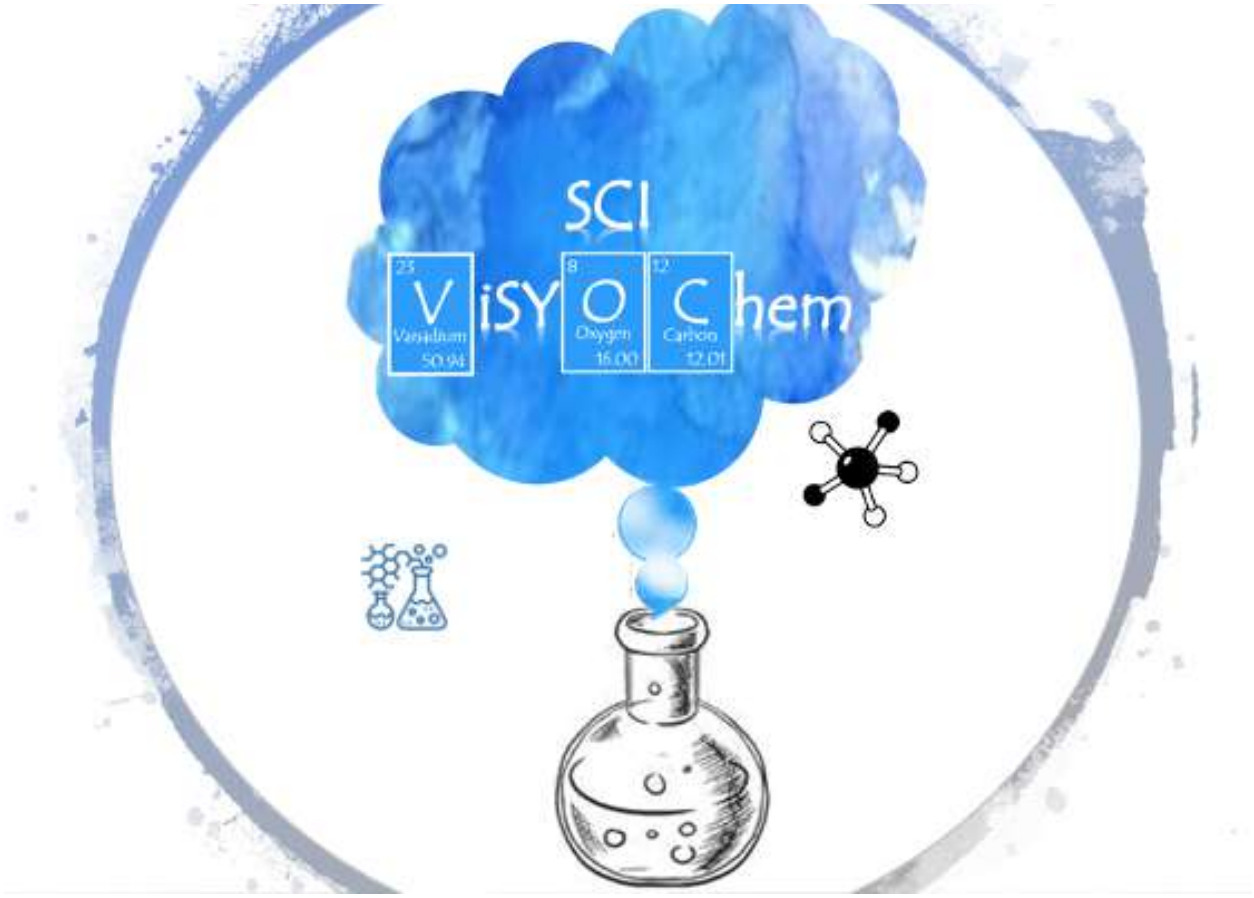
1st SCI Virtual Symposium for Young Organic Chemists



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Marta Da Pian, Giovanni Maestri, Alessandro Palmieri, Lucia Panzella, Ivana Pibiri, Stefano Protti, Luigi Vaccaro.

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Welcome to the **1st SCI-Virtual Symposium for Young Organic Chemists** (**ViSYOChem**).

The event is organized by young professors of the Division of Organic Chemistry of Società Chimica Italiana with the financial support of several sponsors.

In this particular time where on site events are so rare, we wanted to give our students the possibility of presenting their research projects and sharing ideas in a dynamic and stimulating environment. The symposium covers organic chemistry topics belonging to *Life Sciences*, *Synthesis and Methodolgy*, *Environmental Chemistry and Nanotechnology* areas.

As our first edition we are pleased to announce more than 170 participants, coming from more than 30 Italian and European institutions, contributing with 56 Oral Communications and 67 Poster Communications.

Thank you for accepting this challenge with us and we hope you'll enjoy it!

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Chiral Bioactive Cyclopeptoids: Concept and Purposes

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Peptides are an endless source of inspiration for medicinal chemistry, as these biomacromolecules regulate a number of biological activities, showing high affinity towards therapeutic targets and few side-effects. However, peptides have their drawbacks due to their extreme metabolic instability and low bioavailability. Pharmacokinetics and pharmacodynamic properties can be enhanced with *N*-amide substitution and/or using a cyclic scaffold.[1]

In the vast realm of the peptidomimetics, peptoids emerge as compounds able to overcome most of the peptides' drawbacks, while providing the enormous therapeutic and pharmaceutical potential. α-Peptoids,[2] oligomers of *N*-substituted glycines, are easily synthesized *via* solid-phase. The cyclization of such oligomers leads to macrocyclic derivatives with even more interesting properties, including stable secondary structures in the solution state.

Given the outstanding potential of cyclic peptoids, the main topic of this research project has been the synthesis of congeners of cyclic natural derivatives with a cyclopeptoid scaffold. According to this purpose, we investigated the capability of a series of cyclic hexa- and octapeptoids of mimicking cyclodepsipeptides with cytotoxic[3a] and anthelmintic[3b] activity.

The structural rigidity showed by our macrocycles led to an extended investigation about their conformational properties in solution. We conceived a central-to-conformational chirality transfer (with the introduction of a single or multiple stereogenic centres either on the backbone[4a] or on the side-chains[4b]), generating single conformational stereoisomers.

The potential of cyclopeptoids as scaffolds, has been explored utilizing the cyclotrimeric architecture which was functionalized with biologically interesting moieties. We prepared a series of catechol-based siderophores, obtaining selectivity towards iron(III),[5] and two series of compounds functionalized with polyaromatic units, acting as cytotoxic agents towards human cancer cell lines.

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Design and synthesis of morpholinone derivatives as BACE1 inhibitors for the treatment of Alzheimer's Disease

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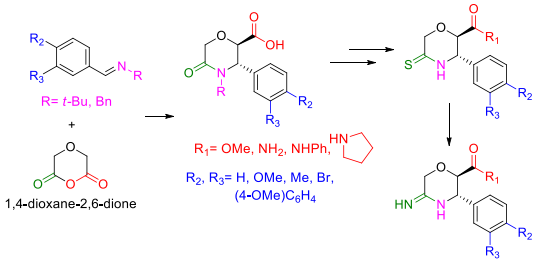
Alzheimer's disease (AD) is the most common neurodegenerative syndrome affecting about 47 million people worldwide. One of the main causes is a progressive deposition of insoluble phosphorylated β-amyloid peptide and Tau protein on nerve cells causing difficulties in axonal transport. The pathogenic peptide β-amyloid is generated when the Amyloid Precursor Protein (APP) is degraded by β-secretase (BACE1) instead of α-secretase. In vivo studies demonstrated that in BACE1 knockout mice the presence of amyloid plaques was suppressed, so this enzyme has been one of the most studied targets for the pharmaceutical treatment of AD since its identification in 2000. There are several promising inhibitor candidates in clinical trials, although none of them could pass final steps.[1-2] Nevertheless, BACE1 is still considered a key therapeutic target for AD.



Scheme 1: Synthesis of morpholinone derivatives from Castagnoli-Cushman reaction and amide elaboration.

A novel approach in the synthesis of BACE1 inhibitors with C-2 aryl substituted morpholinone core was developed. Following the Castagnoli-Cushman reaction four thioamide and four amidine derivatives were obtained in five steps. The thioamide and the amidine derivatives were screened for the biological inhibition against BACE1, showing an unexpected activity for thioamide derivatives. The binding mode was also studied with docking simulation, finding a different interaction with respect to the one described for canonical BACE1 amidine inhibitiors.[3] The promising results found for the morpholinones is a good starting point to introduce the secondary thioamide moiety on bicyclic acetal scaffolds that previously showed good inhibition against BACE1.[4] Indeed, preliminary screening showed a promising biological activity also for these fragments.

Acknowledgments: AIRAlzh grant for supporting this research

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Sequence-structure conjugates to selectively target G-Quadruplex in HIV-1

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The viral transcription of HIV-1 is regulated by the folding into dynamic G-quadruplex (G4) structures of the HIV-1 Long terminal repeat (LTR) promoter. Therefore, the selective targeting of this hot region results in an attractive and innovative therapeutic strategy for the treatment of HIV. Biophysical and biomolecular analysis have identified two stable G4s, LTR-II and LTR-III, which spontaneously fold in physiological ionic conditions.[1] Besides, exploiting G4 stabilizing ligands, it is possible to induce the formation of another putative G4, LTR-IV, adding a new target for antiviral therapy.[2] These three G4 structures are mutually exclusive, therefore we synthesized new naphthalene diimide (NDI) - peptide nucleic acid (PNA) conjugates to counter the lack of ligands specificity usually used. The proposed binding model is based on the cooperative interaction of an NDI, a known end-stacking G4 binders,[3, 4] and a specific PNA moiety complementing to the flanking region of the selected G4.The new NDI-PNA conjugates behavior in the presence of LTR sequences was tested *in vitro* demonstrating that they can stabilize and/or induce the formation of a specific G4 in LTR sequence, destabilizing the folding of the others. In particular, this innovative approach is fundamental to reach the specific discrimination between LTR-III and LTR-IV, provides unprecedented specificity in the field of single G4-targeting.[5]

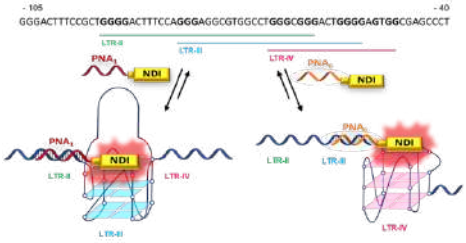

Figure 1: Schematic representation of selective targeting of mutually exclusive DNA G4.

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Sustainable synthesis of novel thymol derivatives for biological applications

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Thymol is a natural mono-terpenoid phenolic compound. It is the main component of *Thymus vulgaris* essential oils, but it can also be found in other plants mainly belonging to the *Lamiaceae* family. Being very abundant in nature, it results a cheap and easily accessible product.

Nowadays, the importance of thymol is well established. As a matter of fact, it is widely used as active ingredient in several industrial fields, as an insecticidal, antibiotic, antitubercular, antileishmanial, and antineoplastic compound.[1] Furthermore, it showed a general non-genotoxicity and cytotoxicity on human cells.[2] Nevertheless, in the last few years, the interest is moving toward brominated thymol derivatives,[3,4] which showed enhanced bioactivity against several bacterial strains, such as *S. aureus, A. baumannii, E. faecalis* and *E. coli*, as well as different fungal strains that are pathogenic for humans, animals or plants, namely *Aspergillus fumigatus*, *Penicillium chrysogenum* and *Candida albicans*.[5] Among the others, 4-bromothymol emerged for its remarkable antimicrobial action, which was up to 15 times higher than that of thymol.[5]

Considering the growing interest in developing new and efficient antimicrobial agents, we synthesized a small library of differently functionalized thymol derivatives, aiming at widening its potential application in several fields, as well as to further enhance its bioactivity. Additionally, thymol structural modification with strategic functional groups can allow the easy coupling with other biologically relevant systems, likely leading to a synergistic effect. Sustainable synthetic protocols have been preferred.

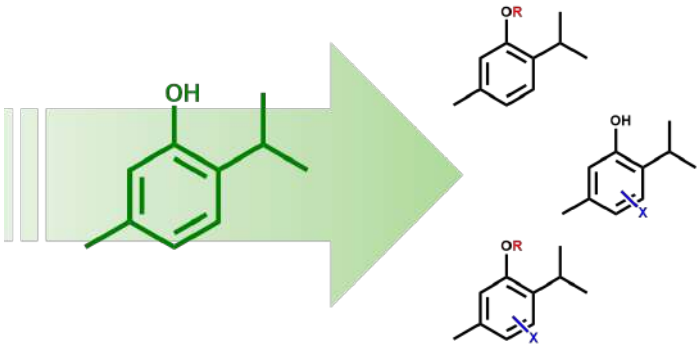

Figure 1: General structure of the synthesized thymol derivatives.

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Strontium substituted hydroxyapatite with β-lactam integrin agonists to promote bone regeneration

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Most biomaterials employed to solve problems related to disorders of the muscolo-skeletal system are based on calcium orthophosphates, and in particular on hydroxyapatite (HA), which is the most similar to bone inorganic phase. Recently, the interest toward this class of compounds has stimulated a number of studies aimed at improving their already good biological performances through functionalization with specific additives, including ions, polyelectrolytes and drugs. [1,2] We functionalized Strontium substituted hydroxyapatite (SrHA) with some β-lactam integrin agonists to develop materials with enhanced properties in promoting cell adhesion and activation of intracellular signalling as well as in counteracting abnormal bone resorption. For this purpose, we selected two monocyclic β-lactams (*Figure 1*) on the basis of their activities towards specific integrins.[3] The amount of azetidinones loaded on SrHA could be modulated on changing the polarity of the loading solution.

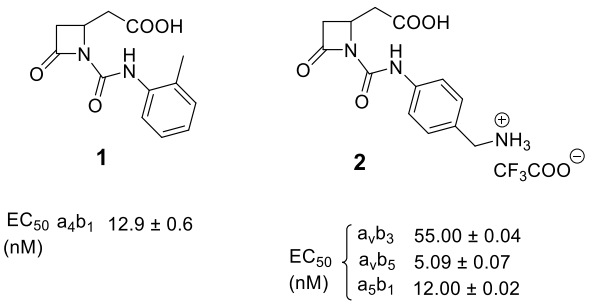

Figure 1: Selected β-lactam integrin agonists

Studies on the release of the β-lactams from the functionalized SrHA in aqueous medium showed an initial burst followed by a steady concentration-dependent profile that ensures persistent bioactivity over time. Co-culture of human primary mesenchymal stem cells (hMSC) and human primary osteoclast (OC) demonstrated that the presence of β-lactams on SrHA favours hMSC adhesion and viability, as well as differentiation towards osteoblastic lineage. Moreover, the azetidinones were found to enhance the inhibitory role of Strontium on osteoclast viability and differentiation.

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Synthesis and characterization of organic/inorganic hybrids for biological applications

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Halloysite nanoclays (HNTs) are promising nanomaterials because of their versatile properties, such as hollow tubular morphology and tunable surface chemistry. HNTs are biocompatible, no toxic and abundantly available at low cost. Due to these characteristics HNTs are suitable for development of hybrid sustainable materials, which are perspective for wastewater remediation, green packaging and drug delivery.[1] In this context, the covalent modification of HNTs surface leads to the synthesis of hierarchal nanostructures which were successful applied for the delivery and subsequent sustained release of biologically active molecules. In this communication we report the development of multifunctional nanocarrier, based on halloysite nanotubes and carbon nanodots (HNTs-CDs) as potential non-viral vector for oral gene therapy. The hybrid organic-inorganic nanomaterial was investigated by means of several techniques which highlighted the presence of different functional groups and interesting photoluminescence properties.[2] The cytotoxicity and the antioxidant activity of the HNTs-CDs were investigated by standard methods (MTS, DPPH and H_2O_2, respectively) using human cervical cancer HeLa cells as model. Studies of cellular uptake were carried out by fluorescence microscopy. Finally, we investigated the loading and release ability of the hybrid versus calf thymus DNA by fluorescence microscopy, circular dichroism, dynamic light scattering and □-potential measurements.[3]

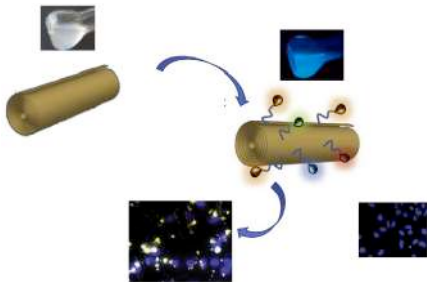

Figure 1: Schematic illustration of the HNTs-CDs nanomaterial as potential non-viral vector for oral gene therapy

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Development of polymeric nanoparticles for multimodal enhanced *in vivo* imaging of pancreatic β-cells

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In vivo imaging techniques allow us to investigate within organisms from a privileged point of view. Whenever we look inside living subjects, we are going deeply into a very complex system, and thus molecular imaging probes should be capable of targeting specific biological markers and be rapidly cleared out of non-target ones, improving the spatial resolution, while added contrast guarantees a more precise and accurate visualization.

This technology could find crucial applications for some pathological conditions. In particular, the targeting of pancreatic β-cells is acquiring tremendous interest, since it reveals precious information regarding the cell viability, and developing an efficient imaging approach can find applications in regenerative therapies for diabetes and early pancreatic cancer diagnosis.

Nanoparticles are a promising candidate as versatile probes, since their surface is ideal for labelling both targeting and contrast agents. In this work, nanoparticles for multimodal imaging have been designed based on the combination of two polymeric components, chitosan and γ-PGA, and formulated as self-assembled polyelectrolyte complexes. The polymeric components have been functionalized for subsequent chemoselective decoration with a ligand for specific targeting of β-cells and different detecting agents, exploiting multiple imaging techniques (PET, SPECT, MRI, MSOT).[1] The composition and the purity of polymers have been verified with different analytical methods. The properties of the nanoparticles have been characterized, and the biocompatibility of both polymers and nanoparticles was examined *in vitro* and *in vivo*. Biodistribution has been tested by PET in mice with Ga-68 labelled nanoparticles.

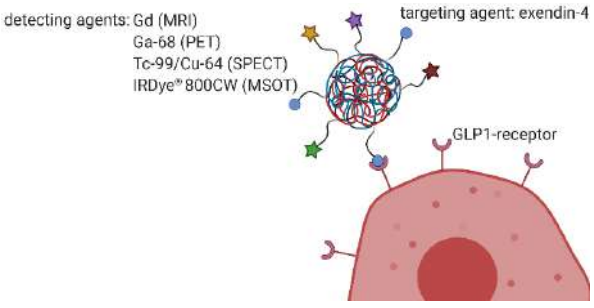

Figure 1: schematic representation of multimodal nanoparticles interacting with β-cells.

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Innovative hybrid label-free devices for human diseases diagnosis

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The wide availability of bioactive molecules and new nanomaterials paves the way towards the obtainment of innovative hybrid complexes provided with enhanced efficacy in the biomedical fields compared to their isolated precursors. In this context, the application of hybrid materials (e.g., bioengineered molecules, nanoparticles or surfaces) for on-demand diagnosis and therapy of human diseases has rapidly become an intriguing research topic. For example, oligonucleotides (ONs) and ON analogues (e.g. peptide nucleic acids) have been explored as bioprobes (i.e., sensing element) for the realization of label-free biosensors for the early diagnosis of human diseases[1]. The construction of the hybrid devices can be done by coupling the *ex-situ* synthesized bioprobe on the transducer surface, or by direct solid-phase synthesis of the growing bioprobe on the transducer surface (used here as the solid support)[2]. In this communication, I will present the different chemical approaches that we have explored in our laboratories for the development of hybrid label-free biosensors provided with great stability, fast response time, high sensitivity and specificity [3, 4].

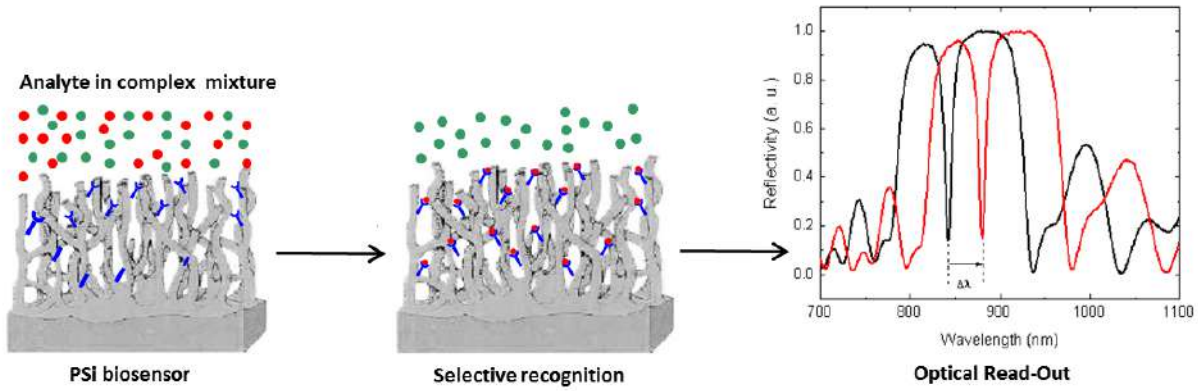

Figure 1: Schematic representation of hybrid biosensor used in label-free optical biosensing.

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A new Morita-Baylis-Hillman Adducts for the selective Nitroreductase-mediated drug release

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The search of new and more efficient ligand-targeted drugs is always a challenge for overtaking the side effects of therapeutic treatments. In these systems, a stimuli sensitive linker has a crucial role and several cleavable linkers are present in the literature. Amongst most commonly used enzymes as target for the design of linkers, Nitroreductase might be a useful aid for drug release.[1] Nitroreductase is over-expressed in hypoxic conditions like in solid tumour cells and in bacterial infected tissues, and its activity drives reduction of aromatic nitro moieties. It is also the most extensively used enzyme for antibody-directed and gene-directed enzyme prodrug therapy (ADEPT and GDEPT) and in fluorescent probes for tumour imaging.[2]

We report here a new system that takes advantages on the reductant ability of Nitroreductase for the release of drugs after reduction of nitro aromatic group. The core structure of the molecules come from a Morita-Baylis-Hillman reaction[3] on *o*-nitrobenzaldehyde and the release mechanism involves the formation of an amino-intermediate that goes through an intramolecular cyclisation followed by the release of the drug. We have successfully applied this system to the release of drugs containing different functional groups, such as phenols, amines or hydroxamic acids.

