.1). TYR is a copper-containing enzyme involved in melanin production and its overactivity is associated to hyperpigmentation-related skin diseases including melanoma.[2] Keeping in mind our previously reported results about 4-(1-piperazinyl)phenol derivatives as efficient TYR inhibitors, we synthesized some BODIPY dyes differently linked to this pharmacophoric moiety (Figure 1).[3]

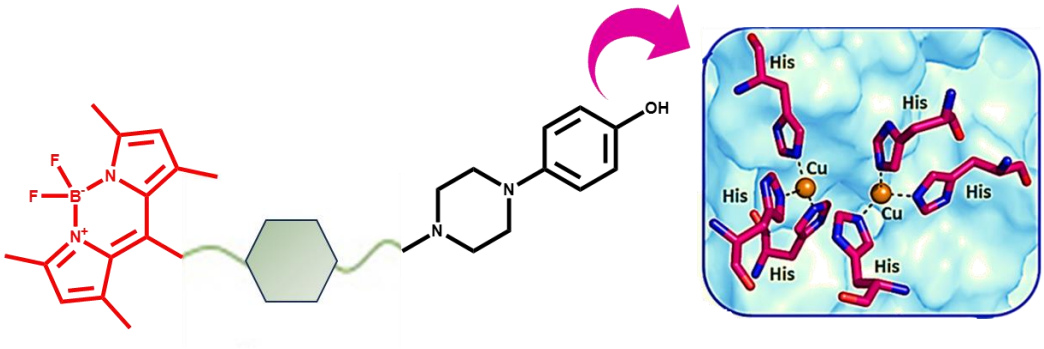

Figure 1: Schematic representation of designed compounds targeting TYR catalytic site.

The obtained compounds were preliminary screened against TYR from *Agaricus bisporus* (AbTYR) and the plausible interactions within the active site were predicted by docking simulations. The cellular internalization and the toxicity of the new synthesized molecules have been assayed both *in vitro* in NIH/3T3 fibroblast cell line and *in vivo* in zebrafish (*Danio rerio*) embryos.

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Sol-gel based halloysite nanotubes functionalized with methyl red for durable colored polyester fabrics

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In recent years, there has been growing interest in exploring inorganic fillers and sol-gel technologies as safer alternatives to harmful chemicals traditionally used in textile finishing processes.[1] Specifically, the attention has turned towards halloysite nanotubes (HNTs) due to their unique properties and potential applications in material sciences and nanotechnologies. With their distinctive characteristics such as higher length-to-diameter ratio, lower hydroxyl density, and stronger charge distribution on the outer surface, HNTs offer improved dispersion within polymer matrices compared to other nanoparticles. This study focuses on developing sol-gel-based hybrid finishes incorporating functional HNT nanofillers to enhance the technical properties of synthetic fabrics like polyester when applied to textiles. The study explores the interaction between the alkoxysilane precursor (GPTMS), HNT nanofiller, and polyester fabric, either with or without a pH-sensitive dye (methyl red, MR).[2] A functionalized methyl red (MR-GPTMS) coating was created in the presence of HNT to effectively anchor the dye onto the fabric, potentially reducing dye leaching seen in conventional dyeing processes. By establishing a covalent bond between the silica sol and the pH-indicator molecule through a coupling agent, the color fading process can be minimized. Spectroscopic analyses using UV-Vis, FT-IR, and NMR techniques were employed to study the chemical structure of the nanosols involved in the process. Additionally, SEM and AFM analyses revealed that the treatment with GPTMS-based sols successfully altered the microstructure of the fabric fibers, resulting in the formation of uniform and durable functional coatings on polyester fibers.