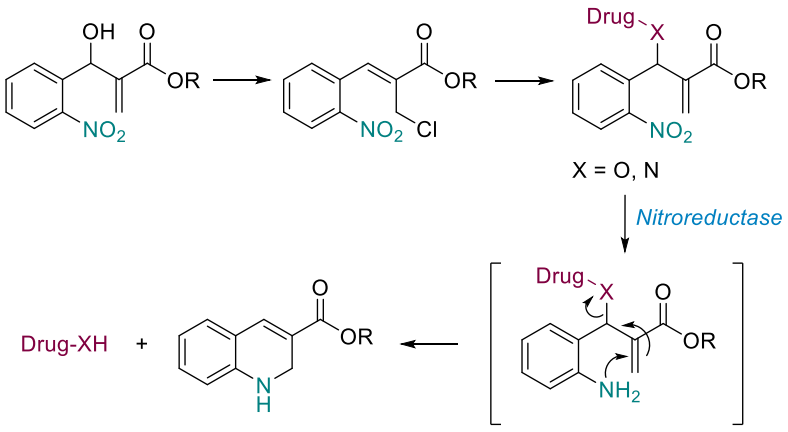

Figure 1

The release was tested in synthetic conditions and by using the enzyme in vitro, It was also verified the plasma stability for these derivatives. The synthesis of functionalizable system, bearing for instance a bioconjugable alkyne functionality, will also be discussed.

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Design, synthesis and applications of chitosan-gelatin based hydrogel for 3D cell culture systems

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The design and synthesis of novel hydrogel polymer systems capable of mimicking the composition, role and dynamism of the extracellular matrix (ECM) have become popular as three-dimensional cell culture platforms. This intricate unique network is characterized by a wide variety of proteins and glycan-based molecules ranging from glycosaminoglycans (GAGs) and proteoglycans (PGs) to glycoproteins.[1] To reflect the complexity of ECM, research has moved towards the synthesis of hybrid biomaterials as highly appealing and strategic platforms able to mimic the complex cell microenvironment and produce advanced organ and tissue models.[2] Gelatin and chitosan, as proteinaceous and polysaccharidic natural polymers, have been selected and functionalized with methylfuran groups to obtain stable and tailorable matrices for the validation of 3D scaffolds and bioprinted models.[3] Taking advantage of mild conditions for the crosslinking formation allowing cell encapsulation without affect cell viability, the functionalized polymers were crosslinked by Diels Alder reaction using 4-arm-PEG-maleimide. The obtained hydrogels were characterized from a chemical-physical point of view, validated through different fabrication methodologies, and finally tested by 3D bioprinting and scaffolding with glioblastoma U87 spheroids as 3D tumor models.

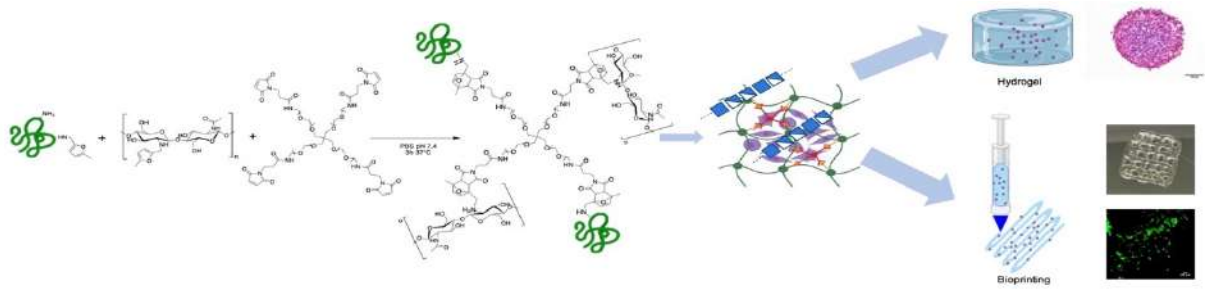

Figure 1: Functionalization strategy and applications of gelatin-chitosan based hydrogel

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Design and synthesis of aza-tanshinone leads and probes as HuR–targeted anticancer agents

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Human antigen R (HuR)[1] is an RNA binding protein (RBP) that belongs to the ELAV (Embryonic Lethal Abnormal Vision) RBPs' family, stabilizes mRNAs and regulates the expression of multiple genes. Its over-expression, or an altered nuclear/cytoplasmic HuR ratio, is often related to pathological features involved in carcinogenesis, growth and propagation of different types of cancer. For these reasons, HuR is a validated antitumoral target.

Dihydrotanshinone I (DHTS I, **1**, **Figure 1**) is a naturally occurring, tetracyclic ortho-quinone inhibitor of the HuR-mRNA interaction[2]. Our earlier efforts led to a preliminary SAR and to *N*-(phenylsulfonyl)-3-phenyl-5,6-dioxoindole **2a** (**Figure 1**), a fully synthetic, dienophile/C-D ring-containing tanshinone analogue built around a bicyclic "aza-tanshinone"scaffold[3]. The affinity of **2a** for HuR is higher than observed with natural tanshinones, due also to its N_1-arylsulfonamide group.

Further modifications at positions I (para), II (ortho, meta and para), III (S-Michael addition, C-radicalic reactions) and IV (reduction to diphenols / **2b**, then prodrug synthesis / **2c**), explored to increase HuR affinity, aqueous solubility and bioavailability, will be described. Detection-promoting (i.e., biotin – affinity chromatography) and photoactivatable groups (i.e., azides and diazirines) were introduced to enable *in vitro* and *in vivo* mode of action (MoA) studies.

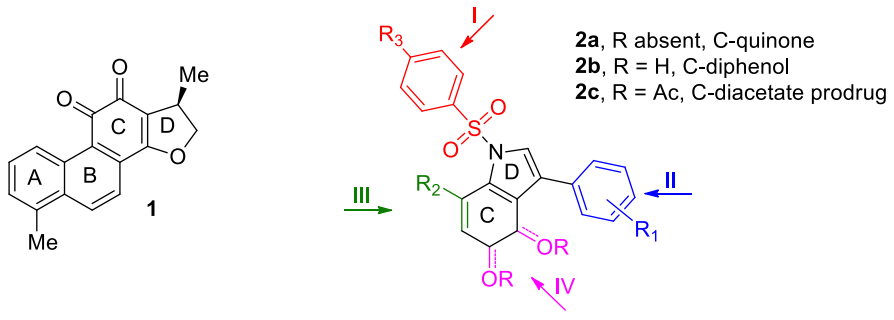

Figure 1: Structure of dihydrotanshinone I (DHTS I, **1**) and of synthetic aza-tanshinone quinonic (**2a**), diphenolic (**2b**) and diacetate/prodrug derivatives (**2c**).

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Synthesis of 2-oxo-1,2-dihydropyridine-3-carboxamide derivatives as potential dualsteric ligands of cannabinoid receptor CB2

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Several evidences suggest the involvement of the endocannabinoid system (ECS) in the modulation of neuroinflammatory disorders. Neuroinflammation is usually characterized by an hyperactivation of microglia, responsible for the secretion of many reactive species, including cytokines and chemokines. In particular the CB2 receptor (CB2R), has been reported to be an attractive target for managing microglial-derived neuroinflammation since its modulation might have beneficial effects for specific symptoms and for the slowdown of disease progression. Our group already investigated the ability of the dual target CB1R/CB2R orthosteric agonist **FM-6b**[1] and the CB2R positive allosteric modulator (PAM) **EC-21a**[2] to modulate the release of pro- and anti-inflammatory cytokines in lipopolysaccharides (LPS)-activated mouse BV2 microglial cells, either alone or in combination. Our results highlighted: a) **FM-6b** was able to induce a CB2R-mediated anti-inflammatory effect which was reverted in the presence of the CB2R antagonist SR144528, confirming **FM-6b** action on CB2R. b) **EC-21a** did not present any effect if administered alone which is in accordance with its allosteric modulator activity (data not published). c) The co-treatment of **FM-6b** with **EC-21a** enhanced the anti-inflammatory effect compared to **FM-6b** alone (data not published). In the light of these results, we decided to synthesize a new series of compounds, **A1**-**A4**, potentially able to bind to both allosteric and orthosteric sites simultaneously, linking the pharmacophoric portion of the PAM **EC-21a** with that of the orthosteric agonist **FM-6b** (Figure 1). Among all the compounds of the series, **A1** (**FD-22a**) (Figure 1) showed to be the most promising. Indeed, its effect in the modulation of the release of pro- and anti-inflammatory cytokines in lipopolysaccharides (LPS)-activated mouse BV2 microglial cells, resulted potentiated, if compared to **FM-6b** alone, and comparable to the effect due to the co-administration of **EC-21a** and **FM-6b**. The presence of the CB2R antagonist SR144528 reverted **A1** (**FD-22a**) effect, confirming a CB2R-mediated action. Binding and functional studies are still on going in order to demonstrate the behavior of **A1** (**FD-22a**). These results may be very important since **A1** (**FD-22a**) might be the first dualsteric/bitopic compound of the CB2R.

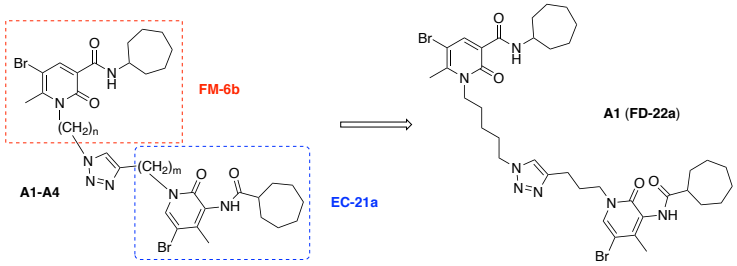

Figure 1: General structure of compounds **A1-A4**.

References:

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Addressing the gelatinases (MMP2 and MMP9) selectivity with D-proline-based compounds

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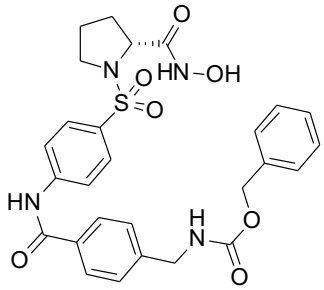
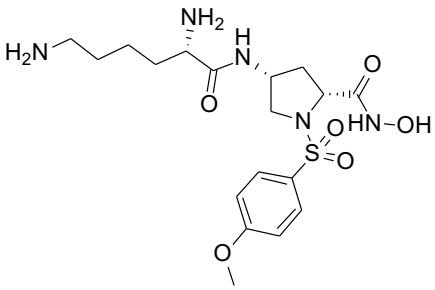
Therapies targeting angiogenesis and metastasis hallmarks are continuously being studied for many malignancies, and among the many different molecular targets matrix metalloproteinases (MMPs) are receiving a renewed interest.[1] The serious dose-limiting side effects occurring in clinical trials, probably due to the non-selective inhibitory activity, have underlined the importance to identify novel inhibitors able to discriminate among MMPs. The selectivity issue is particularly crucial within the gelatinase (MMP2 and MMP9) subfamily, as their inhibition show different behaviour depending on the stage of the tumor progression. In this context, our research group has developed novel D-proline based compounds that can selectively inhibit the MMP2 and/or the MMP9 enzymes. In particular, we have demonstrated how the introduction of long *N*-arylsulfonyl moiety with 1 to 3 rings resulted in a potent and selective inhibition of the MMP2 enzyme (see compound **1** in Figure 1).[2] On the contrary, the functionalization of the C-4 atom of the pyrrolidine ring with a basic amino acid (such as lysine in compound **2**, Figure 1) resulted in a selective inhibition of the MMP9 enzyme.[3]



IC_{50} MMP2 = 48 pM
Selectivity over MMP9: 730



IC_{50} MMP9 = 5.7 nM
Selectivity over MMP2: 200

Figure 1: D-proline-based gelatinase inhibitors.

We gratefully acknowledge Fondazione Cassa di Risparmio di Pistoia e Pescia for financial support.

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Effect of structural modifications on protein binding to integrins: synthesis of peptidomimetic clickable isooxazoline smart delivery systems.

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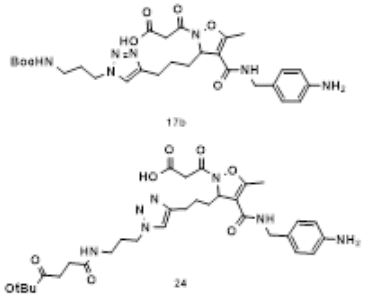
The general approach to overcome limitation of peptides and proteins as potential therapeutics, mainly due to their limited stability to proteolysis and their inability to cross cell membranes, is the introduction of modifications on the peptide/protein to keep unchanged or improve the biochemical properties associated to an efficient drug action. Synthesizing peptidomimetic molecules represents a great advantage in the attempt to modulate specific protein-protein interaction. These "masked" structures revealed their utility in developing more complex molecules that can be exploited as selective delivery vehicles of bioactive molecules to target cells, like cancerogenic ones. So, the construction of small molecule ligand (SML) based delivery systems has been performed starting from a polyfunctionalized isoxazoline scaffold, whose activity towards αvβ3 and α5β1 integrins was already established.[1] The synthesis of this novel class of ligands was obtained by conjugation of linkers to the heterocyclic core via Huisgen-click reaction, with the aim to use them as "shuttles" for selective delivery of diagnostic agents to cancer cells, exploring the effects of the side chains in the interaction with the target. In particular, two compounds showed excellent potency towards α5β1 integrin acting as selective antagonist and agonist, respectively.[2] Further investigations confirmed their effects on target receptor through the analysis of fibronectin-induced ERK1/2 phosphorylation and through confocal microscopy analysis, to follow the fate of EGFP conjugated α5β1 integrin inside the cells.



Compound	α5β1 IC50/EC50 (μM)a
17b	0.0027±0.0004 antagonist
24	6.59±0.16 agonist

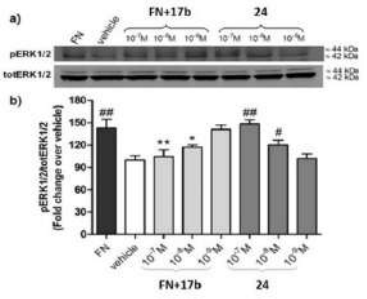


Figure 1: Example of new molecule activity on α5β1 integrin.

References:

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Photo-responsive Prion-Mimic Foldamer to Induce Controlled Protein Aggregation

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Foldamers are synthetic, conformationally restricted mimics of proteins and other biopolymers, and they have been designed to carry out protein-like functions of binding, catalysis and signal relay. In our recent works[1,2] we studied the ability on the photo-induced control of conformational switches in appropriately designed foldamers based on (*E*/*Z*)-3-aminoprop-2-enoic acid [or (*E*/*Z*)-3-aminoacrylic acid] directly incorporated in the foldamer backbone, thus allowing them to dynamically interchange when present in their *E* or *Z* isomeric conformations. The reversible conversion between the $\Delta^{Z}\beta$Ala and $\Delta^{E}\beta$Ala configurations, achieved photochemically, was accompanied by remarkable consequences on the 3D-structure of the peptides. This allowed their molecular self-association through intermolecular hydrogen bonding to be spatiotemporally turned on-off. More recentely,[3] we designed a new foldamer able to act as spatio-temporal aggregation seed, which can be activated by selective photoirradiation without changing other experimental conditions. Whit this tool we follow the early steps of α-syncluclein (aS) aggregation, a process associated with Parkinson's disease etiopathogenesis, that is promptly promoted by a light-mediated binding between aS and the photoactive foldamer. Upon conversion to the *E* isomeric state, the foldamer become available for intermolecular H-bonding, thus promoting self-association that results in the formation of supramolecular fibrillar seeds, acting as molecular templates able to induce a fast β-sheet transition for aS monomers that successively undergo fibrillar polymerization. To date, seeding is the one hindering factor in the study of the aggregation process in cells and in vivo, where the only available approach to trigger aggregation is by direct addition of exogenous, pre-formed fibrils. The method proposed here can be envisioned as a strategy to trigger fibril formation in the intracellular milieu in a time and space-controlled manner.

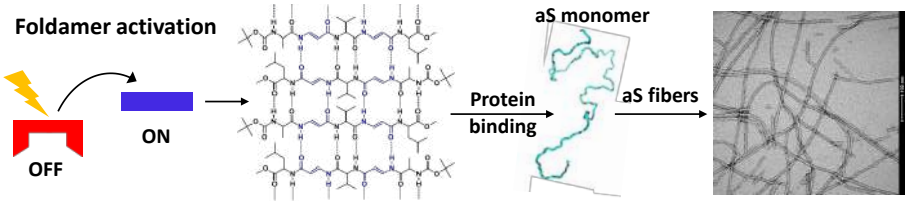

Figure 1: The photo-responsive foldamer acts as aggregation seeds for the fibrillation of a-synuclein.

References:

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Interactome analysis of bioactive molecules: optimization of a *label-free* functional proteomics platform.

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The identification of natural products (NPs) target proteins is crucial to understand their mechanism of action for the development of new molecular probes and/or therapeutic drugs. In this scenario, affinity chromatography coupled to mass spectrometry (AP-MS) has been the last 15 years top-choice technique. Nevertheless, due to the NPs chemical features for the mandatory *on-beads* immobilization step, this strategy is not universally applicable. Furthermore, the covalent modification of NPs functional groups could alter their original bioactivity[1]. Thus, to provide a universally applicable and more comprehensive target identification strategy, we started to develop and optimize a *label-free* functional proteomics platform not requiring any chemical modification of the molecule for both the characterization of its protein partner(s) and their interaction features. This platform is based on two complementary strategies, Drug Affinity Responsive Target Stability (DARTS)[2] and targeted Limited Proteolysis coupled to Multiple Reaction Monitoring MS (t-LiP-MRM)[3]. These approaches share the principle that in native conditions, interacting with a molecule, a protein undergoes conformational changes that might result in its lower sensitivity to limited proteolysis. Thus, in a first step DARTS gives the identification of NPs most reliable interacting proteins and then t-LiP-MRM, which focuses on the identified proteins tryptic peptides, is used to pinpoint the proteins regions directly or distally involved in the interaction with the NPs. These proteomics results are then confirmed by additional techniques, such as Western Blotting and molecular docking.At first, this *label-free* platform proof of concept was achieved through the well-known radicicol/Hsp90s system, then the optimized method was exploited for the *interactome* analysis of several NPs. As an example, we report the case of study of Crellastatin A (CreA), a marine sulphated bis-steroid from the sponge *Crella* sp[4]. DARTS led to the identification of Poly [ADP-ribose] polymerase 1 (PARP-1) as CreA most reliable partner, as also validated by Western Blotting. Subsequently, t-LiP MRM data, corroborated by blind molecular docking, pointed out PARP-1 WGR domain as a putative CreA/PARP-1 binding site. Finally CreA inhibitory activity on PARP-1 was assessed through an *in vitro* assay on the human recombinant PARP1[5].

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Synthesis of nitrogen-containing heterocyclic systems of biological interest through domino strategies

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Nowadays, the organic chemistry is not focused anymore on what it is possible to synthetize but how we can do it, supported by the increasing importance of environmental problems. The chemical resources have a limit and some of them could negatively influence the ecological balance. For that reason, the development of sustainable procedures that are able to reduce the waste, to preserve the resources and to increase efficiency is an emerging requirement. One of the possibility to do that is to replace the common stepwise reactions with domino reactions.[1]

Benzoxazines, ureas and other heteropolycyclic nuclei, scaffolds present in different molecules with biological activity have been synthetized starting from alkenes and allenes through different domino strategies (Figure 1), including oxidative Pd(II)-catalyzed alkene difunctionalizations,[2] hypervalent iodine-promoted dearomatization and consequent intramolecular Diels-Alder reaction, oxidative aminoiodinations[3] and intramolecular enantioselective Rh(I)-catalyzed hydroaminations[4] and alkoxylations of allenes. These results show how it is possible to "play" with chemistry, achieving various products starting from the same substrates, or, on the other hand, obtaining similar structures by means of different methods. Thus, take your pick!

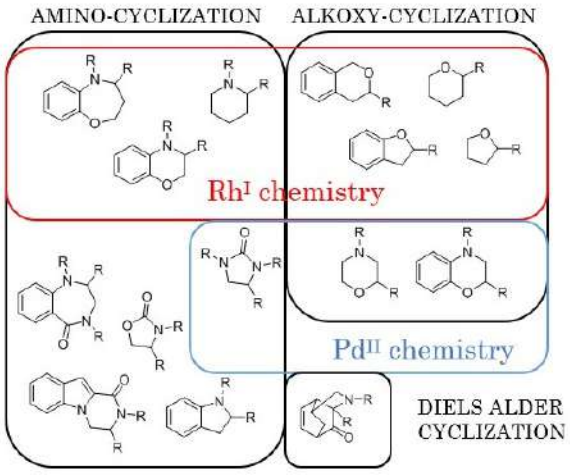

Figure 1: A look into the different strategies employed for the synthesis of hetero(poly)cyclic systems, starting from alkenes and allenes.

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Domino Reactions of 2-alkynylaniline derivatives with electrophiles as a step economic method to generate structural complexity

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In the past decades the concept of efficiency has gained a central role in synthetic organic chemistry. In fact, it is not difficult to understand that classic synthetic sequences, based on the "one bond per step" approach, are not competitive anymore because of economical cost, operational length and the production of significant amounts of waste, especially since more and more complex organic structures are requested, especially from pharmaceutical industry. Domino reactions are chemical transformations that enable the creation of multiple C-C of C-heteroatom bonds in a single step, without changes in the reaction conditions and without the need to isolate the intermediates; they represent therefore an interesting approach to improve the efficiency of a synthetic pathway and their implementation is one of the main goal of modern synthetic organic chemistry. [1]

2-alkynyklaniline derivatives, like β-(2-aminophenyl)-α,β-ynones, [2] are interesting building blocks for domino and multi-bond forming reactions thanks to the compresence of electrophilic and nucleophilic moieties and have been already used by our research group to generate different heterocyclic structures through their reaction with nucleophiles. [3] As part of our interest in discovering new efficient procedures for the synthesis of heterocycles, herein we would like to report the results of our further investigations on the reaction of these derivatives with electrophiles to develop operatively simple and efficient approaches for the synthesis of valuable heterocyclic scaffolds.

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Dearomatization of Indoles Promoted by Graphene Oxide VIA Covalent Grafting Activation Mode

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In recent years a great research interest has been addressed to the application of graphene-based materials in organic synthesis as a benign, sustainable and metal free alternative to traditional synthetic metal-based methodologies.[1]

In this context, our latest findings on the use of graphene oxide (GO) for the dearomative allylic and allenylic alkylation of indoles with alcohols will be presented. The process was realized for the first time under metal-free and environmentally friendly conditions (H_2O/CH_3CN, 55 °C, 6 h), in absence of stoichiometric additives and with very low loading of GO (10 % wt).[2] A broad substrate scope was documented (yield up to 92%) accompanied by high site- and stereoselectivity. The obtainment of allenylated products from propargylic alcohols is noteworthy, being the propargylated isomer usually formed under conventional metal catalysis.[3]

The covalent activation model exerted by the GO functionalities[4] on the alcohol was corroborated by spectroscopic, experimental and computational evidences, suggesting the "grafting" of the electrophile on the GO surface via an epoxide-ring opening event. Regeneration of the GO catalyst via a known simple acidic treatment is also documented.

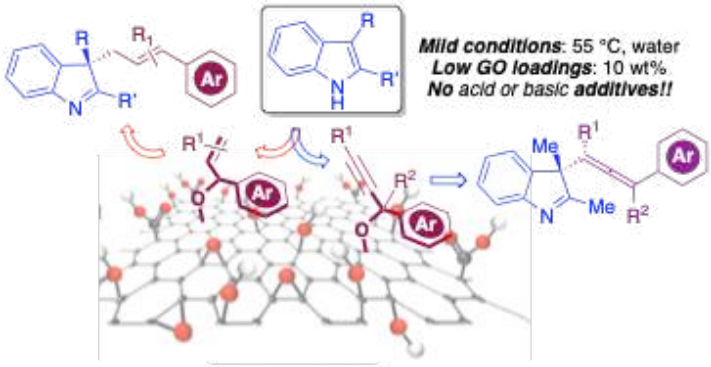

Figure 1: The present GO-assisted metal-free dearomatization of indoles with allylic/propargylic alcohols.

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Asymmetric *N*-acylation of Biginelli dihydropyrimidines based on oxidative NHC catalysis

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Dihydropyrimidinones (DHPMs), well known as Biginelli products, can be simply synthetized through an efficient multicomponent reaction using highly accessible aldehydes, active methylene compounds and (thio)ureas in acidic medium.[1] In recent years, DHPMs have attracted considerable attention, thanks to their several biological and pharmaceutical applications. Moreover, it has been observed that the substitution of the Biginelli compounds with carbonyl groups at the N3 position often leads to an increase of their biological activity and stability.[2] Therefore, the synthesis of optically active DHPMs represents a challenging area of research. So far, these synthetic targets have been obtained through either direct asymmetric synthesis or chemical resolution processes.[1] Instead, optically active N3-acylated DHPMs are usually produced from the corresponding enantioenriched substrate by treatment with stoichiometric, highly reactive acid chlorides or anhydrides at elevated temperatures in the presence of a base.[2] In the present work, a new challenging asymmetric N3-acylation of racemic Biginelli compounds is presented (Figure 1).[3] The reported method uses aldehydes as the acylating agent and substitutional variation around the DHPM scaffold has been investigated through catalytically generated acyl azolium intermediates. The reaction promoted by chiral *N*-heterocyclic carbene catalyst (NHC) in oxidative conditions leads to optically active N3-acylated DHPMs with good yield (up to 72% isolated yield) and stereoselectivity (up to 84:16 *er*). Although the enantioselectivity of the process is moderate, the use of aldehydes as mild acylating compound appears well suited for the (stereo)chemical decoration of the DHPM nucleus and, in general, for the direct *N*-acylation of molecules containing the ureido functionality.

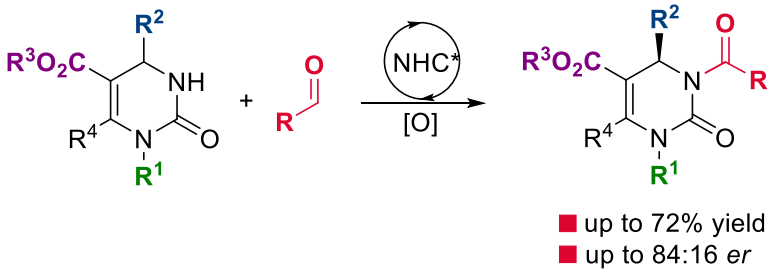

Figure 1: Asymmetric *N*-acylation of DHPMs promoted by NHC under oxidative conditions.

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Efficient Carbon Nanoforms based catalysts for C–C Coupling Reactions

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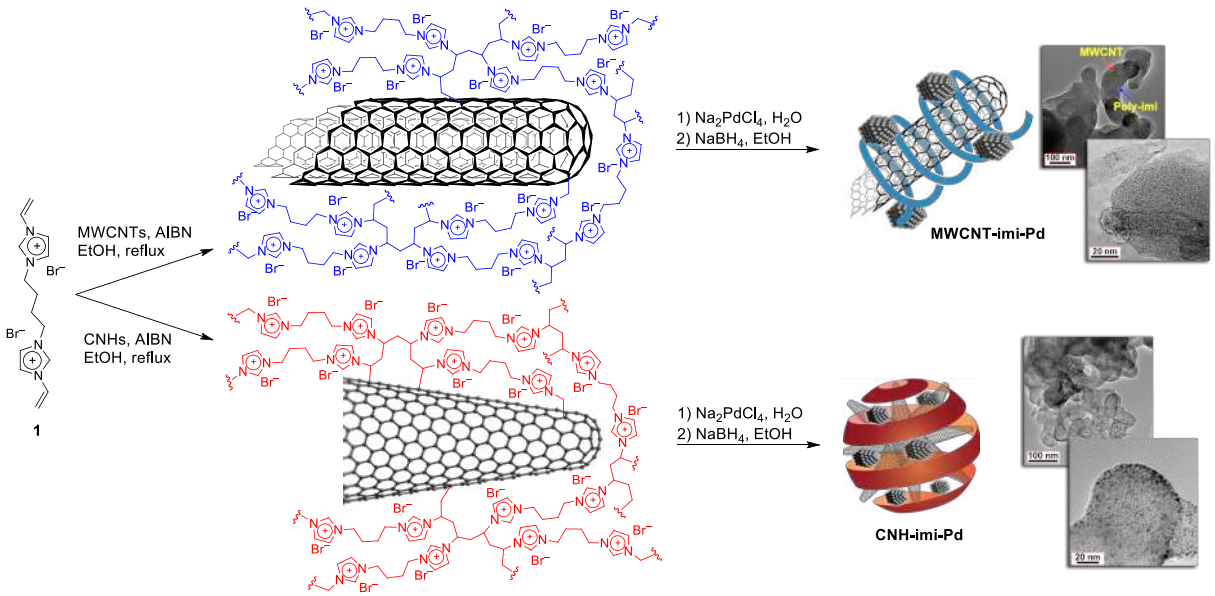
Carbon nanoforms (CNFs) (carbon nanotubes, graphene, carbon nanohorns, etc.) represent a unique class of nanostructured materials with specific properties that make them very attractive for a wide range of applications. Among them, the use of CNFs in the catalytic field has aroused great interest.[1] CNFs can be exploited as suitable support materials to be functionalised to obtain nanoarchitectures on which to immobilise metal nanoparticles (MNPs).[1-3] We chose multi-walled carbon nanotubes (MWCNTs) and carbon nanohorns (CNHs) as support materials for the preparation of two catalytic systems, namely **MWCNT-imi-Pd** and **CNH-imi-Pd** (**Scheme 1**). Interestingly, both MWCNTs and CNHs acted as templates during the growth of the polymeric network formed after the radical polymerization of the bis-vinylimidazolium salt **1**, which covered the whole surface of MWCNTs and CNHs with a cylindrical or spherical coating, respectively. The so-obtained nanoarchitectures were employed as supports for palladium NPs obtained after anion exchange between bromides and $PdCl_4^{2-}$ followed by reduction with $NaBH_4$ (**Scheme 1**). Both **MWCNT-imi-Pd** and **CNH-imi-Pd** were used as heterogeneous and recyclable catalysts for the C–C coupling reactions of Suzuki and Heck with low catalytic loading (down to 0.007 mol% Pd).[4]



Scheme 1: preparation of **MWCNT-imi-Pd** and **CNH-imi-Pd**

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Green and Sustainable Pathways en Route to Heterocyclic Scaffolds of Pharmaceutical Interest

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Nowadays, the environmental, health, and safety constraints imposed by current society are forcing chemists to reshape long-established paradigms, while concepts such as biorenewable resources, sustainability and circular economy are being rapidly implemented in the chemical industry.[1] Over the last few years, our research group was focused on the sustainable advancement to the synthesis of heterocyclic compounds such as tetrahydrofuran,[2] thiophene,[3] and triazole derivatives[4] in the so-called *Deep Eutectic Solvents* (*DESs*) and water. In this communication, we report on the synthesis of *N*-containing heterocyclic compounds such as 2,5-diarylpyrazines **1**,[5] 2-aroylimidazoles **2**, and 2,4-diaroyl-6-arylpyrimidines **3**,[6] which are important scaffolds in several biologically active and pharmaceutically relevant molecules, from phenacyl azides, under mild conditions, and using *DESs* as environmentally responsible media both as solvents and catalysts.

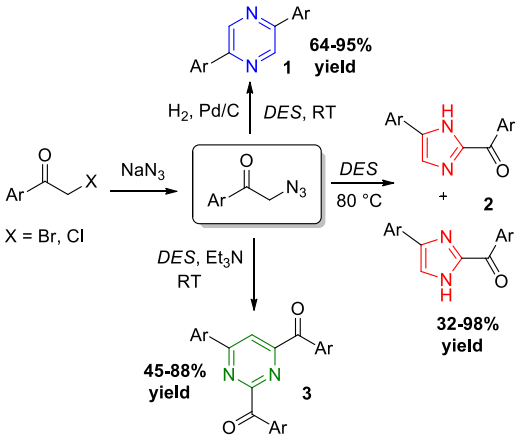

Figure 1: Synthesis of symmetrical 2,5-disubstituted pyrazines **1**, functionalized imidazoles **2** and pyrimidine derivatives **3** in *DESs* from phenacyl azides (RT = room temperature).

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Enantioselective Nickel Catalyzed Arylative Carboxylation of Unactivated Alkenes

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Carbon dioxide is facing an exponential growth of interest in organic synthetic methodology as a valuable and desirable C1-synthone due to the low toxicity, the abundance and the low cost. The last decades have produced an incredible amount of strategies for the activation of this un-reactive gas, to make it synthetically useful in the construction of complex molecular motifs.[1]

Particularly appealing is the possibility to employ a catalytic system for the C1-homologation reaction (carboxylation, carbonylation, methylenation), both in the metal-catalyzed and metal-free directions, but, despite the incredible amount of annual publications, stereoselective methodologies are still underdeveloped.[2]

Based on our interest in the 3d-TM catalysis we present an enantioselective Nickel-catalyzed double functionalization of unactivated alkenes. The intramolecular cascade process (Heck-coupling/carboxylation) is promoted by the use of PyOx ligands and a reductive system, generating high chemical complexity starting to cheap and simple starting materials (**Figure 1**).

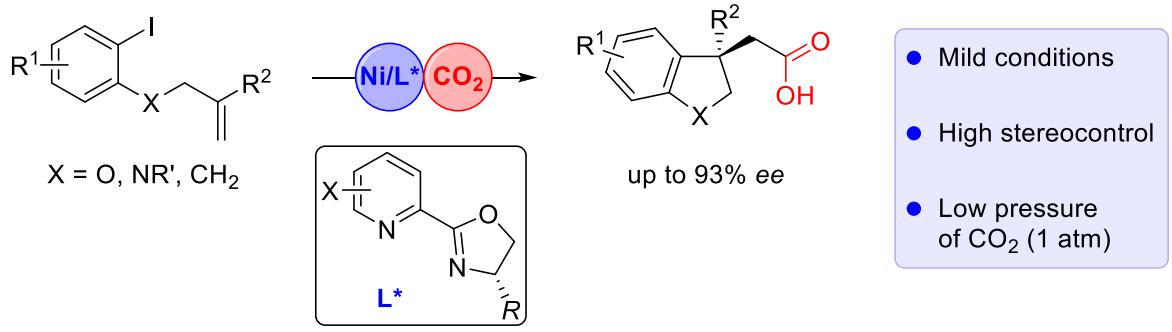

Figure 1.

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Asymmetric organocatalysis in the synthesis of heterocyclic scaffolds

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In the past 20 years, the field of asymmetric organocatalysis provided an effective alternative to the more conventional metal and enzymatic catalysis. Certainly, several advantages can be recognized in the employment of small organic molecules as catalysts: *i)* various and simultaneous activation modes; *ii)* these catalysts are in general cheaper, readily available and easy to synthesize; *iii)* frequently, inert atmosphere and dry solvents are not necessary due to the high stability of the organocatalysts. Furthermore, the development of efficient methods for the asymmetric construction of complex heterocyclic frameworks is an ongoing challenge within the synthetic community. To achieve such a goal, organocatalyzed cascade reactions and sequential catalysis have been shown to be excellent candidates because of the number of steps that can occur under the same reaction conditions, thereby leading directly to high molecular complexity.[1] In this presentation, the asymmetric synthesis of isochromanones, polycyclic ethers, and pyrazolone derivatives will be described, with particular attention on domino-sequential processes and mmulti-step syntheses.[2]

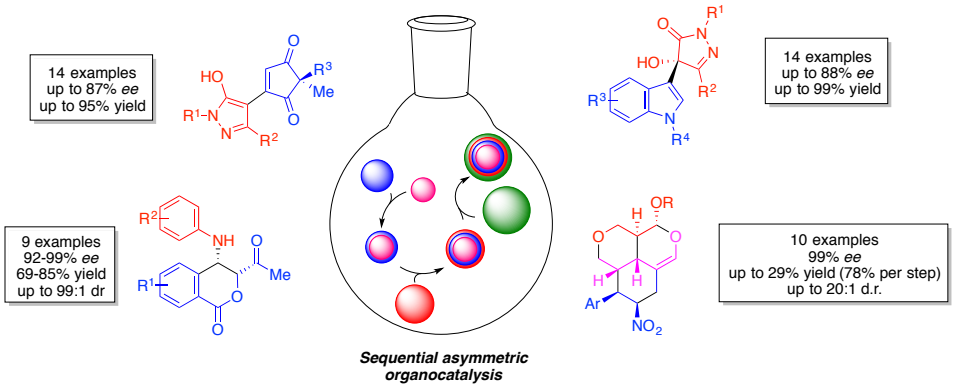

Figure 1: Asymmetric organocatalysis in the synthesis of heterocyclic scaffolds.

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An unexpected benzylic oxidation in the multicomponent synthesis of simplified analogues of Anchinopeptolides and Eusynstyelamides

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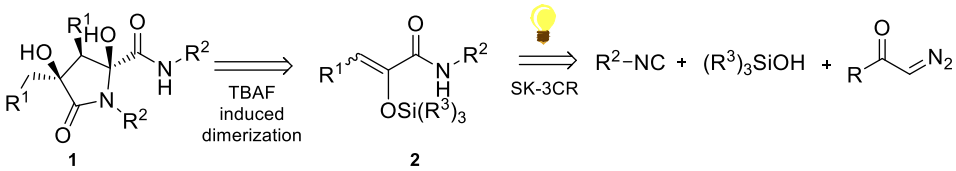
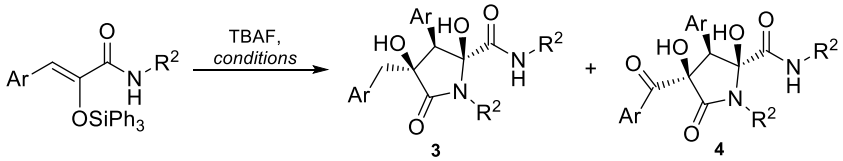
Silyl enol ether chemistry is nowadays well-grounded and established, as they proved to be invaluable intermediates in organic synthesis. Recently, we reported an unprecedented photoinduced multicomponent synthesis of α-silyloxyacrylamides, a class of silyl enol ethers that were practically unachievable from their precursor (a secondary α-ketoamide).[1] This reaction, namely the Silylative Ketene 3-Component reaction, affords α-silyloxyacrylamides stereoselectively and efficiently, and we investigated several synthetic applications for these intermediates.



Scheme 1: 2-step sequence to access analogues of natural products (Eusynstyelamides and Anchinopeptolides) of general structure **1**. TBAF: tetrabutylammonium fluoride; SK-3CR: silylative ketene 3-component reaction.

Among the possible applications, we reported the simple and mild TBAF-induced dimerization of silyl enol ethers **2** to Eusynstyelamides, Anchinopeptolides and their simplified analogues **1** (Scheme 1).[2] Six new bonds and 2 quaternary carbons are crafted in just two synthetic steps, thus making this sequence extremely appealing towards the syntheses of these natural products and their derivatives. However, while investigating the scope of this protocol we came across an unexpected benzylic oxidation of some derivatives (Scheme 2).[3] Herein I report our investigations on this unexpected process, showing which factors influence the most the oxidative or non-oxidative outcome of the dimerization reaction.



Scheme 2: Unexpected benzylic oxidation (products **4**) of simplified analogues of anchinopeptolides and eusynstyelamides (products **3**). Several conditions were tested.

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Isomerization of (*E*)-β-Nitroenones into β-Nitro-β,γ-Unsaturated Ketones and their applications

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In the last years, a growing interest has been showed towards β-nitroenones, since they proved to be versatile building blocks for the preparation and derivatization of important heterocycles such as furans,[1] indoles, pyrroles,[2] and further highly functionalized molecules.[3,4]

Now, we disclosed a new behaviour of β-nitroenones **1**, which isomerize into β-nitro-β,γ-unsaturated ketones **2** under microwave irradiation. Isomerization of **1** into **2** is diastereoselective and is promoted by alcoholic solvent, whose proton participate in the reaction mechanism giving preferentially the *E*-isomer.

Moreover, compounds **2** have been applied as precious precursor of pyrroles **3** and pyridazines **4** under mild reaction conditions.

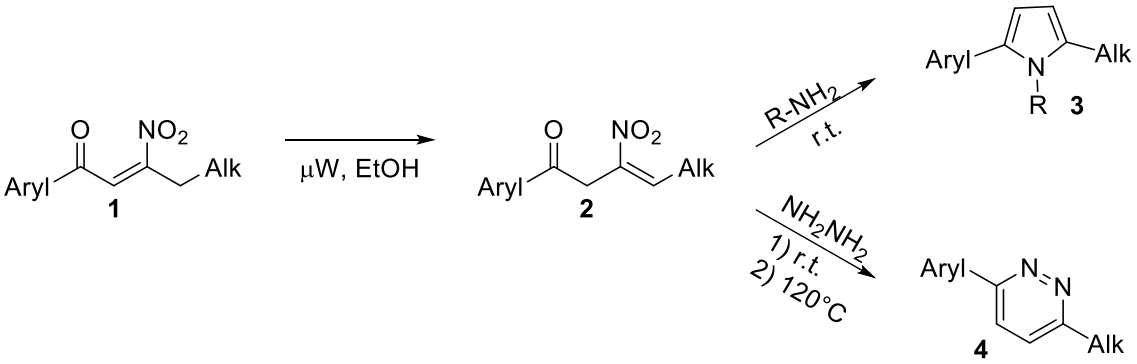

Figure 1: General scheme.

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Cp_2TiCl_2-Catalyzed Photoredox Allylation of Aldehydes with Visible Light

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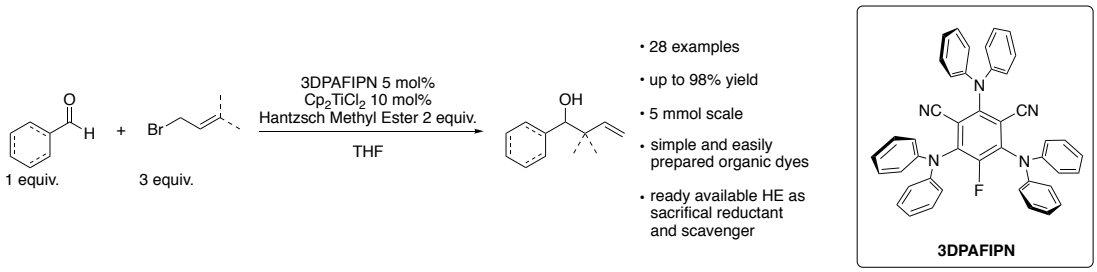
A practical and straightforward radical-polar crossover photoredox allylation of aldehydes mediated by titanocene complexes, giving access to a wide range of homoallylic alcohols in good to excellent yields will be discussed.[1] The reaction uses 1,3-dicyano-5-fluoro-2,4,6-tris(diphenylamino)-benzene (3DPAFIPN) as the photocatalyst, in the presence of the readily available Hantzsch's ester as sacrificial reductant and scavenger for the titanium complex.