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Environmentally friendly synthesis of hexaaryl-substituted borazines in continuous-flow

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The B–N bond, being isoelectronic with the C–C bond, serves as a valuable functional group for incorporation into polycyclic aromatic hydrocarbons (PAHs).[1] The difference in electronegativity between boron and nitrogen induces bond polarization, altering the electronic properties of PAHs and graphene when B–N bonds are introduced. Borazine, known also as inorganic benzene, has garnered significant attention for its diverse applications[2] since its discovery in 1926 by Stock and Pohland.[3] However, its synthetic challenges hinder further development. The most common method involves the complexation/condensation reaction of boron halides (mostly BCl_3) with substituted anilines to form *B,B',B''*-trichloroborazine (TCB), followed by nucleophilic substitution with Grignard reagents or aryllithiums to yield hexaaryl-substituted borazines. Although effective, this approach requires meticulous control, the use of hazardous reagents, handling of air- and moisture-sensitive intermediates, long reaction times, and poses challenges for scale-up, highlighting the need for improved synthetic approaches.

To address these limitations, we have developed the first flow procedure for B arylation and synthesis of hexaaryl-substituted borazines. Various parameters including greener solvents (like 2-MeTHF), basic scavengers for HCl produced during TCB synthesis, residence time, and reactor volume, were optimized to make the process eco-friendly and reproducible. This new approach enabled the synthesis of 14 substrates, including novel structures, with high yield and an E-Factor as low as 45 in large scale.[4]

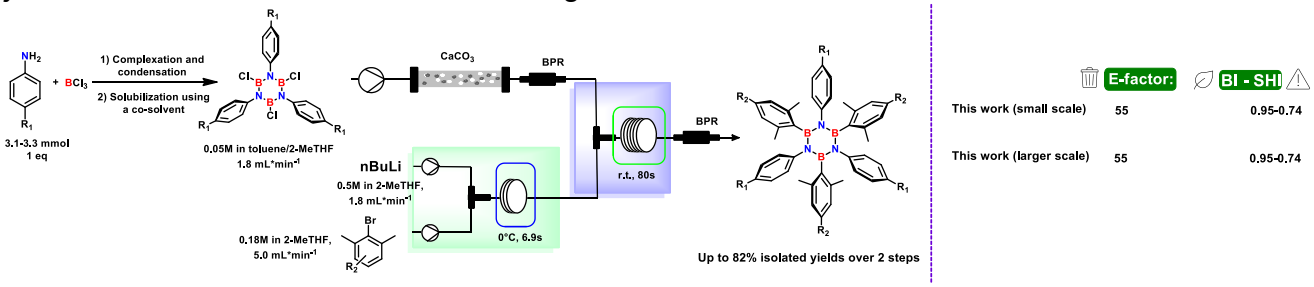

Figure 1. Optimized flow procedure for the synthesis of HABs.

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Smart Functionalization of Pyrrole-Pyrazole Peptidomimetics for Tailored Nanomaterials

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1,3-Cycloaddition reactions are a fascinating class of organic transformations known for their substrate compatibility and efficiency in forming complex cyclic and bicyclic structures.[1] Cycloaddition reactions were utilized to generate a pyrrole-pyrazole scaffold **3** that could be considered a γ-amino acids, which served for the synthesis a series of new peptidomimetics **4**. This scaffold offers multiple functionalization sites, allowing the incorporation of different functional groups to tailor the properties of the resulting materials.

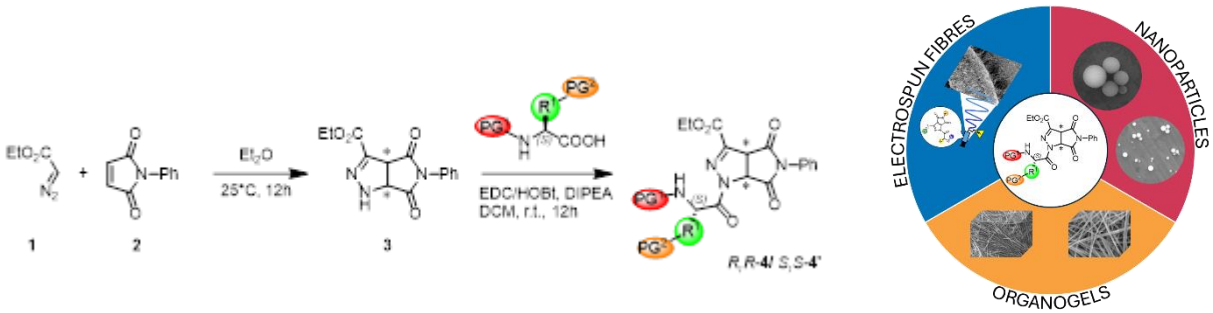

Figure 1: Synthetic pathway for synthesis of dipeptides **4**.