Allylation of carbonyls under Barbier conditions, giving access to transient organometallic reactive allylating species, is a key strategy for the preparation of functionalized building blocks in the total synthesis of natural products.[2] Photoredox catalysis, by the use of metal complexes, dyes, or semiconductors, can give interesting approaches to form radical species by electron transfer (ET) or energy transfer.[3] The combination of photoredox catalytic cycle with other catalytic cycles, working cooperatively, opens the way to new reaction pathways.[4] Metallaphotoredox catalysis, i.e. metal catalysis merged with photoredox catalysis, is a new and rapidly growing research area.[5] Now, photoredox catalysis is starting to explore the possibility to use a clean and rapid access to radicals for generating nucleophilic reagents.[6] The concept of combining radical and polar chemistry is also called reductive radical-polar crossover (RRPC).[7] In this approach, a suitable alkyl radical is converted into a nucleophile by reduction or by capture with a suitable transition metal complex. These so formed nucleophilic species can then react with electrophiles such carbonyls or imines.

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Antimony–Oxo Porphyrins as Photocatalysts for Redox-Neutral C–H to C–C Bond Conversion

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The most practical strategy for the functionalization of organic molecules consists in the direct functionalization of C-H bonds, since it waives chemists from designing complicated procedures to install activating groups in the molecule. In recent years, synthetic photocatalysis has offered an extremely powerful methodology to synthesis practitioners for the direct conversion of C-H bonds: photocatalyzed Hydrogen-Atom Transfer (HAT).[1] It relies on photocatalysts (PCs) bearing an oxyl-radical group in their triplet excited states able to cleave homolytically a C-H bond in the H-donor to afford an organoradical to be exploited for synthesis (Figure 1, left). Despite proven benefits in terms of atom-efficiency and step-economy,[2] the diffusion of this methodology is still frustrated by the scarce number of photocatalysts known to operate through this manifold, especially under visible light irradiation. Hereby, we report the use of a high-valent antimony–oxo porphyrin as a new visible-light photocatalyst for the redox-neutral C–H to C–C bond conversion (Figure 1, right).[3]

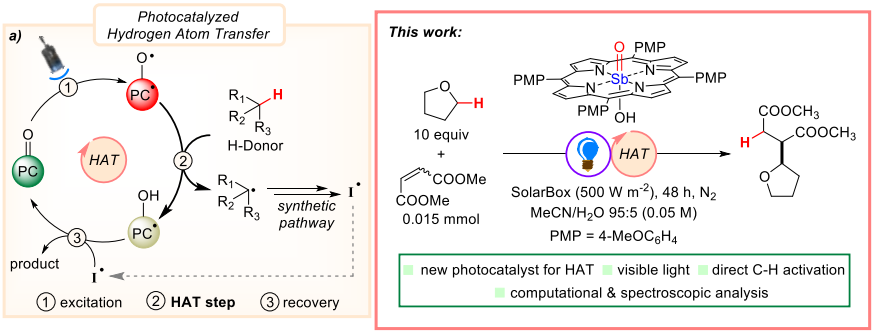

Figure 1: left: typical mechanism of photocatalyzed HAT; right: highlights of this work.

Starting off from computational investigation, we experimentally demonstrated that a thermally unreactive Sb^{V}–oxoporphyrin can be exploited to trigger a redox-neutral C–H to C–C bond conversion under visible light irradiation. Quenching experiments and kinetic isotopic effect indicate the involvement of a HAT step, while meticulous spectroscopic investigation confirmed the triplet nature of the excited state of PC and allowed to determine the quenching constant value, as well. Furthermore, according to our computational analysis, the Sb^{V} center remains in the high-valent oxidation state under the conditions explored, serving uniquely to carry the oxo moiety and to activate the coordinated ligands. Thus, antimony has a spectator role in the key steps of the photocatalytic cycle, suggesting that other high-valent porphyrin complexes featuring an oxo ligand may be envisaged as suitable PC for HAT.

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Infrared irradiation-assisted Palladium-catalyzed direct C-H bond arylation of (hetero)arenes

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Organic π-conjugated small molecules and polymers based on (hetero)aryl structural units have been extensively investigated in recent years. The development of efficient methods for the generation of aryl-aryl bonds is the key step to produce these compounds. In particular, direct C-H bond arylation of (hetero)arenes has opened new approaches for the generation of aryl-aryl bonds, replacing the more traditional transition metal-promoted cross-coupling reactions with organometallic derivatives.[1] Although significant efforts have been made in the last decades towards more sustainable conditions, including the use of recoverable catalysts and green solvents,[2] some issues still remain, in particular the need of high temperatures and long reaction times.

The use of non-conventional heating sources has earned increasing attention, due to the possibility of minimizing reaction time, improving product yield and avoiding undesired byproducts.[3] In particular, infrared (IR) irradiation represents a very promising tool for fast, cheap and green organic synthesis.[4] However, the true potential of IR-assisted reactions is still almost unexplored, especially for Palladium-catalyzed coupling chemistry.

In this context, here we report the IR irradiation-promoted Palladium-catalyzed direct C-H bond arylation protocol, performed in solvent-free, non-anhydrous conditions (**Figure 1**). The reaction was successfully applied to several heteroarenes, including benzothiophene, thieno[3,4-*c*]pyrrole-4,6-dione and 1,2,3-triazole with functionalized aryl iodides, giving the corresponding direct C-H bond arylation products in good yields after very short times (15 minutes or 1 hour).

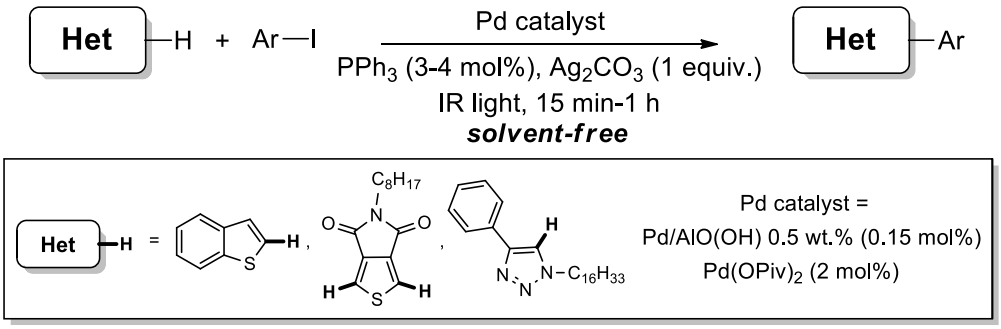

Figure 1. IR irradiation-promoted, solvent-free Pd-catalyzed direct C-H bond arylation of heteroarenes (benzothiophene, thieno[3,4-c]pyrrole-4,6-dione, 1,2,3-triazole) with functionalized aryl iodides.

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New applications of esters surrogates in organic synthesis

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Masked esters/amides are compounds endowed with a great potential in the field of organic synthesis.[1] In particular, acyl pyrazoles can be easily converted into enolates and then treated with opportune electrophiles to obtain useful acyclic and cyclic derivatives. In the presence of both electrophilic and nucleophilic reagents, such as azomethine imines, a Mannich type reaction followed by cyclization occurred when using acyl pyrazole enolates, thanks to the leaving group ability of the corresponding pyrazole. With this strategy, we carried out a convenient and mild synthetic access to bicyclic pyrazolidinones (Figure 1, A).[2]

Moreover, we developed a variant of the Ehrlich-Sachs reaction, that is the condensation of active methylene compounds with nitroso derivatives for the synthesis of imines or nitrones. A facile route to new α-iminoacyl pyrazole derivatives was developed, by reacting nitrosoarenes with masked esters. This product represents a versatile intermediate for practical one-pot syntheses of important derivatives, frequently applied in organic synthesis (Figure 1, B).[3] Interestingly, we applied a similar approach to rapidly access ketonitrones, by reacting readily available arylacetic esters with nitrosoarenes under mild reaction conditions (Figure 1, C). [4]

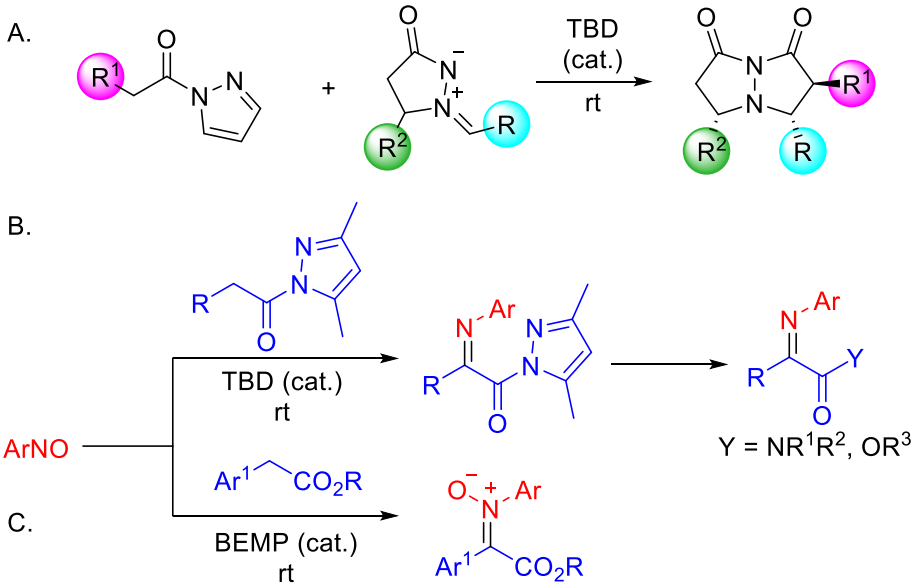

Figure 1: Reaction of acyl pyrazole enolates with electrophiles.

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Base-free Oxidative Esterification of Furfural under Au/CeO_2 Catalysis: Protecting Agent and Microwave Irradiation Features.

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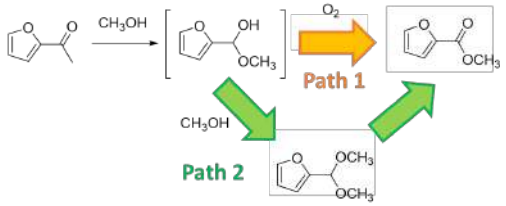
The actual urge for a greener approach in synthetic processes led to an intensification of researches focused on biomass-derived chemicals. Among these compounds, furfural (2-FA) is currently one of the few which is completely obtained from renewable resources.[1] 2-FA is an extremely versatile platform molecule, proposed for sustainable production of chemicals.[2] The 2-FA oxidative esterification to Me-2-F is among the large variety of reactions aimed to upgrade lignocellulosic biomass wastes and with this purpose transition-metal or organo-homogeneous catalysts are currently applied.[3] However, in view of process intensification, cost reduction and low environmental impact, heterogeneous catalysts would be the most advisable choice. In particular, supported gold nanoparticles have proved to be extremely active, under mild conditions, employing O_2 as benign oxidant and even without the use of a base,[4] thus paving the way to a sustainable process. In this work, a very efficient catalyst (AuCePVA) was explored, obtained using polyvinyl alcohol (PVA) as protective agent. Complete conversion and selectivity in 2-FA oxidative esterification to Me-2-F was obtained, under conventional heating and in base-free conditions. Au/CeO_2 was then exploited as benchmark catalyst and compared to AuCePVA, pointing out the role played by PVA during the reaction. The polymer chains acted not merely as metal stabilizer, but also showed an active function. Furthermore, in a perspective of process intensification, the microwave-assisted (MW-assisted) 2-FA oxidative esterification was explored. Surprisingly, AuCePVA led to the oxidation of the hemiacetal into the ester rather than the re-oxidation of the acetal into the ester. This behaviour was explained by the formation of Ce^{3+} sites under irradiation, acting as acid centers. Two reaction paths have been proposed (Scheme 1): Path 1 involved the direct 2-FA conversion to Me-2-F with the hemiacetal species as labile intermediate. In this case, the activated C=O bond of the aldehyde underwent a nucleophilic attack by methanol and further deprotonation to form the hemiacetal. Alternatively, the reaction proceeded following Path 2 and 2-FA can form the acetal right after the hemiacetal intermediate and furtherly converted to Me-2-F.



Scheme 1: Proposed reaction paths, MW-assisted 2-FA esterification to Me-2-F.

References:

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Microwave assisted hydroformylation under micellar catalysis

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Hydroformylation reaction is one of the most applied catalitic method for the preparation of aldehydes through H_2 and CO addition to double bond.[1] The common reaction conditions for this transformation are: transition metal catalysts like Co, Ru, Pt, Fe and Rh in the presence of specific ligands such as phosphine or phosphites to tune the regioselectivity of the addition of H_2 and CO (syngas) addition. This process requires a high pressure of syngas (50-80 bar) in autoclaves, long reaction times (1-4 days) and hazardous organic solvents (*i.e.* toluene).

We here reported our last findings, after several studies,[2] toward the development of a fully sustainable hydroformylation process in water under mild conditions (70 °C, 40-60 min, 9 bar of Syngas) taking advantages form both micellar catalysis[3] and microwave irradiation.[4] Linear aldehydes have been obtained as major or single products with high yields, chemo- and regioselectivity. The sustainability of the overall process is ensured by the in situ transformation of the aldehyde into the corresponding bisulphite adduct avoiding any purification step involving organic solvents to get the final product as a pure compound (Figure 1).

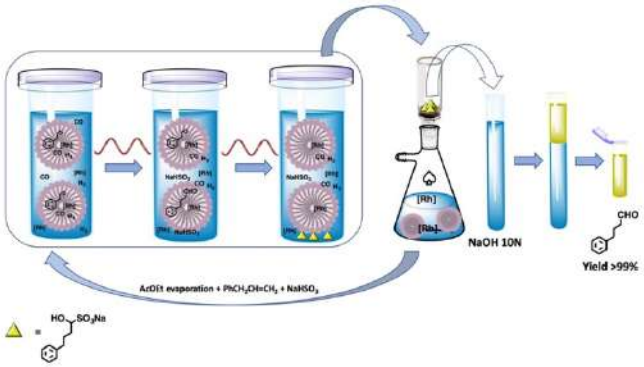

Figure 1: Hydroformylation reaction and in situ aldehyde transformation in Bertagnini's salt under micellar catalysis and microwave irradiation.

The method is efficient starting from terminal alkenes containing a wide range of functional groups including reduction-sensitive ones (i. e. nitrile, benzyl ether, internal alkenes). Starting from alkenes with hydroxy groups in β-position, hydroformylation tandem with intramolecular hemiacetalization occurs producing cyclic hemiacetals. The protocol can be applied in gram scale with very good performances with a full recovery of the catalyst and micellar water phase that can be reused at list for 5 times without affecting reaction yields.

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Metal-mediated and Metal-catalysed Reactions in Nonconventional Solvents: Mechanistic and Synthetic Aspects

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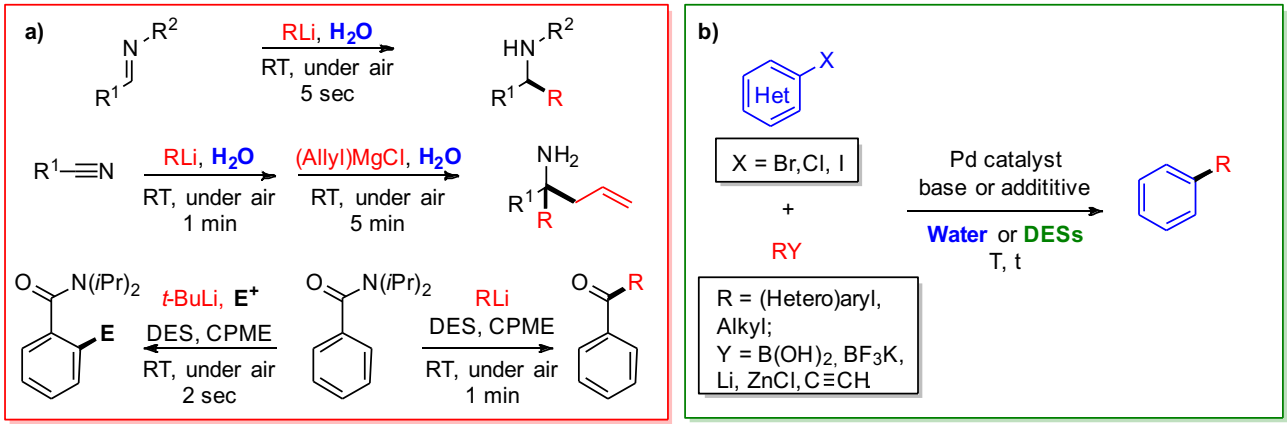
Green chemistry integrates environmentally safe and sustainable technologies for chemical research and production. Classical synthetic protocols, even with widespread applicability, have various drawbacks due to the use of harsh conditions, long reaction times, and the generation of large amounts of waste. Over the past few years, our research group has been focusing on the development of methodologies with a low ecological footprint using the so-called Deep Eutectic Solvents (DESs) and water as environmentally responsible reaction media and catalysts, thereby reshaping several organic transformations, which are traditionally carried out using toxic and often harmful petroleum-based volatile organic compounds.[1a–g] In this communication, we showcase how several metal-mediated and metal-catalysed organic reactions can successfully be accomplished, in DESs or "on water", often working at room temperature and under aerobic conditions, even when using highly polarized organometallic compounds like Grignard and organolithium reagents (Scheme 1a, b).



Scheme 1: a) Metal-mediated and b) metal-catalysed reactions in unconventional solvents.

References:

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POLITAG-Pd(0) for Phenols Valorization Using Sodium Formate as H-source

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Generally, the biomass-valorisation processes regarding lignin feedstock are focused on the bio-oil production with subsequent hydrotreatment for oxygen removal to increase stability and volatility of the oil and reduce the viscosity. Phenols, in polymeric form in lignin, are the second most abundant renewable feedstock and are commonly considered biomass-treatment waste. In this context, their upgrading to obtain value-added chemicals is of great interest.[1] Among the phenols valorisation processes, selective hydrogenation to cyclohexanone is particularly intriguing. Indeed, cyclohexanone is a key chemical for the preparation of Nylon 6, Nylon 66, and polyamide resins. The definition of milder and more energy efficient cyclohexanone production are of relevant interest if compared with the existent industrial protocols which proceed toward reduction to cyclohexanol with subsequent dehydrogenation in high-temperature gas-phase.

Although some protocols have been proposed for this step-economical process, these usually failed in selectivity when different substrates are employed.[1,2] In this context the development of novel heterogeneous catalytic systems is needed. Herein is presented the synthesis and utilisation of polystyrene-based Pd(0) catalysts for selective reduction of phenols under flow conditions (fig. 1).

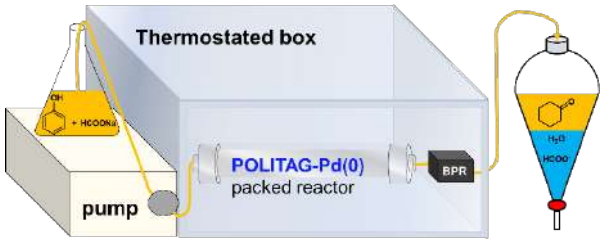

Figure 1: POLITAG-Pd(0) catalysed selective phenol hydrogenation.

The catalytic systems presented are named POLITAG-Pd(0) (POLymeric Ioni-TAG)[3] and showed promising performance in in-situ hydrogen production when sodium formate is used as H-source. Formic acid and its derivates are a valid alternative to hydrogen storage and transportation issues and a promising tool for increase the selectivity of the process.[1]

Acknowledgements: Grateful acknowledgement to project AMIS - ''Dipartimenti di Eccelenza 2018-2022'' for financial support

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Quali-quantitative Monitoring of Chemocatalytic Cellulose Conversion into Lactic Acid by FT-NIR Spectroscopy.

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Chemocatalytic conversion of cellulose into lactic acid is a valuable alternative to simple sugar fermentation[1]. Nevertheless, the procedures still need optimization to be translated to the industrial scale. Such translation would benefit by on-line monitoring of reaction parameters by fast, inexpensive, direct spectroscopic techniques[2].

In this work, we propose the application of FT-NIR spectroscopy as a suitable analytical tool for monitoring the chemocatalytic conversion of cellulose into lactic acid, from both a qualitative and quantitative point of view. Simple sugars and cellulose were converted into lactic acid according to our previously reported combined ultrasound/microwave (US/MW) method[3], mediated by a mesoporous MCM-Er catalyst[4]. Comparison between different FT-NIR spectra at different reaction temperatures and times was exploited to qualitatively indicate the feasibility of the reaction. Besides, an FT-NIR prediction model was proposed for rapidly estimating the molar distribution of cellulose catalytic degradation components in the reaction mixtures. The calibration model was based on reference samples analyzed by HPLC. The model was validated by an external validation set. Relevant statistical values of Ratio Performance to Deviations (RPD) referred to both calibration and external validation were obtained, thus demonstrating the potential of such an analytical technique in process monitoring.

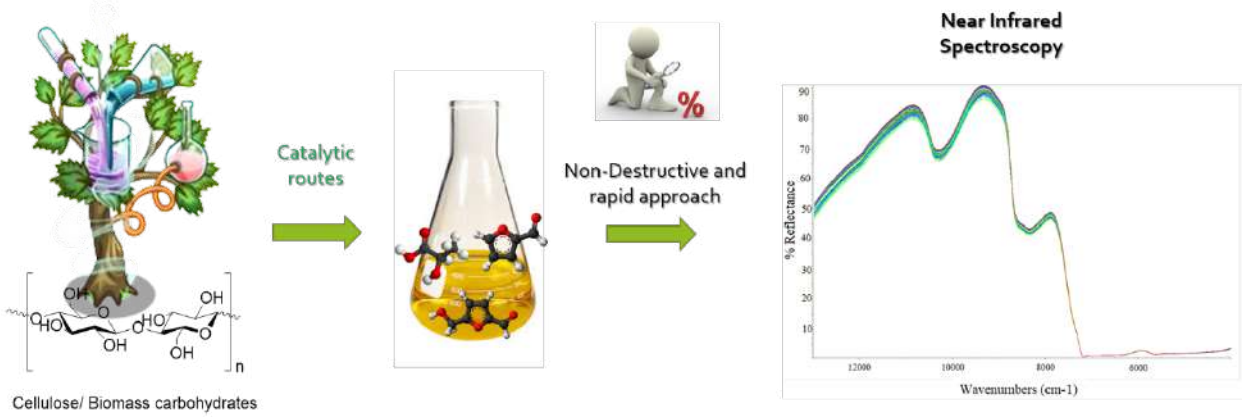

Figure 1: Quali-quantitative monitoring of chemocatalytic cellulose conversion into lactic acid by FT-NIR Spectroscopy.

References:

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Hybrid ionogels: adsorbent for the removal of pharmaceutical active compounds from wastewater

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The huge consumption of pharmaceutics has recently caused the water contamination from pharmaceutically active compounds (PhACs). The biggest limitation to the purification of wastewater is due to the presence of PhACs in low concentrations and to the wide structural diversity of PhACs, making difficult their detection and removal. The consequence of this phenomenon is the contamination of the drinking water all over the world.[1]
To overcome the above issue, carbon nanomaterials such as nanotubes, graphene or fullerene have been applied as they warranty good selectivity and removal efficiency, however their use can cause leaching problems in water after the purification process.
For this reason, it can be convenient to include carbon nanomaterials in a semisolid matrix like gels. Hybrid supramolecular ionogels, formed by imidazolium organic salts as gelators, have been recently applied to this aim, reaching good results in terms of PhAC removal efficiency from wastewater.[2]

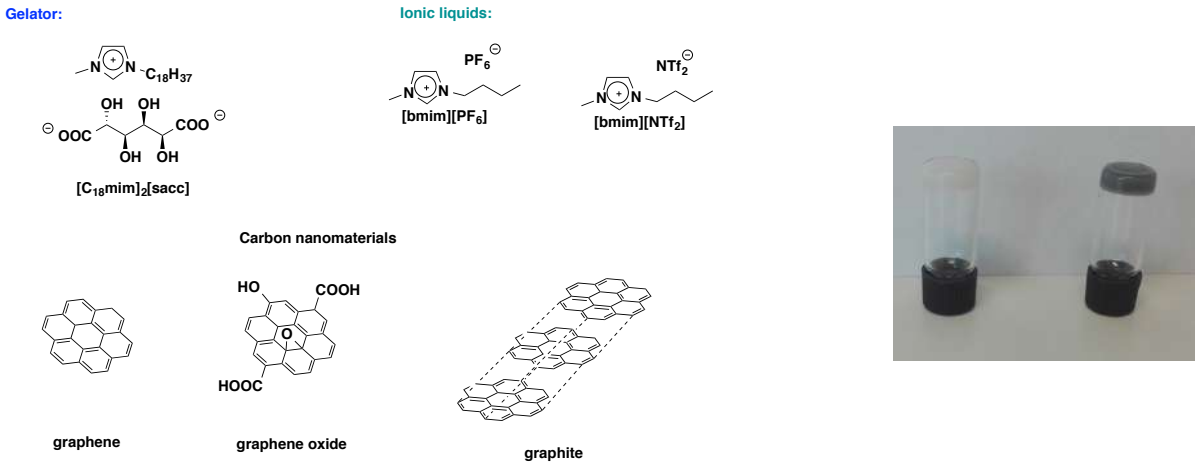

Figure 1: gelator, ILs and carbon nanomaterials used to form ionogels; picture of pure and hybrid ionogels.

The above study has been extended, applying new hybrid ionogels as sorbents and four classes of PhACs as model contaminants (antibiotics, anti-inflammatories, anticonvulsant). Chemical-physical properties of gels and their ability to remove PhACs from wastewater have been tested mimicking realistic system. In particular, the removal efficiency of a PhAC mixtures has been analyzed as well as the use of the gels inside membranes and columns for an easy and fast adsorption process.

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Design and synthesis of liquid crystalline monomers for the development of smart materials

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Liquid Crystalline Elastomers (LCEs) are smart materials with an anisotropic molecular structure and shape-changing capabilities. Exploiting the combination of their response to optical stimuli with 3D structuration at the microscale, we demonstrated different synthetic microrobots entirely powered by light and able to reproduce diverse animal. Developed microrobots are able to perform humanoid tasks as walking and swimming but also to grab and manipulate objects.[1]
The same polymers have been recently demonstrated as cell instructive biomaterials. LCEs are able to induce a spontaneous unidirectional alignment of cells during their culturing, opening to a new methodology for the morphogenesis control of biological tissues *in vitro*.[2] Possible other LCE uses range from photonic devices to regenerative medicine towards artificial muscles preparation.
This variety of application are possible tailoring the molecular structure of the polymer obtained by copolymerization of different liquid crystal, which determine final material properties. Starting from simple commercially available phenols, hydroquinones and benzoic acid derivatives, we synthesized a small library of polymerizable liquid crystalline monomers. Regarding the polymerizable unit, different groups have been inserted such as the acrylate one (for classical free radical polymerization) or thiols and alkynes (for radical click reactions).[3] In the communication, we will show the main synthetic step for the preparation of polymerizable liquid crystals and their use for LC polymers for different applications.

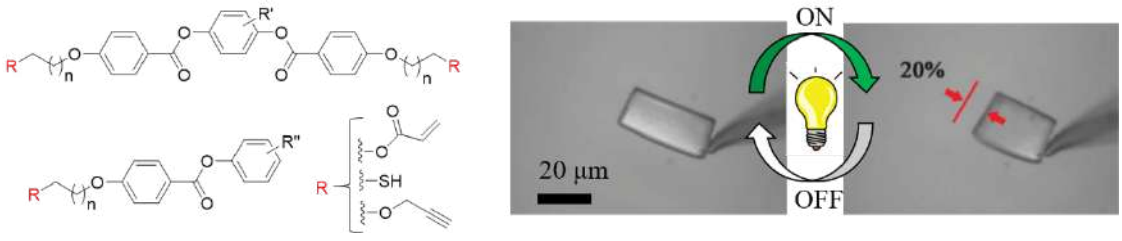

Figure 1: example of monomer structures and deformation of a LCE microstructure under light.

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Gel-to-crystal transition in supramolecular hydrogels

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Low molecular weight gelators (LMWGs) are a fascinating class of compounds able to self-assemble into supramolecular architectures, like fibres and gels. It is possible to easily tailor their structures, obtaining materials suitable for several applications (environmental remediation, medicine, biomineralization, electronics). LMWGs assemble through non-covalent interactions, such as hydrogen bonding and π-π stacking, forming reversible materials. The gelation process usually starts when a trigger is added to the gelator solution: the gelator molecule self-assembles in long structures which entangle together, forming a network able to trap the solvent.[1]

Most supramolecular gels are stable with time and aging effects are often not studied. However, a small number of systems exhibit gel-to-crystal transitions. In these cases, crystals form over time, typically at the expense of the network underpinning the gel, which converts into solution.

In this work, the unusual behaviour exhibited by (2-(naphthalen-2-yloxy)acetyl)-L-alanyl-L-alanine (2NapAA) was investigated. This gelator forms metastable hydrogels[2] when glucono-delta-lactone (GdL) is used as a trigger. A slow crystallisation process, whose rate depends on the quantities of GdL used, occurs over time from the gel phase. The gels were characterised through rheology, microscopy and powder X-ray diffraction. 2NapAA was then used in combination with another gelator, (2-(naphthalen-2-yloxy)acetyl)-L-phenylalanyl-L-phenylalanine (2NapFF), to prepare multicomponent gels with increased rigidity containing crystals (**Error! Reference source not found.**).

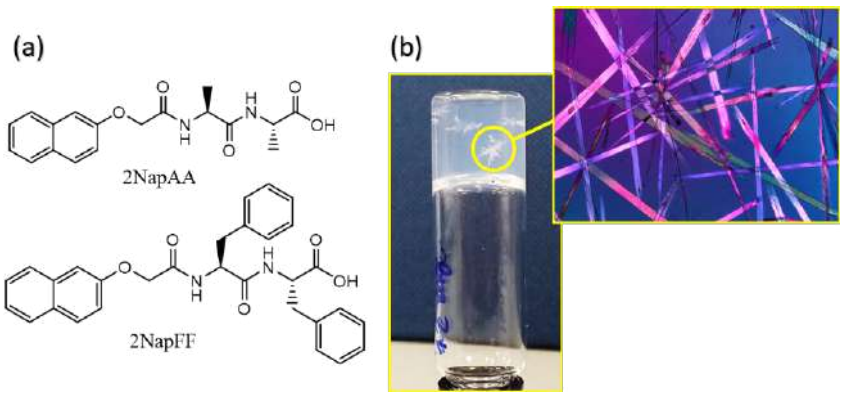

Figure 1: (a) structure of gelator 2NapAA and 2NapFF. (b) photo of a gel containing crystals; inset of the optical microscope image of the crystals.

References:

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A novel cyanine-type acidichromic chromophore based on the red hair benzothiazine system

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In recent years cyanine dyes, featuring peculiar chromophoric and fluorescence properties, outstanding biocompatibility and low toxicity to living systems, have largely been exploited as biological reporters and in other technological applications.[1,2] This class of compounds typically features organic nitrogen centers, one of the imine (acceptor) and the other of the enamine (donor) type to form a push-pull system. In this frame, inspired by $\Delta^{2,2'}$-bibenzothiazine photochromic and acidichromic chromophore of red human hair pigments trichochromes, a new class of cyanine dyes termed trichocyanines was designed in which a highly tunable cyanine-type chromophore was implemented using the benzothiazine nitrogen as the acceptor moiety at high basicity allowing for a marked bathochromic shift even at slightly acidic pHs.[3]

Starting from this background, a new red hair-inspired 1,4-benzothiazine-based scaffold is disclosed herein, built upon a modular D-π-A architecture *via* condensation of the easily accessible 3-phenyl-2H-1,4-benzothiazine with indole-3-carboxaldehyde (Figure 1).[4] The cyanine thus obtained, characterized as 2Z-((1H-indol-3-yl)methylene)-3-phenyl-2H-1,4-benzothiazine) (**1**) by complete spectral analysis, exhibited a reversible acidichromic behaviour with a marked bathochromic shift upon acidification from yellow (444 nm at neutral pH) to violet (544 nm at pH 2) with molar extinction coefficient in the order of 12000 $M^{-1}cm^{-1}$ (acid form). Notably, the chromophore resisted at least fifteen hydrochloric acid/sodium hydroxide cycles without appreciable alterations.

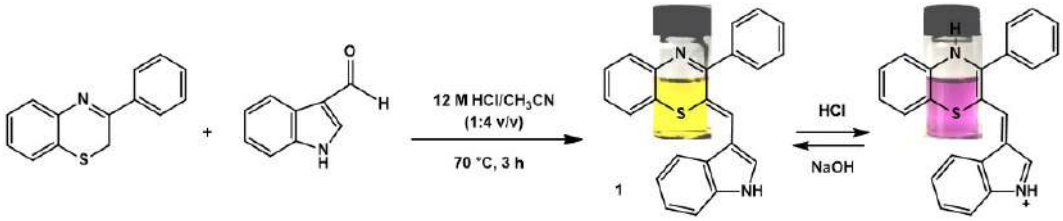

Figure 1: Synthesis and protonation equilibrium of cyanine **1**.

The expedient and scalable synthetic procedure and the preliminary assessment of the dyeing ability of the cyanine together with the pH sensitive chromophoric properties would make the new compound an attractive prototype of novel modular chromophores for pH-sensing devices and related applications. Other possible applications include pH sensing on various surfaces underwater further to in the incorporation of the cyanine into adhesive formulations.

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Design of KuQuinone-Co_3O_4 nanoparticle hybrid dyads for photoelectrochemical applications

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KuQuinones (KuQs) are pentacyclic, fully conjugated quinoid compounds, which exhibit a broad absorption band in the visible region and a low reduction potential at the excited state.[1] These peculiar spectroscopic and electrochemical features make them excellent candidates as photosensitizers for the light-driven water oxidation.[2,3] The design of hybrid dyads, characterized by organic dyes covalently bound to abundant first row transition metal oxide nanoparticles, constitutes an appealing method to catalyze the photoinduced water oxidation reaction.[4]

In this work we studied the grafting of KuQ photosensitizers on Co_3O_4 nanoparticles, obtaining advanced hybrid photocatalysts. Diverse KuQuinone derivatives, presenting a carboxylic or a phosphonate anchoring group in side-chain, have been synthetized in order to allow their chemisorption on Co_3O_4 nanoparticles.

The hybrid dyads have been deposited on indium tin oxide (ITO) and evaluated as catalysts for the photoinduced water oxidation reaction, showing better performances with respect to the non-decorated nanoparticles.

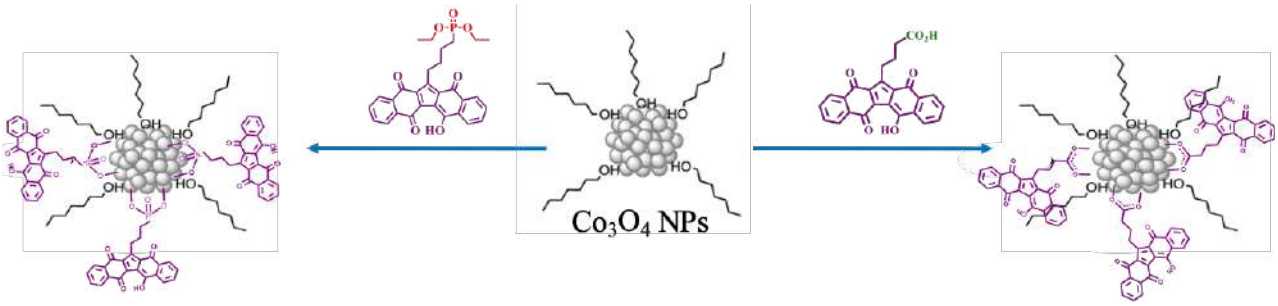

Figure 1: Graphic representation of the grafting of KuQ photosensitizers on Co_3O_4 nanoparticles.

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Biocatalysts for the synthesis of pharmacologically active compounds

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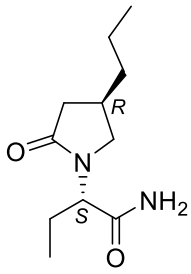
Many pharmaceutically active compounds contain a chiral core inside their structure. The required chemo-, regio-, and stereo-selectivity can be achieved using biocatalysts (enzymes or microorganisms), which transform a wide range of substrates under mild reaction conditions.

Our research work focuses on the biocatalytic synthesis of key building blocks of active pharmaceutical ingredients.

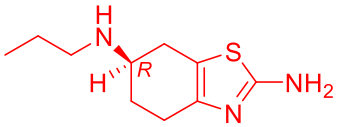
In this communication, two examples of this approach will be described: the synthesis of the enantiopure key intermediates of brivaracetam and pramipexole.

I) Brivaracetam is a recently approved anticonvulsant drug. The crucial step in the synthetic pathway of this drug is the obtainment of the precursor (*R*)-4-propyldihydrofuran-2(3H)-one[1], bearing the propyl moiety essential for its pharmacological activity. We achieved this enantiomerically pure intermediate through a convenient biocatalytic approach.

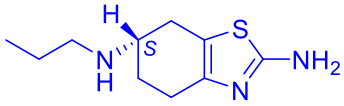


brivaracetam

II) For the preparation of (*S*)-pramipexole, a dopaminergic agonist employed as anti-Parkinson agent, and (*R*)-pramipexole, a potential treatment for eosinophilic asthma and hypereosinophilic syndrome, we investigated the activity and selectivity of different microorganisms (mainly yeasts). This approach allowed us to obtain enantiomerically pure synthons[2], but now we improved our previous results using enzymes as biocatalysts, i.e. lipases in organic solvents[3].



(*R*)-pramipexole



(*S*)-pramipexole

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Controlling the generation of highly fluorescent pyrazolines for a light-triggered bioorthogonal ligation

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Click chemistry represents a useful method to create covalent bonds among two reagents, with high yields, fast reaction kinetic and under mild conditions. During the last years, this powerful strategy has been extensively employed in bioorthogonal ligation for labelling biological molecules (proteins, DNA, RNA), in order to monitor and understand the mechanism of many physiological processes[1].

Recently, Lin and co-workers reported the use of 2,5-diaryl tetrazoles as photoactivable moieties for bioorthogonal ligation on proteins[2]. These compounds, under irradiation, generate a 1,3-nitrile imine dipole (NI), an intermediate able to react with different types of dipolarophiles, to produce fluorescent pyrazolines. However, NI can be trapped by various nucleophiles, such as water and amines and this represents a relevant drawback. Furthermore, fluorescence quantum yield of products is often too low to be useful for imaging applications in biological context.

In order to overcome these limits and to optimize their photophysical properties, we have synthesized a library of 2,5-diaryl tetrazoles, properly functionalized, in order to investigate how substituents can modulate NI generation and reactivity, in particular in aqueous solutions, and fluorescence emission of corresponding products. For each compound, we measured quantum yield of NI generation at 310 nm, to identify most active ones, then cycloaddition efficiency was explored by irradiation of substrates in various conditions, in order to identify candidates able to react preferentially with alkenes. Furthermore, spectroscopic properties of pyrazolines have been examined and a product with very high fluorescence quantum yield in water (Φ_f = 0.7) has been individuated. In addition, we have discovered that reaction pathway is governed by solution's acidity: indeed, at specific pH values, which depends on the kind of substituents introduced, pyrazoline becomes the major product, even at low concentration of alkene.

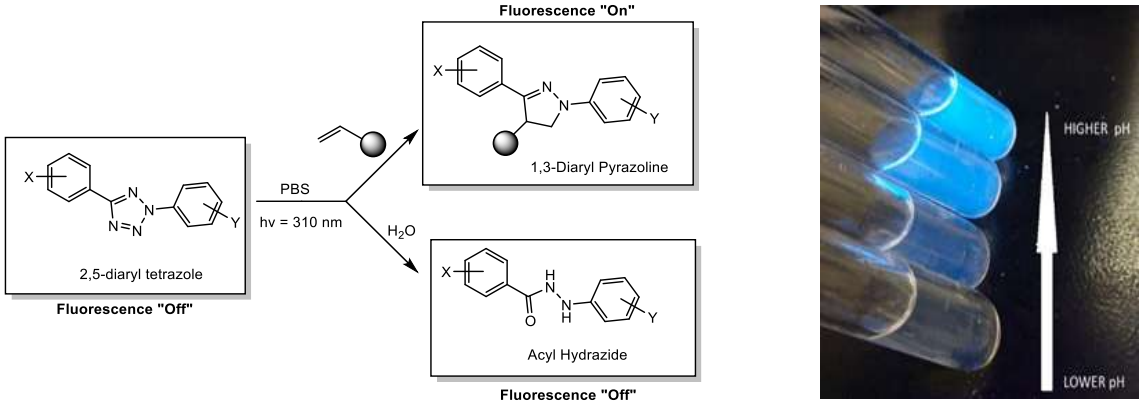

Figure 1: Photoinduced reaction of 2,5-diaryl tetrazoles.

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Mechanochemistry: an Eco-Efficient Tool to Re-Design Old Organic Processes

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In the last two decades, Mechanochemistry has established its role as a powerful tool in organic synthesis. The latest insights into mechanistic aspects of this technique enable the possibility to further extend the scope of synthetic transformations in the ball-mill, opening the routes for a wide number of applications.[1,2,3]

The mechanochemical approach meets the demand for more sustainable processes resulting in growing interest from the industrial environment.

In this work, the Beckmann rearrangement has been explored in a more environmental-friendly key for efficient and green amide preparation, starting from the corresponding carbonylic compounds and a harmless activating agent. The methodology was successfully applied to the synthesis of value-added marketed compounds such as paracetamol and Ɛ-caprolactam.

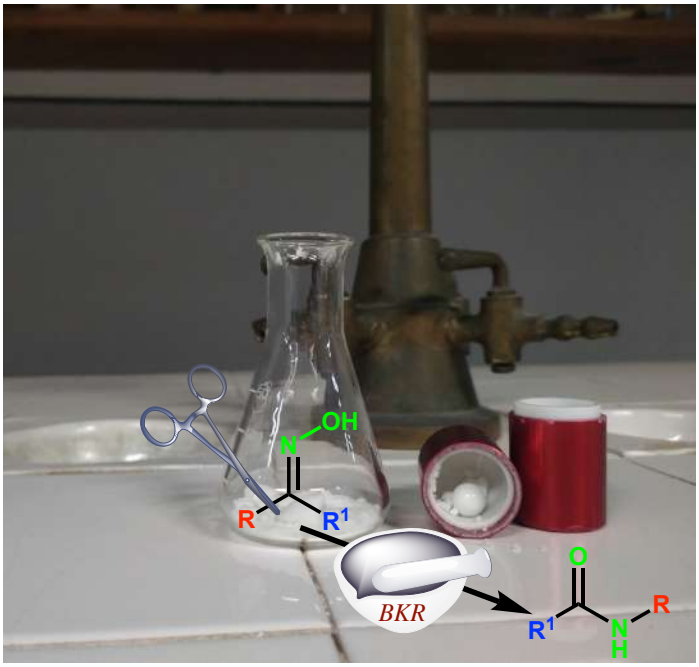

Figure 1: Mechanochemical Beckmann Rearrangement.