These modifications conferred the dipeptides with unique chemical and physical characteristics, enabling their application in different techniques. For instance, bulky groups on the ester moiety (*i.e.* -tBu) and alanine facilitated the formation of grooves during the self-assembly of the materials, capable of trapping aromatic solvents, forming organogels[2]. In contrast, small groups (*i.e.* -Et) and glycine improved the production of fibres through electrospinning[3] Additionally, ongoing exploration focuses on using these compounds to create nanoparticles via solvent-displacement procedures. By introducing amino acids with acid or basic functions in the side chains we planned to produce pH-sensitive elements, enabling targeted release of active compounds.

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From in batch to Microwave-Assisted Synthesis: A Repositioning Attempt for Potential ALDH1A1 Inhibitors

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Aldehyde dehydrogenases (ALDHs) are NAD(P)$^+$-dependent oxidoreductases playing crucial roles in the cell detoxifying action and redox homeostasis. The ALDH1A1 isoform has gained attention due to its role as a cancer stem cell (CSC) biomarker and overexpression in solid tumors along with in other pathological conditions such as obesity and diabetes. Hence, the modulation of its function could be translated into several therapeutic applications.

Recent studies reported isatin derivatives as promising ALDH inhibitors, making isatin chemical features worthy of interest for drug design. Interestingly, this compound shares structural similarities with the dihydrobenzo[4,5]imidazo[2,1-c][1,2,4]triazine-3,4-dione (BITD) core, previously investigated by our group as aldose reductase (AKRB1) inhibitor. The latest trend of repurposing approaches encouraged us to test in house BITDs against ALDH1A1 and design new derivatives by introducing diverse substitution patterns at positions N2 and N10. For their preparation, we shifted from the traditional in-batch protocol to a more efficient microwave-assisted one, significantly reducing reaction time and providing a greener, more sustainable approach.

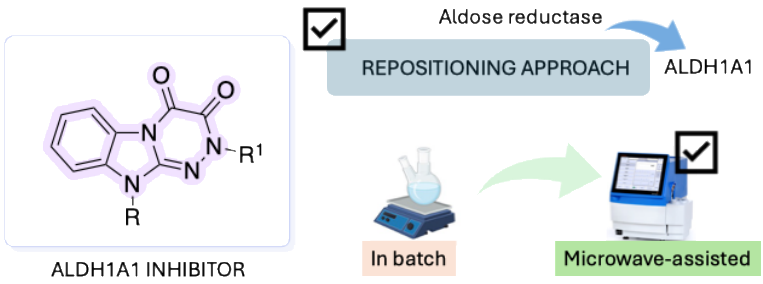

Figure 1: BITD core repositioned for potential ALDH1A1 inhibitors.

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Novel unfolding small molecules for G-Quadruplex

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G-quadruplexes (G4s) are guanines self-assembled nucleic acid secondary structures involved in the regulation of different biological processes and disorders. Traditionally, research was mainly focused in G4 stabilization by small molecules. However, in recent years, G4s destabilization has obtained aptention to better understand their role in gene regulation, disease pathology, and antiviral applications.[1,2] For this reason, three unfolding small molecules have been synthesized: two novel dipeptides of non-natural amino acids (DIP1 and DIP2, Figure 1) and an already known guanine binder (GClamp, Figure 1). All the three compounds can create a clamp around a singol guanine stabilizing the interaction by hydrogen bonds. DIP1 and DIP2 can fold around guanine thanks to their mobile structure and GClamp thanks to the etero-phenoxazine core, implemented with the amine moiety. Biophysical tests were conducted, demonstrating unfolding ability of all three compounds and yielding the most promising results with G-Clamp. Ten different oligonucleotides folded into G4s were used in biophysical tests, highlighting a topology-dependent interaction of GClamp, which preferentially unfolds parallel-G4s.