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Organo-gold catalysis with bifunctional phosphine ligands for alkyne activation

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Gold(I) complexes featuring bifunctional phosphine ligands with pendant H-bond donor groups have been prepared and tested in a variety of reactions involving alkyne substrates. Results collected so far indicate that, thanks to their H-bonding ability, these complexes can contribute to the solution of two long-standing issues in the field of Au(I) activation of alkynes:[1]

1 - The realization of challenging Au(I)-catalyzed enantioselective transformations of alkynes by placing the chiral information not on the ligand backbone, but on the counterion.[2] The successful implementation of this strategy has been demonstrated in the formal (4+2) cycloaddition of 1,6-enynes (Figure 1, left). This conceptually new approach lies at the intersection of metal catalysis, H-bond organocatalysis[3] and asymmetric counterion-directed catalysis.[4]

2 - The necessity of a silver co-catalyst, which has the drawback of mandating the use of an additional precious metal, while often negatively impacting selectivity.[5] The novel Au(I) chloride complexes display good activity at room temperature in the silver-free model cycloisomerization of *N*-propargyl benzamide (Figure 1, right).

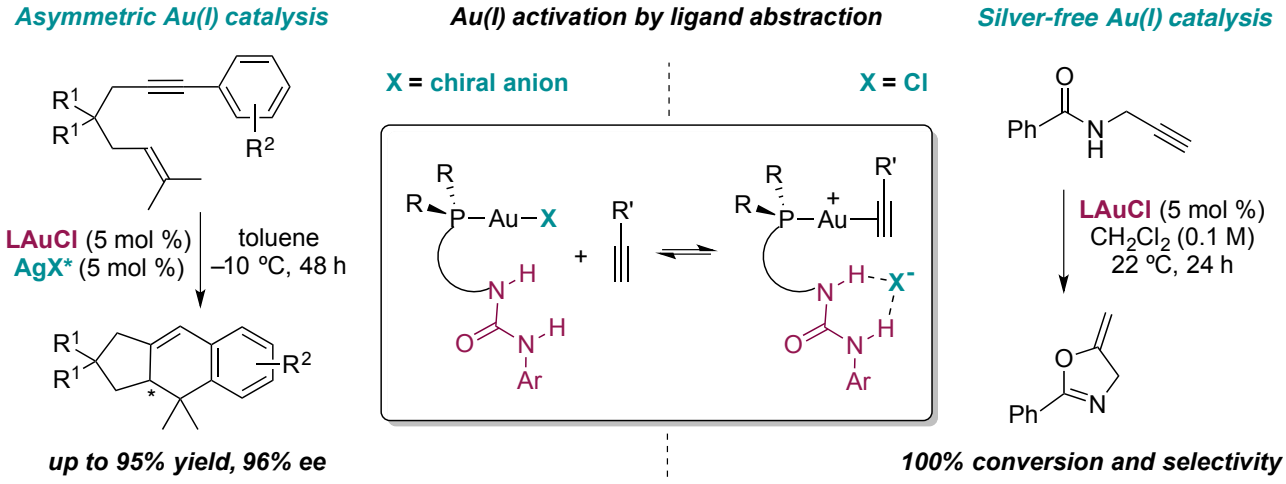

Figure 1: Bifunctional phosphine Au(I) chloride complexes for enantioselective (*left*) or silver-free (*right*) Au(I)-catalyzed reactions of alkynes.

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Carbenoids-Mediated Homologation Pathways for Constructing Functionalized Derivatives

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Homologation event refers to a synthetic operations enabling the formation of a new carbon-carbon or carbon-heteroatom bond through the addition of methylene unit (*e.g.* –CH_2X, X = Halogen, CN, OR).[1] Carbenoids are organometallic compounds employed in organic synthesis in order to realize a homologation event *via* the introduction of a reactive fragment featuring a precise substitution pattern.[2] Functionalized methylenic units (*e.g.* MCH_2X, M = metal, X = halogen) act as nucleophilic synthons enabling the transfer of the CH_2X unit into a proper electrophilic partner. We devoted several studies to design and develop synthetic methodologies paved on the initial C-C bond forged with nucleophilic halomethyl- lithiums that we want to present.[3] Depending on the inclusion (or not) of the halogen(s) inserted with the carbenoid in the final compound, we could individuate three different outcomes for the processes: 1) the *interrupted* homologation in which the halogen(s) remains in the resulting structures thus, being available for later functionalizations; 2) the *ring-closure* through simple internal nucleophilic displacement (*e.g.* Corey-Chaykovski mode) and, 3) the *pure* homologation in which the halogen is conveniently displaced during the molecular rearrangement of the so-formed carbon skeleton, often exploited in ring-enlargement operations.[4] Evidently, the pathway is governed by both the nature of the substrate and the carbenoid. More reactive electrophiles (ketones, aldehydes and, in general, carbonyl-like substrates) are more prone to undergo ring-closure phenomena compared to less reactive ones (Weinreb amides, esters, etc) for which the interrupted homologation is preferentially observed.[5]

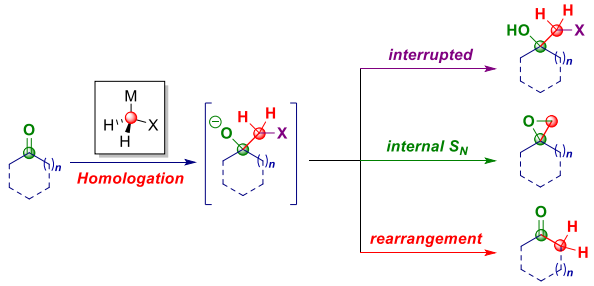

Figure 1: Traditional homologation pathways of a carbonyl with MCH_2X reagents.

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Overcoming Limitations in Dual Photoredox/Nickel catalyzed C–N Cross-Couplings due to Catalyst Deactivation

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Dual photoreodox/nickel catalyzed C–N cross-couplings are an attractive alternative to the palladium catalyzed Buchwald-Hartwig reaction, [1] but are limited to aryl halides containing electron-withdrawing groups. Here we show that the formation of catalytically inactive nickel-black is responsible for this limitation and causes severe reproducibility issues. We demonstrate that catalyst deactivation can be avoided by the combination of nickel catalysis and a carbon nitride semiconductor. [2] The broad absorption range of the organic, heterogeneous photocatalyst enables a wavelength dependent reactivity control to prevent nickel-black formation. A second approach, that is applicable to a broader set of substrates, is to run the reactions at high concentrations to increase the formation of nickel-amine complexes that reduce nickel-black formation. This allows reproducible, highly selective C–N cross-couplings of electron rich aryl bromides and enables efficient reactions of aryl chlorides. By combining an oscillatory pump with a microstructured plug flow photoreactor this semi-heterogeneous dual photoreodox/nickel catalyzed C–N cross-coupling was demonstrated in a multi-gram scale. [3]

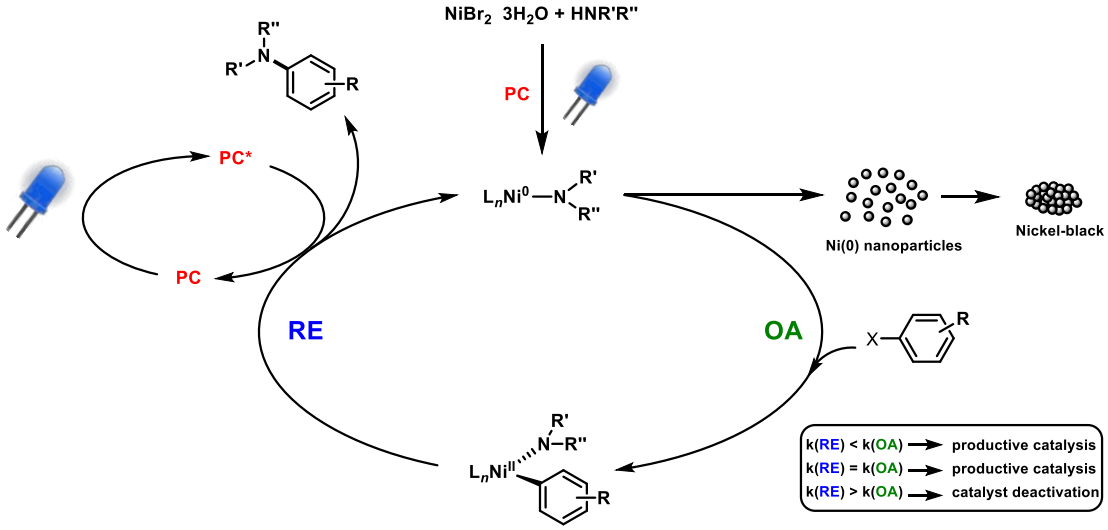

Figure 1: Catalyst deactivation due to photo-generated Ni(0) agglomerates (Nickel black).

References:

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Hydrogen Peroxide: A Powerful Reagent for Green Organocatalytic Oxidations

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The Kokotos' group from the Laboratory of Organic Chemistry of the University of Athens has developed an environmentally friendly, sustainable and organocatalytic oxidation protocol, utilizing H_2O_2 as the oxidant and 2,2,2-trifluoroacetophenone as the catalyst.[1,2] This protocol was extended via the introduction of an one-pot procedure for the isolation of compounds that are highly desirable in Chemical Industry. Utilizing a plethora of substrates bearing useful moieties, we synthesized numerous of isoxazolines, lactones and dihydrobenzofurans in good to excellent yields.[3-5] Furthermore, we extended this organocatalytic oxidative protocol to the selective oxidation of sulfides to either sulfoxides, or sulfones by employing different reaction conditions.[6]

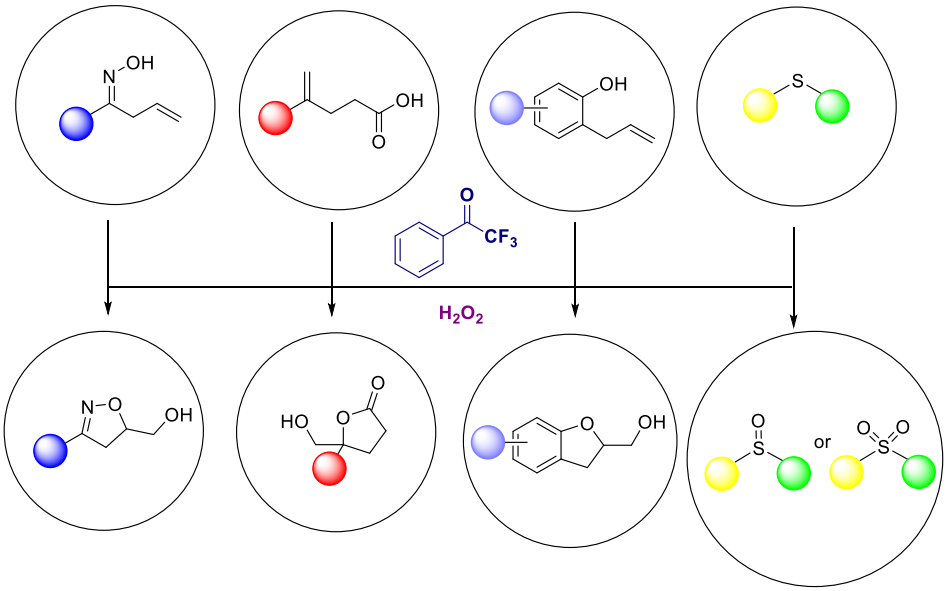

Figure 1: Green organocatalytic oxidations utilizing H_2O_2 and $PhCOCF_3$ as the organocatalyst.

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Triarylborane catalyzed amination reaction: a novel metal-free approach

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Metal-free C-N coupling reactions have drawn considerable interests over the transition metal catalysed reactions as it avoids the problem associated with metal impurities and toxicities. C-N coupled compounds are ubiquitous structural units in natural products, pharmaceuticals, agrochemicals and functional materials.[1] Hence metal-free approach for the facile synthesis of C-N coupled products are highly desirable.

However, forming C–N bonds without a toxic metal catalyst is still one of the major challenges in the field of cross-coupling chemistry. In the last few decades considerable step forwards have been made in this field using metal catalysis exploiting palladium, copper or nickel as catalysts.[2,3]

In the presented work, we have demonstrated a novel metal-free triarylborane catalysed C-N coupling reactions which provide a wide-spectrum platform to address this challenge.

Boron as efficient catalyst has expanded in recent years and triarylborane has demonstrated extensive applications in a wide range of reactions as borylation, hydrogenation, hydrosilylation, C-C coupling reactions.[4]

Objectives of this studies is to use Lewis acidic borane as efficient catalyst for the coupling between varieties of disubstituted carbon compounds and commercially available nitrogen nucleophiles to afford the C-N coupled products using mild reaction condition. Direct amination of a wide range of poly-functionalized building block-molecules, which allowed the synthesis of nitrogen-containing molecules of remarkable pharmaceutical interest, avoiding high-priced, toxic metals and in a substantially greener fashion has been investigated.

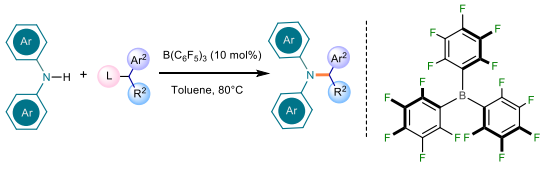

Figure 1: Triarylborane catalysed N-alkylation of amines with aryl esters.

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Phytotoxic metabolites produced by the fungal pathogens of forest trees: *Hymenoscyphus fraxineus* and *Fimetariella rabenhorstii*

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Pathogenic fungi are one of the main causal agents of forest plant diseases causing huge economic and environmental losses especially for greenhouses and wood industries. Pathogenic fungi are able to produce phytotoxins, i.e. secondary metabolites, which are involved in different steps of plant diseases inducing different symptoms. These metabolites belong to different classes of natural compounds and they could show biological properties of biotechnological interest.[1,2]

The European ash (*Fraxinus excelsior* L.) epidemic disease, known as "ash dieback", is caused principally by the alien and invasive pathogen *Hymenoscyphus fraxineus*. The fungus induces on woody hosts wilting and V-shaped necrotic sector visible in trunk cross section. A new toxin has been isolated, together with four known furanoditerpenoids, from the organic extract of the *H. fraxineus* culture filtrate.[3]

Fimetariella rabenhorstii is an endophytic fungus and recently identified as a specie associated with symptomatic *Quercus brantii* trees in Kurdistan (Iran). Two new phytotoxins have been isolated from the organic extract of the fungal culture filtrate together with the known moniliphenone and coniochaetone A.[4]

In this oral communication the isolation and the chemical and biological characterization of the new phytotoxins produced by *H. fraxineus* and *F. rabenhorstii* will be described.

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Towards the emergence of modern cells

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The complexity of modern biochemistry suggests that a systems chemistry approach is required to understand and potentially recapitulate the intricate network of prebiotic reactions that led to the emergence of life. Early cells probably relied upon compatible and interconnected chemistries to link RNA, peptides and membranes. In this context, understanding how and when phospholipid membranes appeared on early Earth is critical to elucidating the prebiotic pathways that led to the emergence of primitive cells. Starting with a mixture of activated carboxylic acids of different lengths, iterative cycling of acylation and hydrolysis steps allowed for the selection of longer-chain acylglycerol-phosphates through accumulation-induced compartmentalization of self-assembling amphiphiles at the expense of non-self-assembling shorter chain analogues.[1] Our results suggest that a selection pathway based on energy-dissipative cycling could have driven the selective synthesis of phospholipids on the early Earth. Moreover, I will show that several types of vesicles, formed from prebiotically plausible mixtures of amphiphiles, allow activation of amino acids, peptides and nucleotides (Figure 1). Interestingly, activation chemistry drives the advantageous conversion of reactive amphiphiles into inert cyclophospholipids, thus supporting their potential role as major constituents of primitive cells. Activation of prebiotic building blocks within fatty acid-based vesicles yields lipidated species capable of localizing and functionalizing primitive membranes. Our findings describe a potentially prebiotic network of reactions in which the components of primitive cells could have selectively undergone activation and reacted to yield new species, which enabled the emergence of cells with increasingly advanced functionalities.[2]

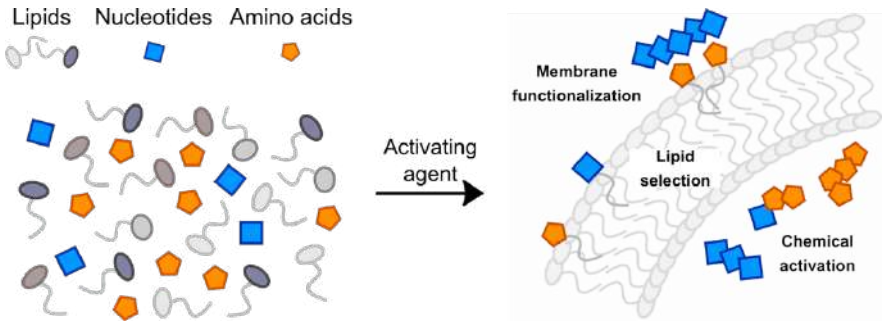

Figure 1: The constituent monomers of primitive lipid membranes could coexist with nucleotides and amino acids, thus driving activation chemistries, lipid selection and membrane functionalization.

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Mechanistic insights in the rotational path of novel molecular motors

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Artificial molecular machines are a topic of current interest due to their potential to control and exploit dynamics in molecular systems, materials and devices. The photochemically driven overcrowded alkene-based molecular motors were pioneered in 1999,[1] and since then this "traditional" scaffold has been widely explored and major advances in molecular motor designs have been achieved (see Figure 1). Not only has this uncovered fascinating fundamental research into the control of dynamic movement at the nanoscale, but molecular motors have already been explored in applications towards smart materials and biomedical sciences. With this basis of photochemically driven motion established, the field has recently opened to new photochromic scaffolds – such as imines, N-alkylated indanylidene pyrrolidinones and hemithioindigos – that can undergo unidirectional 360° rotations, and these new scaffolds are exploited for their different functions.[2]

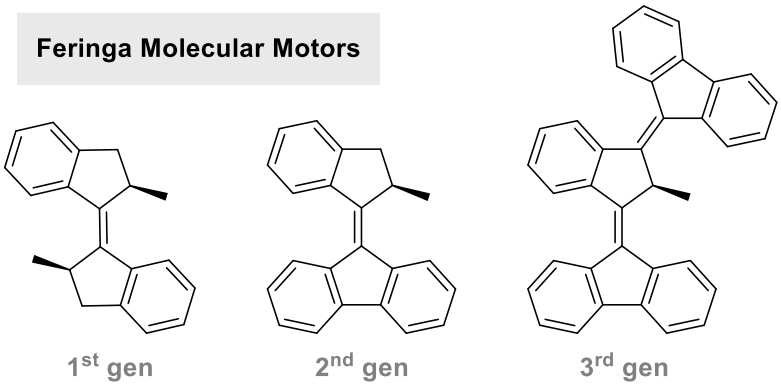

Figure 1: Different generations of Feringa-type molecular motors.

The tools offered by physical organic chemistry allow to design and understand novel structures and discover the mechanisms underlying their unidirectional rotation.[3,4] New molecular motors structures that aim to overcome the limitations of the typical Feringa-type molecular motor will be presented, along with their more prominent mechanistic features.

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Hydroxysteroid Dehydrogenases: an enzymatic entry to chiral alcohols

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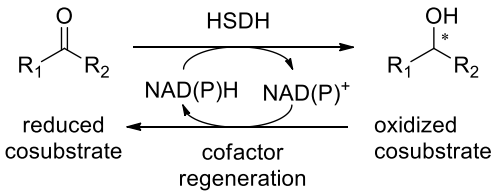
Bacterial hydroxysteroid dehydrogenases (HSDHs) are NAD(P)H-dependent enzymes that belong to the superfamily of short-chain dehydrogenases/reductases (SDRs). These enzymes display peculiar features that make them attractive for industrial applications. Indeed, they catalyse the reversible oxidoreduction of the hydroxyl/keto groups of steroidal compounds with selectivity, being highly regioselective for specific hydroxyl groups at different positions of the steroidal skeleton (*e.g.*, at C-3, C-7, and C-12). Additionally, for each one of these positions, different HSDHs usually display high stereoselectivity, discriminating the hydroxyl group above the plane of the steroid molecule (β configuration) from the one below (α configuration).[1] Although these enzymes have been thoroughly investigated during the last years, little is currently known regarding their possible uses on alcoholic or ketonic substrates that differ from steroids.[2]

In order to fill this gap, the substrate promiscuity of a library of fifteen different 7α-, 7β-, or 12α-HSDHs, originated both from known and well-characterized microbial sources as well as from newly identified (meta)genomic sequences and prepared by recombinant expression in *E. coli*, was investigated. Accordingly, these enzymes were tested for the stereoselective reduction of a panel of carbonyl substrates, as shown in Scheme 1. The screened compounds include selected ketones that partially resemble the structural features of steroids and two α-ketoesters of pharmaceutical interest. All the reactions were optimized and coupled with a suitable cofactor regeneration system.[3]



Scheme 1: stereoselective reduction of ketonic moieties catalyzed by HSDHs.

Nearly all of the tested HSDHs showed a good activity toward simple α-ketoesters, yielding the reduced α-hydroxyester with high conversion and high enantiomeric excess. Moreover, few of the screened HSDHs showed an appreciable activity toward complex ketone substrates with promising selectivity.

Part of this work has been recently published,[3] but the study is ongoing to better characterize the substrate scope of HSDHs.

References:

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A modular, self-assembling metallaphotocatalyst for cross couplings using the full visible-light spectrum

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The combination of photo- and nickel catalysis (metallaphotocatalysis) has emerged as a powerful strategy for carbon–carbon and carbon–heteroatom cross couplings.[1] Key to the success are redox or photosensitization events between a nickel- and a photocatalyst (PC). These protocols rely on a few photocatalysts that can only convert a small portion of visible light (<500 nm) into chemical energy. The high-energy photons that excite the photocatalyst can result in unwanted side reactions. Dyes that absorb a much broader spectrum of light are not applicable due to their short-lived excited states. We demonstrate a self-assembling catalyst system that overcomes this limitation. Immobilization of a nickel catalyst on dye-sensitized titanium dioxide results in a material that catalyzes carbon-heteroatom and carbon-carbon bond formations. The modular approach of dye-sensitized metallaphotocatalysts (DSMPs) accesses the entire visible light spectrum and allows tackling selectivity issues resulting from low-wavelengths strategically. The concept overcomes current limitations of metallaphotocatalysis by unlocking the potential of dyes that were previously unsuitable.[2]

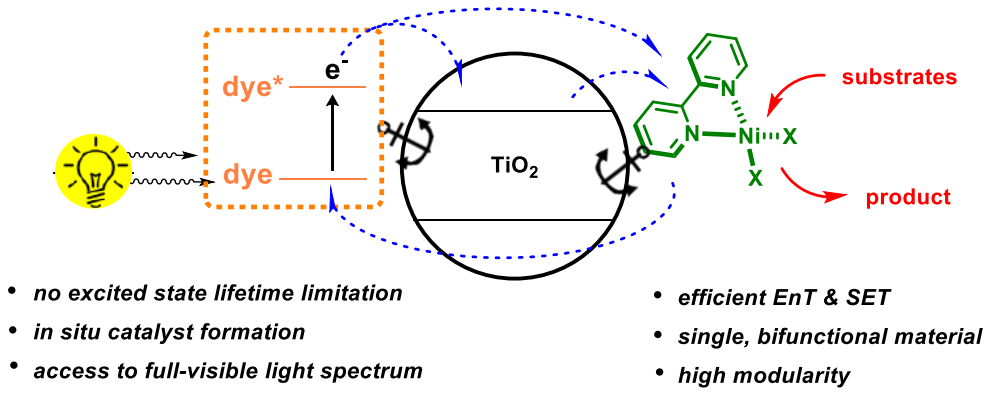

Figure 1: Concept of dye-sensitized metallaphotocatalysts (DSMP) overcoming excited state lifetime limitations.

References:

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[2] S.Reischauer, V. Strauss, B. Pieber, ChemRxiv. Preprint https://doi.org/10.26434/chemrxiv.12444908

Thioxanthen-9-one: A Powerful Organocatalyst for Photochemical Organic Transformations

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Photoredox Catalysis has brought a revolution in the field of modern Catalysis. Photoorganocatalysis, the use of small organic molecules as promoters for photochemical transformations, has provided new chemical reactivities and synthetic pathways through the mild generation of radical species. The Kokotos group has developed a number of methods that harness the power of light through the use of small organic molecules. Herein, we report that thioxanthenone is a potential alternative to the expensive metal-based photocatalysts, opening a new pathway combining photochemistry with greener attitude and sustainability. Herein, the use of thioxanthenone will be presented to be employed in a photoorganocatalytic protocol for the synthesis of acetals from aldehydes[1,2] and in a photochemical oxidation protocol of alcohols providing the corresponding aldehydes and ketones,[3] utilizing air as the oxidant.

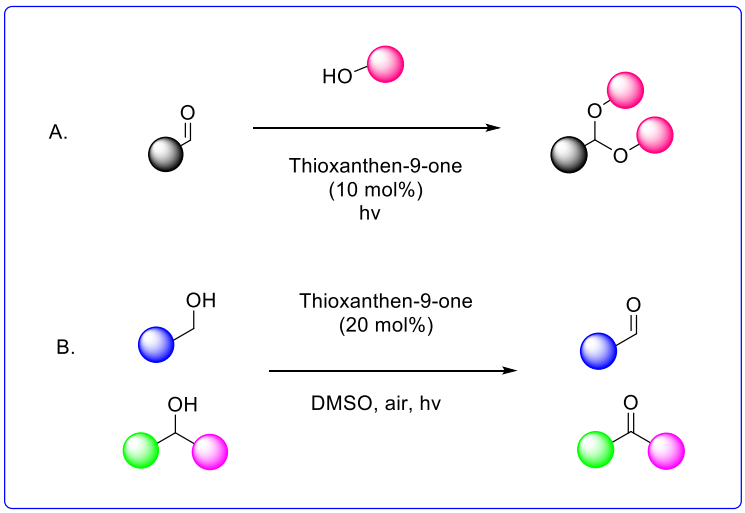

Figure 1: Thioxanthenone-mediated photochemical transformations.

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Photocatalytic Umpolung Synthesis of α-Functionalised Ethers

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Dialkyl ethers are ubiquitous chemical architectures in biologically relevant molecules, from active pharmaceuticals to natural products.[1,2] Despite the relevance of this structural unit, several challenges remain to be addressed to access these compounds, especially towards the synthesis of sterically hindered α-tertiary dialkyl ethers.[2] Over the past decade, photoredox catalysis has expanded the synthetic toolbox due to its unique capacity to generate nontraditional sites of reactivity from common functionalities.[3] In this context, we have developed two efficient photocatalytic methodologies for the construction of dialkyl ethers from readily available starting materials.[4,5] Pivoting on *in situ* generation of oxocarbenium ions – from ketals/acetals[4] and enol ethers[5] – followed by photocatalytic single-electron reduction to generate α-alkoxy radicals, efficient Giese-type reactivity to a variety of electrophilic coupling partners is demonstrated, affording complex α-tertiary dialkyl ether structures in moderate to excellent yield.

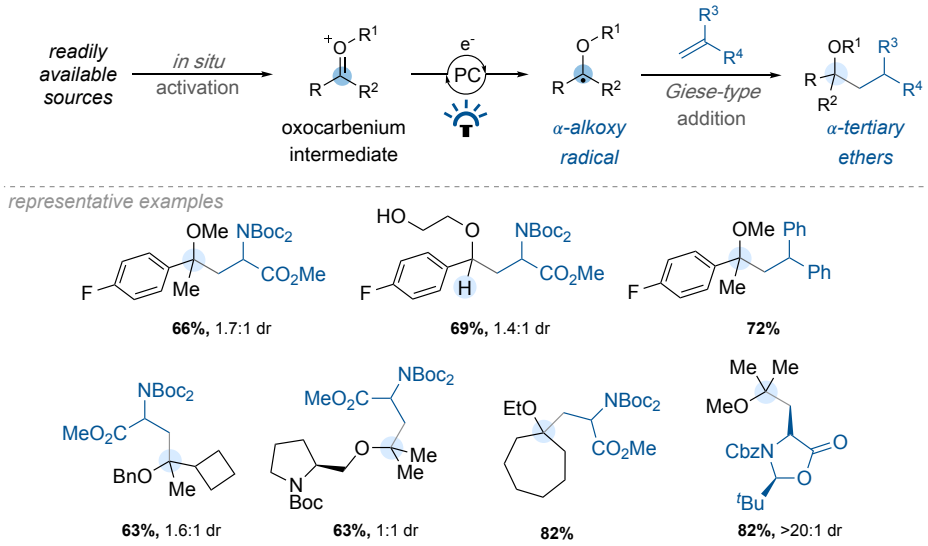

Figure 1.

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A visible light-mediated oxidative debenzylation strategy

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Orthogonal protecting groups are of utmost importance in the total synthesis of complex molecular scaffolds. The chemical synthesis of oligosaccharides, for example, requires the appropriate choice of orthogonally protected building blocks that carry temporary (*t*PG) and permanent protecting groups (*p*PG).[1]

The limited availability of non-participating, temporary PGs represents a bottleneck in carbohydrate synthesis.[2] Benzyl ethers are suitable non-participating PGs, but they are regarded as *p*PG due to the harsh deprotection conditions (catalytic hydrogenolysis, Birch reduction) that suffer from poor functional group tolerance.

We developed a mild, visible light-mediated debenzylation protocol using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as photo-oxidant that can be either used in stoichiometric or catalytic amounts. A high functional group tolerance was achieved using 525 nm irradiation as demonstrated for several carbohydrate building blocks equipped with multiple protecting groups. A flow approach can be used to significantly enhance this protocol, reducing the reaction times from hours to minutes. Benzyl ether can be cleaved in presence of azides, alkenes and alkynes, and other functionalities that are not stable using traditional debenzylation strategies. This protocol enables use of benzyl ether as orthogonal, temporary PG in synthetic chemistry.

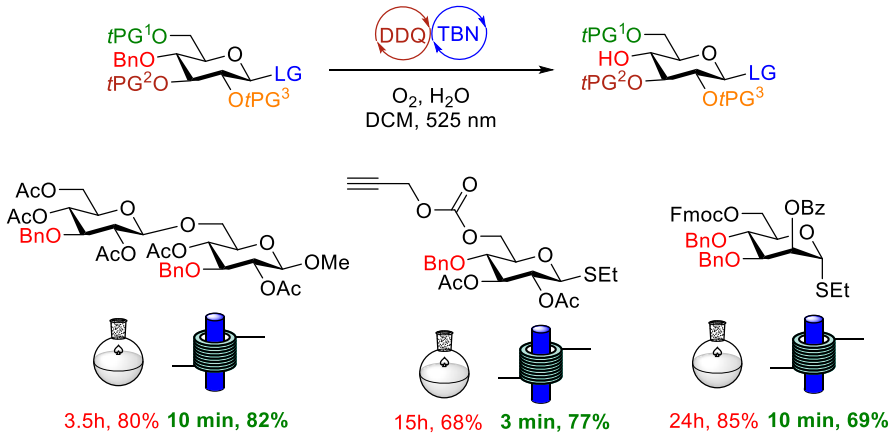

Figure 1: Visible light-mediated oxidative debenzylation: reaction conditions and comparison between batch and flow for selected examples.

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Flash communications

F01	Giada Moroni
F01	Antonella Ilenia Alfano
F03	Enrico Cadoni

Design, Synthesis and Characterization of Thermochemiluminescent Acridine-Containing 1,2-Dioxetanes as Ultrasensitive Labels for Bioanalysis

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Thermochemiluminescence (TCL) is the proton emission originating from the thermolysis of relatively unstable molecules yielding a product in an excited state, which decays emitting light. TCL represents an innovative reagent-less sensitive detection approach for bioanalytical applications. However, to fully exploit its advantages, TCL labels with low emission-triggering temperatures (80-110 °C) and high detectability are required.[1] To remove the limitations of previously reported compounds, novel acridine-containing 1,2-dioxetanes, combined with the latest progress in nanotechnology, have been recently proposed.[2]

In this context, this work is focused on the design and synthesis of TCL compounds containing a N-substituted acridine and a 1,2-dioxetane moiety using enabling chemical technologies as flow synthesizers and photochemistry.[3] To improve the photochemical properties, the acridine scaffold was variably functionalized with different electron donating and electron withdrawing groups, thus balancing the electronic effect of different substituents (**Figure 1**). The aim is obtaining a library of stable molecules that can efficiently generate TLC emission with a trigger temperature below 100 °C.

The great versatility and innovation of these molecules make them extremely attractive as ultrasensitive probes in bioanalytical applications, such as labels for immuno and gene probe assays.

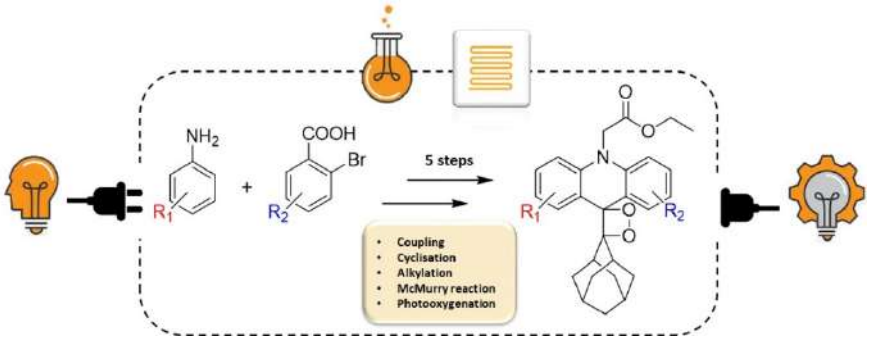

Figure 1: General scheme for the synthesis of acridine-based 1,2-dioxetane derivatives.

References:

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Continuous flow synthesis of (spiro)indolines and (spiro)indolenines

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Organic synthesis is an enabling science with immense impact in many areas of research, including modern medicine and biology. The field of organic synthesis has markedly expedited drug-discovery and drug development research since the late 20th Century, leading to the development of numerous breakthrough medicines and first-in-class drugs. Over the recent years, however, the environmental impact of drug fabrication has become a serious problem in the world, and the management of pharmaceutical wastes became a crucial focus for the pharmaceutical industries. Yet, the pharmaceutical sector has received only very little attention from the 'sustainability community' in terms of its contribution to the global carbon footprint. The need for more efficient and sustained research as well as more scrutiny in the pharmaceutical industry and adjacent chemical industries to reduce overall environment impact lead to the emerging importance of "green chemistry" and sustainability concepts applied to the pharmaceutical production. In this context, flow chemistry can be seen as one of the most innovative technological approaches towards a greener and more sustainable organic synthesis. Flow chemistry realises reactions in "microreactors" or' meso-scale' reactors, and facilitates performing fast screening of the reaction conditions, fast library generation and, once optimised, scale-up.[1,2]In our presentation, we report the application of this technology-based greener synthesis approach to the formation of privileged (spiro)indolenine and (spiro)indoline scaffolds.[3,4] The aim was to demonstrate that these new technologies do not only serve to obtain efficient synthetic routes suitable for facile scale-up, but that they additionally help to comply with environmental constraints. Our flow chemistry protocol for the synthesis of 3,3-disubstituted indolenines is chemically based on interrupted Fischer indolisation reactions. The screening and systematic optimization of a variety of reaction conditions, *e.g.*, reagent mixing, temperature, residence time, led to the identification of a reliable protocol which allowed for a straightforward and scalable route for the preparation of 3,3-disubstituted indolenines, applying ethanol as green solvent. We further broadened the approach coupling the indolenine flow synthesis to a reduction step in semi-flow mode to achieve formation of corresponding indolines. The telescoped approach allowed generation of a library of indolenines and indolines with limited solvent consumption for both reactions and work-up procedures, and required minimum operator input. This newly developed protocol also displays the potential to turn into an effective coupling point for additional flow reactions for multistep syntheses.

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Visible-light triggered templated ligation on surface using furan-modified PNAs

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Oligonucleotide templated reactions, both exploiting the formation of a covalent linkage (templated ligation) or inducing the modification of one of the two strands, are becoming widely employed in sensing strategies.[1] The main problems related to these reactions are connected to hydrolysis or degradation of the reactive moieties, thus requiring special precautions to maintain the integrity of the system. The exploitation of external stimuli for the activation of a pro-reactive unit can be a valid alternative to extend the shelf-life of probes and devices, allowing spatiotemporal control over system reactivity and avoiding collateral reactions. In this context, the exploitation of visible light-triggerable systems offers several advantages: the wavelength can be modulated in order to achieve biocompatibility, and its use is universally considered as eco-sustainable.[2]

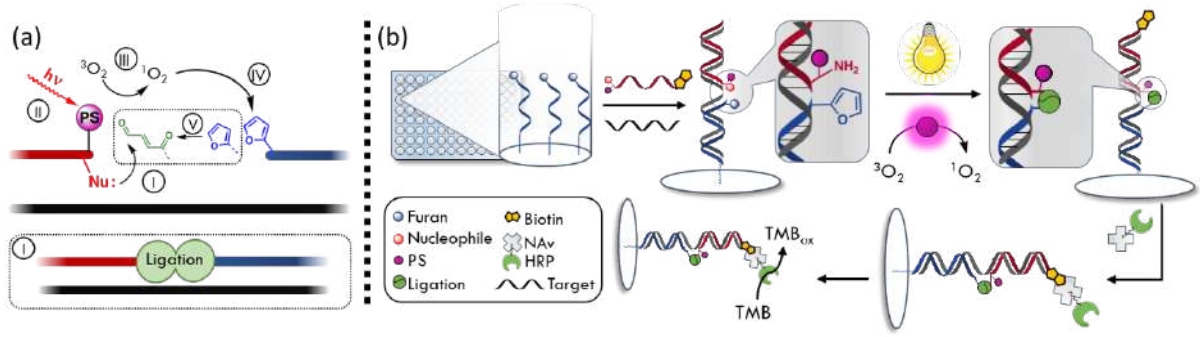

Figure 1. (a) Light-triggered templated ligation. (b) Cartoonist representation of the templated ligation on surface in a 96-well plate format. Visible light irradiation of a photosensitizer allows excitation of molecular oxygen into reactive singlet oxygen. $^1O_2$ then acts as mediator for furan oxidation. The generated keto-enal further reacts with a nucleophile for the formation of a ligation product. (I) Ligation reaction; (II) activation of the antenna system (photosensitizer); (III) activation of a mediator (from $^3O_2$ to $^1O_2$); (IV) chemical activation of the pro-reactive furan; (V) properties change.

We here report a novel peptide nucleic acid (PNA) based D(R)NA-templated ligation exploiting a stable pro-reactive furan ring which can be oxidized to a reactive keto-enal,[3] via light induced singlet oxygen production,[4] and chemoselectively reacts with suitable nucleophiles (see Figure 1A). This white light triggered templated PNA-PNA ligation was first optimized in solution so that the only external action required was light irradiation. It was then transferred to surface for the realization of a 96-well plate biosensor for selective detection of 22mer D(R)NA, in an ELISA-like platform (Figure 1B). Application of this methodology on the glass surface of microarray slides was also demonstrated, showing the feasibility of the methodology and the possibility to move toward the miniaturization of the system for high-throughput label-free multiplex analysis applications.

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Poster communications

P01	Roberta Amuso	P23	Matteo Gastaldi
P02	Ioannis Anastasiou	P24	Marco Giordano
P03	Rita Argenziano	P25	Giuliana Giorgianni
P04	Marco Ballarotto	P26	Marco Grunwald
P05	Giuliana Baronissi	P27	Alberto Lanfranco
P06	Floriana Billeci	P28	Melania Lettieri
P07	Giorgiana Denisa Bisag	P29	Valeria Lino
P08	Francesca Cadamuro	P30	Camilla Loro
P09	Claudia Maria Cafiero	P31	Gabriele Lupidi
P10	Carla Calabrese	P32	Alberto Luridiana
P11	Nicola Camedda	P33	Stefano Mancuso
P12	Filippo Campana	P34	Enrico Marcantonio
P13	Marcello Casertano	P35	Filippo Marchetti
P14	Chiara Cavagnero	P36	Stefania Marzorati
P15	Andrea Citarella	P37	Federica Moccia
P16	Andrea Cocco	P38	Anthony Morena
P17	Alessio Dessì	P39	Riccardo Moro
P18	Max Ebert	P40	Rita Nasti
P19	Tommaso Fantoni	P41	Stefano Nejrotti
P20	Francesco Ferlin	P42	Paolo Novelli
P21	Claudia Finamore	P43	Vincenzo Patamia
P22	Ambra Maria Fiore	P44	Riccardo Pedrazzani

P45	Marzia Petrilli	P54	Silvia Scarpato
P46	Simone Potenti	P55	Finn Schulz
P47	Pasquale Rapacciuolo	P56	Martina Sciarretta
P48	Paolo Ravarino	P57	Daniele Sciosci
P49	Giacomo Renno	P58	Arianna Sinibaldi
P50	Patrizio Russo	P59	Romina Strangis
P51	Nihad Salameh	P60	Francesca Valentini
P52	Sara Sangiorgio	P61	Veronica Vida
P53	Federica Santino	P62	Jacopo Vigna

Synthesis of new 1,3-oxazindionic derivatives by carboxylation reaction of 3-ynamides

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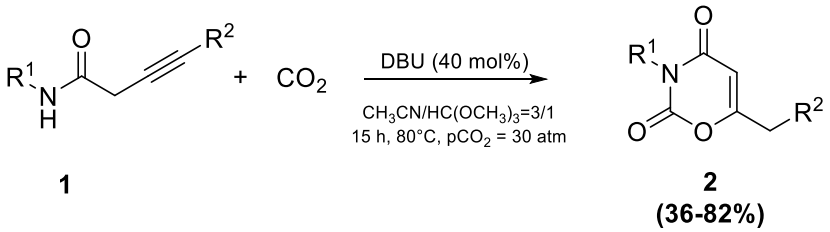
1,3-Oxazinedione derivatives **2** are a very important class of heterocyclic compounds. A variety of molecules incorporating this heterocyclic motif has shown a wide range of biological activities,[1,2] including antimicrobial, anti-ulcer and anticoagulant activity.[3]

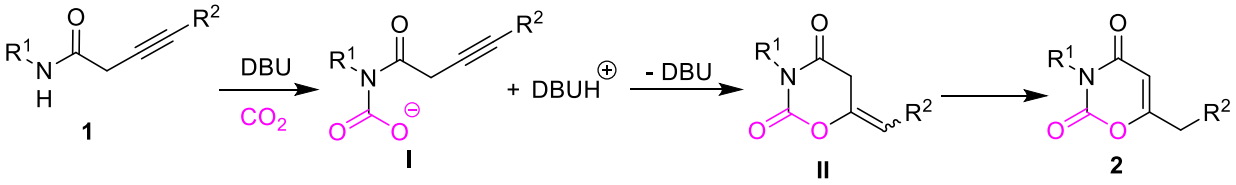
In this communication, we report a novel synthesis of 1,3-oxazinediones **2** by catalytic incorporation of CO_2 into readily available alkynylynamides **1**. Reactions are carried out in the presence of DBU as catalyst, (40 mol%), in a 3/1 $CH_3CN/HC(OCH_3)_3$ solvent mixture, at 80°C for 15 h under 30 atm of CO_2. Products **2** are obtained in moderate to high isolated yields (36-82%, Scheme 1).