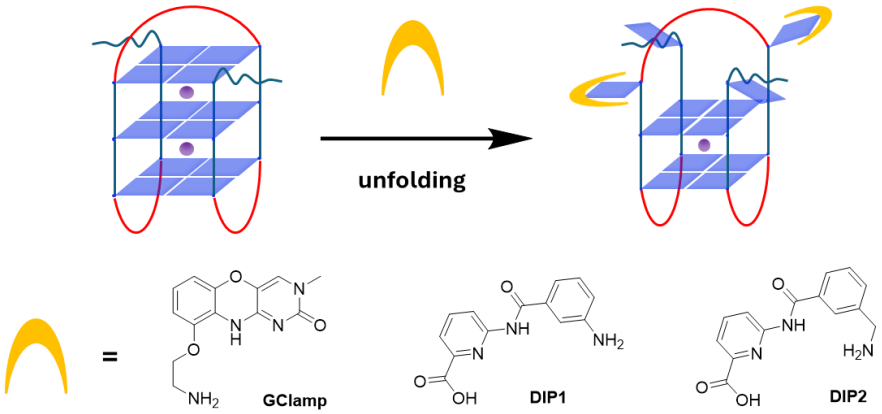

Figure 1: G4 unfolding by guanine binders: GClamp, DIP1 and DIP2.

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Facile synthesis of Pt-Cu-Fe nanoparticles anchored on surface-functionalized reduced graphene oxide

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The hydrogen evolution reaction (HER) plays a critical role in the feasible generation of pure hydrogen. Platinum (Pt)-based catalysts can effectively improve the HER by reducing the activation energy and substantially increase the reaction rate. Although platinum-based materials are regarded as the state-of-the-art electro-catalysts for HER, high cost and limited availability hamper their scale-up utilization in industrial deployment.

Owing to its novel properties, such as high electrical conductivity and large specific surface area, graphene has been found as a suitable support material for the electrocatalyst design. Therefore, the exploration of PtM alloy catalysts anchored on reduced graphene oxide with low Pt loading, high HER activity and stability has become the focus of HER research[1].

However, the particle migration and coalescence (PMC) kinetics of a supported metal are the main deactivation mechanisms restricting the successful industrialization of supported nanoparticles. Covalently grafted *p*-phenyl SO_3H-, *p*-phenyl NH_2- or *p*-phenyl OH- groups onto the graphene surface are used as "spacers" to coordinate the metal nanoparticles and prevent their migration and coalescence during the HER[2] (Figure 1).

This study is focused on understanding the electronic structure change and its effects on the electrocatalytic performance when mono-, bi- and trimetallic nanoparticles are electrochemically reduced on functionalized GO through chronoamperometry.

A series of preliminary cyclovoltammetry tests were conducted at different metal alloy compositions (Pt@rGO-R, PtCu@rGO-R, PtFe@rGO-R, PtCuFe@rGO-R) on functionalized and non-functionalized reduced graphene oxide.

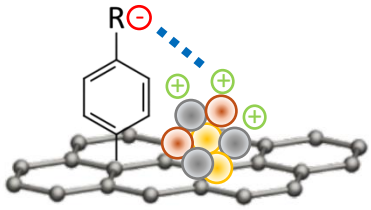

Figure 1: The donated electron density from the functionalized graphene prevents the trimetallic nanoparticles migration and coalescence.

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Synthesis and characterization of multi-spin radical systems for quantum computing applications

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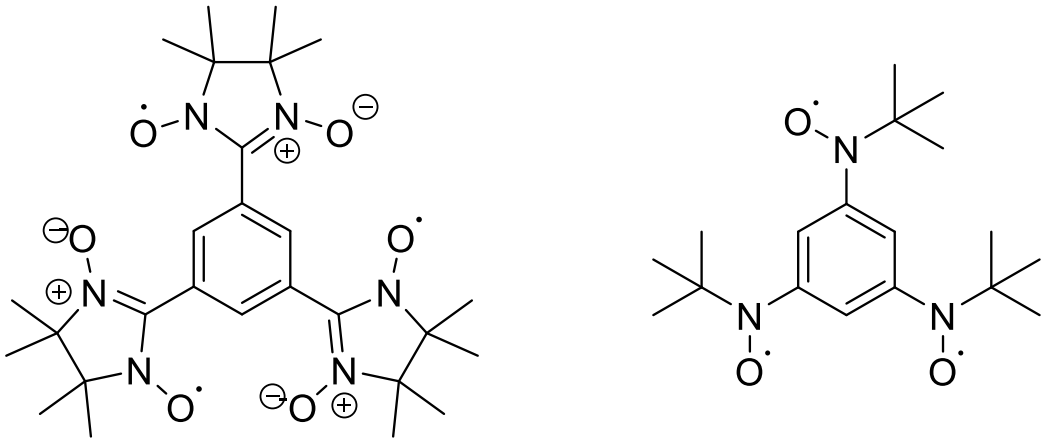
Radical systems have recently attracted interest for their potential use as a qubit for quantum computers.[1] The aim of this research is to synthetize triradical systems to explore the effect of the molecular ligand on the spin-spin interactions with the superconductor and to understand the physical interactions leading to topological states. The chosen molecules, containing nitronyl and imino nitroxides (compound **1**, Figure)[2] and *N-tert*-butyl nitroxides (compound **2**)[3], have been studied and synthetized using synthetic routes that consider any critical points such as oxidation, stability and degradation under oxygen conditions.
In this context, some complications have emerged, in particular the poor reproducibility of the synthesis of the bis(hydroxyamino)intermediate, its instability and the high sensibility of functional group in the reaction with *t*BuLi. An alternative route of synthesis was found and the molecules have been characterized using EPR spectroscopy and SQUID magnetometry.



Compound 1 **Compound 2**

Figure 1: multi-spin radical systems

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Electrifying Cyclization/Bromination of Alkenes

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In the last few years, the electrosynthetic approach has increasingly emerged as a powerful and green technique for achieving many valuable transformations in organic synthesis.[1] The *in-situ* electro-generation of highly reactive species could provide simplified approaches using safe reactants. Moreover, the electrochemical methodology could lead to greater chemo- and regioselectivity as well as lower waste. For this reason, the development of green and sustainable electrochemical cascade reactions as a green and efficient method to synthesize high-valued molecules is extremely intriguing.[2]

Following our interest in domino reactions to access functionalized heterocycles,[3] recently we undertook the study of electrochemical cascade cyclization/bromination reactions. Pursuing the search for a new class of homonucleoside derivatives, a diastereoselective palladaelectro-catalyzed alkoxybromination was developed to access 2-bromomethyl morpholines (Figure 1A).[4] Some examples of electrochemical alkoxybromination reactions are reported in the literature, but analogous aminobromination procedures have been much less developed. Moreover, due to the key role of brominated heterocycles as precursors for biologically relevant molecules, we planned an amination/bromination procedure to access five-, six- and seven-membered heterocycles with TBAB in the dual role of electrolyte and bromine source (Figure 1B).

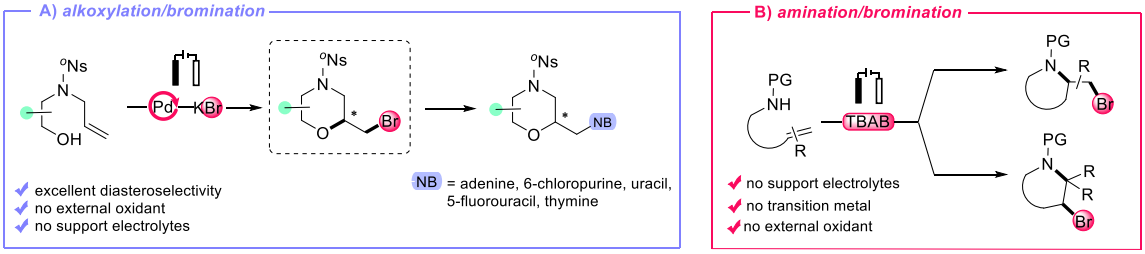

Figure 1: Cyclization/bromination reactions.

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A new microemulsion drug delivery system based on a supramolecular copolymer

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Polymeric nanoparticles[1] have attracted a great deal of attention in nanomedicine applications over inorganic nanoparticles due to their better biocompatibility and biodegradability. Supramolecular polymers[2] can be successfully used in the design of stimuli-responsive nanoparticles thanks to the non-covalent interactions on which they are based. We have recently reported a new photoactive AA/BB-type supramolecular copolymer able to detect spermine, a cancer marker, and suitable for the construction of a biomedical sensor.[3] The copolymer is constituted by a bis-pillar[5]arene dicarboxylic acid (**H**) as host monomer and a mixture of the bis-imidazole derivative **G1** and the fluorescent perylene bis-imidazole **G2** as complementary guests. The adaptivity of the copolymer is ensured by the presence of **G1**, while **G2** provides the sensing abilities; it has been shown that the assembly or disassembly state of the copolymer can be revealed by a change in luminescence due to the complexation/decomplexation of **G2** in the pillararene cavities.
Herein we report the formation and analysis of nanoparticles based on such copolymer and their potential applications in the biomedical field.

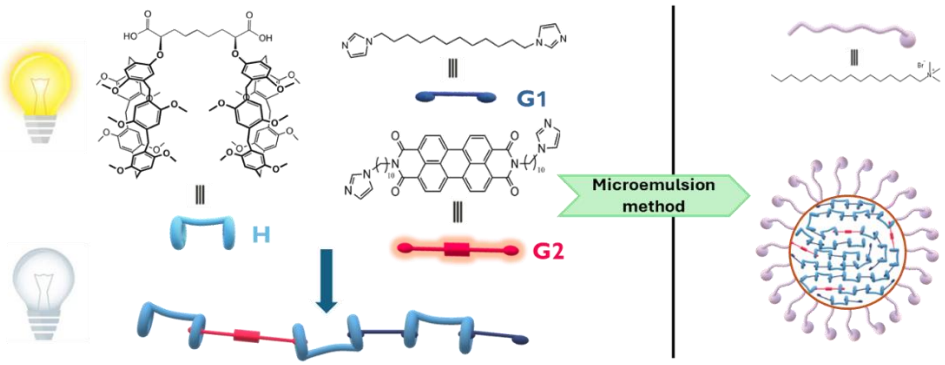

Figure 1: Illustration of the **H**/**G1**/**G2** supramolecular copolymer and its nanoparticles.

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Selective removal of organic dyes with smart pillar[5]arene-based PDMAEMA/PES beads

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Access to safe and clean water is in high demand due to the consequences of climate change, the growing global population, and the anthropological activities that have an impact on many industrial sectors and their associated needs for water. However, traditional techniques for cleaning (waste)water have not yet been able to fully eliminate the so-called "emerging contaminants," such as organic dyes, which are now extensively utilised in the leather, paper, plastic, textile, and cosmetics sectors. In fact, because of their chemical permanence and toxicity, they pose a serious risk to human health. For this reason, research and development is currently underway to develop innovative, cutting-edge methods for remediating (waste)water[1].

This study successfully carried out and reported the synthesis and characterisation of a smart polymer (P5-QPDMAEMA), obtained through the quaternarization of PDMAEMA with a pillar[5]arene derivative[2]. The goal of this polymer was to combine the host-guest properties of the covalently linked pillararenes with the responsiveness of the PDMAEMA polymer.

In addition, PES/P5-QPDMAEMA blended polymers were developed and employed with the standard Non-solvent Induced Phase Separation (NIPS) procedure, which was performed at different coagulation pH levels, to obtain functional beads.

The polymeric structures and reactivity of all the final functional beads were examined using ATR-FTIR, XPS and SEM techniques; additionally, the adsorption performances in the removal of MB and MO, as representative cationic and anionic dyes, respectively, were assessed in water. For the beads with the best removal capabilities, calculations of adsorption kinetics and isotherms were performed. Finally, zwitterionic beads were obtained by the post-functionalization of PDMAEMA and P5-QPDMAEMA beads, and the adsorption behaviour towards the elimination of the aforementioned cationic and anionic dyes is also reported.

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Hetero-polymetallic dithiooxamide based systems: synthesis and DFT-guided NMR analyses

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Homo and hetero-polymetallic complexes, in which the metal atoms are transition elements connected by π-conjugated organic bridge units, are particularly suitable to get insight into the chemical-physical properties of organometallic systems[1]. In fact these species might offer the possibility to investigate electronic communication between the redox-active metal center, molecular magnetism, nonlinear optical proprieties and light-harvesting processes[2]. Until now, very few standard synthetic procedures have been developed in order to obtain in a sequential way hetero-polymetallic systems under topological and stereochemical control. In this regard, dithiooxamide ligand represent a very intriguing building block, suitable to synthesize hetero-metal complexes in time sparing and low cost way. In the present contribution, we report the synthesis and spectroscopic characterization about a new hetero-trimetallic complex based on Ru-Pt-Pd metal scaffold. In our research, in order to obtain the target compound, a step by step procedure was adopted. This strategy involved the use of a square-planar complex of platinum in the form of a "metal dithiooxamidate" as starting synthon, the latter proved to be particularly useful since it turns out to be a bis-chelating system. Our synthesis exploited some dichloro-metal dimer as metalloligand to generate hetero-metallic chains of the type ^{1}*LM*-**Pt(dto)**-^{2}*LM* (Figure 1). In this less explored landscape, because of their chemical heterogeneity, stereochemical complexity and the presence of heavy atoms involving orbitals with high quantum number *L*, organomultimetallic complexes require considerable focus during their NMR spectral interpretation. Our combined approach (experimental/theoretical), exploiting a solid calibration set, provides a comprehensive overview of the ^{1}H, ^{13}C and ^{195}Pt NMR simulation trends when DFT parameters are scanned. Specifically, we tried to develop a valid algorithm with the aim of predicting the ^{1}H, ^{13}C and ^{195}Pt resonances of homo- and hetero-polymetallic NMR spectra.

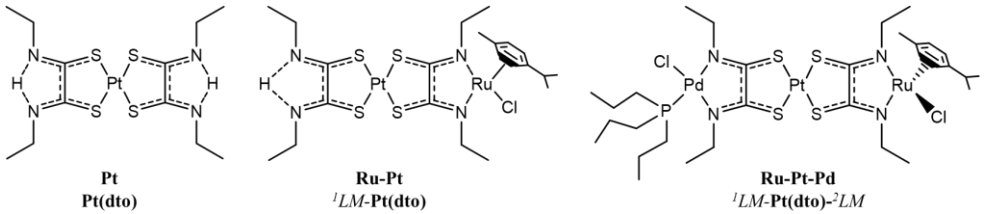

Figure 1: Mono nuclear platinum, hetero bi-nuclear ruthenium/platinum and hetero tri-nuclear ruthenium/platinum/palladium structures.

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Beatrice Bonaldi	University of Milan

Are the winners of the 5 prizes awarded by the Scientific Committee for the originality and exposition of the scientific content exhibited.