1 **2** **(36-82%)**

Scheme 1. Synthesis of 1,3-oxazinedione derivatives by catalytic incorporation of CO_2 into ynamides.

The proposed mechanism for this carboxylation reaction involves: acid-base reaction in which DBU deprotones the amide nitrogen of substrate **1**; *6-eso-dig* cyclization of the carbamate intermediate **I** followed by protonation by $DBUH^+$ with formation of intermediate **II**; isomerization of **II** to give the 1,3-oxazinedione product **2** (Scheme 2).



1 **I** **II** **2**

Scheme 2: Proposed mechanism for the DBU-catalyzed carboxylation of 2-ynamines.

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[4]

Heterogeneous Pd-Catalyzed C(sp3)-H Arylation in flow

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The creation of new carbon-carbon or carbon-heteroatom bonds by C(sp^3)-H activation is currently one of the most challenging fields in organic chemistry.[1] A significant success has been observed in transition-metal catalysis and particularly in Pd-catalyzed C-H activation reactions.[2]

Despite that, the large-scale adoption of C–H activation reactions techniques outside of academia is still hampered by some limitations, like the harsh reaction conditions and high catalyst loading. Among the possible solutions aimed at overcoming these limitations, flow technologies may represent a very promising tool for improving the larger applicability on the C-H activation processes.[3] Many C-H activation protocols have been developed since today, under both homogeneous and heterogeneous flow conditions. However, there are very few examples of flow processes for C(sp^3)-H activation, and even less in heterogeneous continuous flow conditions.[4]

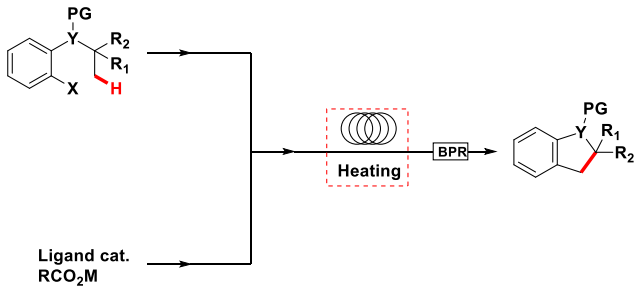

Figure 1: Flow process for C(sp^3)-H arylation

In these study we investigate the heterogeneous Pd(0) catalyzed C(sp^3)-H arylation. The approach is characterized by the use of a reusable heterogeneous catalytic system. Moreover, we also investigated a continuous-flow procedure which allows the production of C–H arylated products on bigger scale.

Acknowledgments: Università degli Studi di Perugia and MIUR for financial support to the project AMIS, through the program “Dipartimenti di Eccellenza 2018-2022”

References:

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5,6-dihydroxyindole derivatives for melanin-based functional antioxidant and film forming systems

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The development of innovative and versatile dip-coating technologies for surface functionalization has been a very active issue over the past decade following the discovery of the extraordinary wet adhesion properties of polydopamine (PDA), a black insoluble eumelanin-like material inspired to the robust adhesion properties of catechol- and amine-rich mussel byssus proteins.[1,2] New opportunities in PDA based surface chemistry have derived from the discovery that hexamethylenediamine (HMDA) markedly enhances film deposition from the polymerization of dopamine and a variety of catechol substrates, including the key eumelanin precursor 5,6-dihydroxyindole (DHI), leading to films with attractive properties in terms of morphology and functionalities. Recent studies have provided evidence for the remarkable antioxidant properties of synthetic eumelanins from the other primary melanin precursor 5,6-dihydroxyindole-2-carboxylic acid (DHICA) and its methyl ester (MeDHICA).[3] Full exploitation of these materials would greatly expand might the reaction with HMDA confer adhesive properties. On this basis this work was aimed at i) assessing whether HMDA can promote film deposition from other eumelanin precursors besides DHI, in particular MeDHICA ii) investigating the mechanisms by which HMDA can induce film deposition from non-adhesive melanin type polymers; iii) evaluating the antioxidant properties and biological compatibility of the films from MeDHICA/HMDA. MeDHICA was prepared by a biomimetic one-pot synthesis from DOPA methyl ester. The oxidative polymerization of MeDHICA was run in aqueous buffers at pH 9.0 at different concentrations and in the presence of HMDA at different molar ratios. The most promising results were obtained using MeDHICA and HMDA at 1 mM at 1:1.5 molar ratio. Under these conditions a light brown pigment is formed over 24 h exhibiting good film forming properties on glass and quartz slides or on polystyrene supports. HPLC analysis of the film solubilized in organic solvents indicated a mixture of oligomers of MeDHICA up to hexamers. Further polymerization of the film was obtained by exposure to ammonia vapors or by irradiation at 310 nm. The antioxidant potential of the films obtained was evaluated by two widely used chemical tests. The biocompatibility of the MeDHICA/HMDA films and the ability to support cell growth was assessed using HaCat cells.

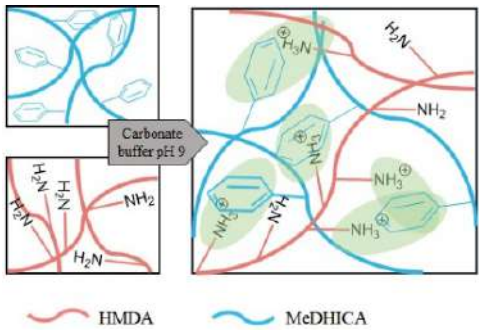

Figure 2. MeDHICA/HMDA film forming mechanism.

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Diels-Alder approach to the synthesis of highly substituted 6*H*-benzo[c]chromenes

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The 6*H*-benzo[c]chromene core is a commonly observed motif in numerous natural products and synthetic biologically active molecules, thus occupying a prominent role in medicinal chemistry.[1,2] A few notable examples are found in the cannabinoid family, of which tetrahydrocannabinol (THC) and cannabinol (CBN) are well known representatives. Due to its pharmacological importance, the development of a protocol for an efficient synthesis of this scaffold is an ambitious target for both medicinal and organic chemists.

The classical synthesis begins with two aryl fragments that are at first coupled using a transition metal catalyst and then cyclized, or vice versa. Although this approach allows for the rapid synthesis of variably substituted compounds for screening purposes, the low functional group tolerance and the required purification from the catalyst hinder the possibility for production on a larger scale.[3]

Here we report our results towards a transition metal-free synthetic protocol for highly substituted 6*H*-benzo[c]chromenes. The *de novo* construction of the 3,4-fused benzene ring has been achieved through a Diels-Alder cycloaddition followed by aromatization of the intermediate cycloadduct to obtain the desired compounds.

Starting from commercially available salicylaldehydes, α,β-unsaturated carbonyl compounds and alkynes substituted with an electron withdrawing group, the chromene core is quickly assembled in a 3-step sequence. The degree of substitution of the final product can be easily modulated by choosing the appropriate starting materials.

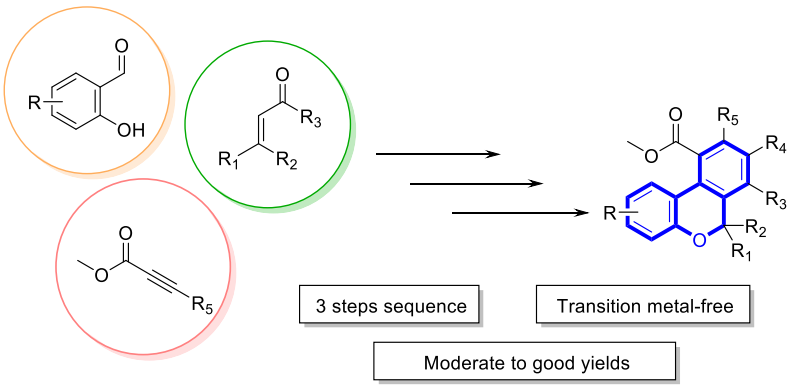

Figure 1: General scheme for the synthesis of benzo[c]chromenes.

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Design and Synthesis of Novel Quinoline Derivatives for the Treatment of Inflammatory Bowel Disease.

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Inflammatory bowel disease (IBD) is a chronic condition of the gastrointestinal tract. The etiology of IBD remains unknown, but its pathogenesis is associated with dysregulated immune responses that drives a persistent inflammatory state within the intestinal mucosa. Recently, an increasing number of NRs has been validated as potential drug targets for therapeutic interventions in patients with IBD. Moreover, new evidence suggests that also some G protein-coupled receptors (GPCRs) are critical signaling molecules implicated in the immune response, cell proliferation, inflammation regulation and intestinal barrier maintenance.[1] In particular, cysteinyl leukotriene receptor type 1 ($CysLT_1R$) along with $CysLT_2R$ are two G protein coupled receptors (GPCRs) activated by the three endogenous leukotrienes LTC_4, LTD_4, and LTE_4. $CysLT_1R$ is broadly expressed in most types of leukocytes, lung, spleen, intestines, pancreas, prostate, and smooth muscle. It is a key player in allergic and inflammatory disorders and is involved in cardiovascular diseases and several types of cancer.[2] In addition, antagonizing $CysLT_1R$ has been demonstrated useful in reducing colonic inflammation caused by IBDs. A library of selected group of $CysLT_1R$ antagonists was investigated for the effect on the main bile acid receptors (GPBAR1 and FXR). Results showed that REV5901, a well-known CysLT1R antagonist, is an agonist of GPBAR1 (EC_{50} of 2.5 μM).[3] In two different rodent models of colitis, REV5901 attenuated inflammation and immune dysfunction in a GPBAR1-dependent manner. Therefore, we recently focused our efforts on the manipulation of the quinoline scaffold of REV5901 in order to obtain a new library of compounds with improving CysLT1R antagonist/GPBAR1 agonist dual modulation.

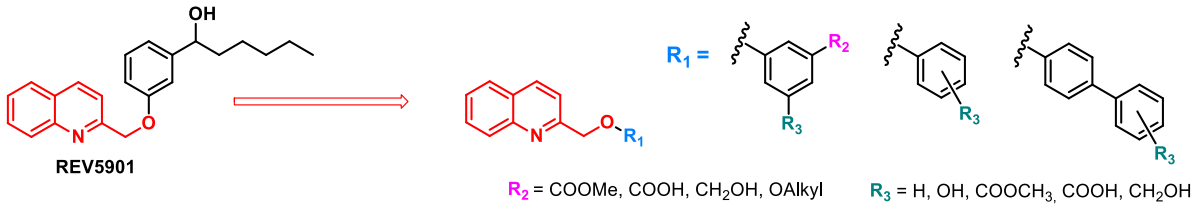

Figure 1. REV5901 derivatives

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Fluorescent interaction Eu-IL: when the anion plays a role

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Ionic Liquids (ILs) are well-known for their advantageous properties. Their wide use has led to a growing interest both on the improvement of the properties and the minimisation of environmental impact. In the light of this, in this work, we synthesized imidazolium ILs (imILs) bearing on the cation structure a moiety deriving from natural starting materials (Figure 1-a).

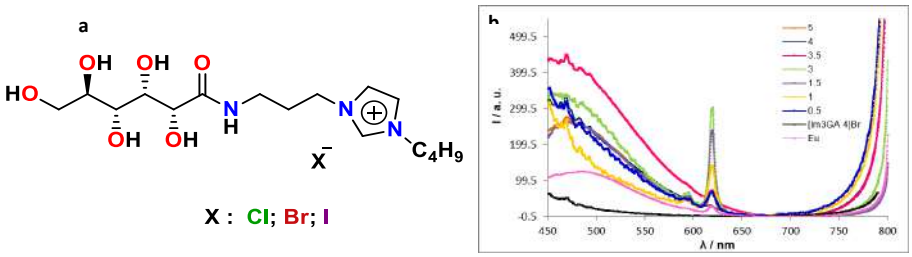

Figure 1: a) structure of imILs synthesised; b) fluorescence spectra increasing ligand/Eu ratio for the system: $[Im_{3GA\ 4}]Br + Eu^{3+}$ in $[C_1C_4pyrr][NTf_2]$.

Despite of the aromatic nature of the cation, these imILs showed very low cyto- and eco-toxicity.[1] Their tunable structure led us to study the possible formation of complexes with Eu^{3+} ion (from $Eu(NO_3)_3$ hydrate salt). Indeed, the combination of ILs with *f*-element compounds could be the way to design new luminescent materials for organic light-emitting diodes (OLEDS).[2]

The interaction among imILs and Eu^{3+} was studied recording fluorescence spectra (Figure 1-b) at different ligand/Eu^{3+} ratios to achieve the highest luminescence in solution. Fluorescence intensity depends on the halo-anions of the ligands, indeed the different chemical interaction "cation-halo-anion"[3] in IL ligand affects the coordination and the fluorescence properties of the complexes.

Moreover, the effect due to the nature of the solvent used to dissolve Eu salt and IL ligand was also studied.

For all the systems the Jobs plots were recorded to study the stoichiometry of the complexes. These systems were also investigated by using ^1H NMR. Conductivity investigation was also performed.

These preliminary analyses allowed obtaining promising results and further investigation will be carried out to obtain red-fluorescent materials.

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Unexpected synthesis of 2*H*-chromenes from sulfoxonium ylides and salicylaldehydes: discovery, development and mechanistic insights

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Sulfur ylides are formal internal salts characterised by a carbanion flanked by a positively charged sulfur atom. These ylides can be divided into two main classes, sulfonium and sulfoxonium ylides,[1] depending on sulfur oxidation state. Sulfoxonium ylides are able to react via a typical (2 + 1) pathway with a broad range of carbonyl compounds, such as ketones/aldehydes,[2] imines,[3] and α,β-unsaturated systems.[4] However, sulfoxonium ylides display also less conventional reactivity, and are even capable of undergoing different (catalyzed) insertion reactions[5] into X-H, C-H, C-X and X-Y bonds. For these latter reactions, sulfoxonium ylides are considered appealing alternatives to the arguably problematic diazo compounds.

This communication presents the reaction between sulfoxonium ylides and salicylaldehydes, in the presence of diphenylphosphate as catalyst. The literature reports the reaction of unstabilized sulfoxonium ylide with these aldehydes, but giving benzofurans as products.[6] In contrast, using a stabilized sulfoxonium ylide, a 2*H*-cromene scaffold was recovered from the reaction mixture. Moreover, performing the reaction with electron-poor salicylaldehydes, a peculiar five-membered ring is formed, even in the absence of a catalyst (Figure 1). Mechanicistic insight and comparison with the reactivity of sulfonium ylides are also given.

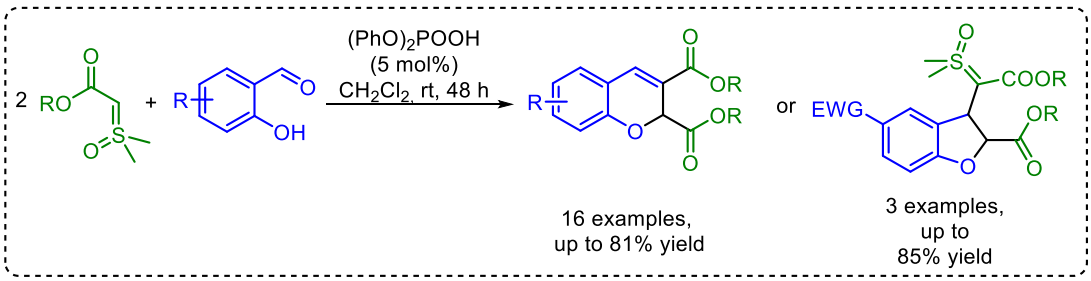

Figure 1: tandem cyclization between sulfoxonium ylides and salicylaldehydes

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Synthesis of glyco-conjugate biomaterials to study the effect of extracellular matrix glycosignature in cell fate modulation

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Cell microenvironment plays a crucial role in mediating cell adhesion, survival, proliferation and differentiation in physiological and pathological states. For this reason, the extracellular matrix (ECM) is largely studied in tissue engineering to replicate it in 3D tissue model for drug test and tissue regeneration. Glycans are tethered to the extracellular matrix components as poly- or oligosaccharides and on cell surface, and they play a key and dynamic role in regulating cellular functions and behaviour, including cell-cell and cell-ECM communication.[1,2] The study of differential ECM glycosignature effects is limited today by the lack of glyco-tools able to resemble both, glycan and proteins identities. Here in this work a panel of differential glycosylations were developed on collagen type I and gelatin, in order to characterize the effect of both glycosignature and ECM proteins motifs. The functionalization of proteins is not trivial due to the high molecular weight and the limited chemical reactions possible in aqueous solvents exploiting the few functional groups present in the protein chain. Collagen type I and gelatin have been conjugated to different glycans exploiting the primary amine group of lysine residue present in both proteins using a reductive amination reaction. The structure and degree of functionalization of glycosylated materials have been characterized with NMR, FT-IR, Ninhydrin and Anthrone assay. Moreover, the biomolecular interaction of glycocosylated ECM mimetics were tested on solid-phase assays for the interaction with Siglec-9, Siglec-10 and DC-SIGN, carbohydrate-binding proteins expressed at extracellular level and with immunomodulatory functions.

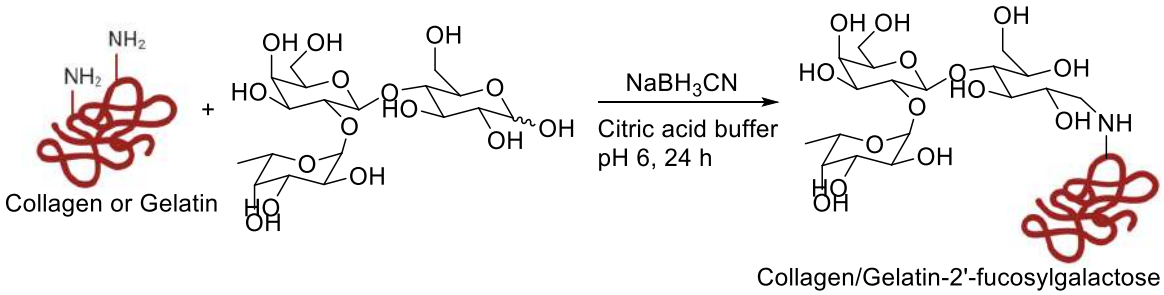

Figure 1: Example of functionalization of collagen/gelatin with 2'-fucosyllactose

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Functionalised supramolecular nanostructures for bacteria sensing

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The use of the gold nanoparticles (AuNPs) in modern biomedical applications targeting bacteria detection is rapidly increasing. The chemistry of the AuNPs surface can be engineered to control and modulate many important features, such as the biocompatibility, the biodistribution, and the site-specific recognition.[1,2] In this scenario, we aim at developing a sensing strategy based on the use of a library of positively charged gold nanoparticles (AuNPs) coated with fluorescent anionic polymer.[3] For this purpose, we have designed a first series of hydrogenated (H-) and fluorinated (F-) thiols (figure 1) to functionalise the AuNPs to generate an array of supramolecular systems able to interact with the bacterial wall with different binding affinities. Changing the ratio and the chain length of the hydrogenated and fluorinated ligands is a critical parameter to modulate the hydrophobic properties of AuNPs surface and the interactions between the AuNPs and the bacterial walls.[4,5]

To improve the specific-site interactions and increase the diversity in the AuNPs library, three amphiphilic thiols based on dipeptides were also designed. The use of amino acids as component of the hydrogenated ligands should allow further interactions with the different molecular patterns present on the bacterial walls. The implementation of a transduction mechanism will be performed to convert the bacteria recognition event in a detectable signal. For this purpose, we have chosen three different anionic fluorescent polymers that will be used to analyse and study the interaction with the different AuNPs and the bacteria cells.

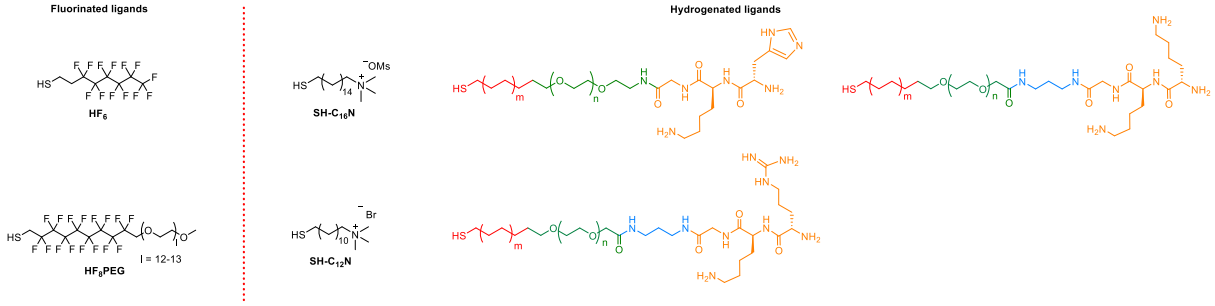

Figure 3. First blends of thiols for AuNPs preparation.

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POSS nanocages as hybrid supports for catalytic applications

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Polyhedral oligomeric silsesquioxanes (POSS) are organic-inorganic nanostructures finding a wide range of applications due to their hybrid features such as the easy tunability of peripheral organic moieties combined with the high thermal and chemical stability of the inner inorganic core.[1]

Herein, a series of imidazolium-functionalised POSS hybrids were grafted onto silica supports in order to be employed as heterogeneous catalysts for sustainable applications, namely the conversion of carbon dioxide into cyclic carbonates and the formation of C–C bond.[2-3] The proposed catalysts were easily prepared *via* a modular synthetic procedure allowing to generate high local concentration spots of imidazolium surrounding the POSS core. The catalytic tests for the fixation of CO_2 were run under solvent- and metal-free reaction conditions showing a full selectivity toward the cyclic carbonate. On the other hand, imidazolium-modified POSS nanocages grafted onto mesostructured SBA-15 were used as solid support for palladium active species in order to catalyse Suzuki-Miyaura and Heck cross-couplings. In both applications all the catalysts were easily recycled from the reaction media and tested with a broad scope of substrates showing outstanding performances in terms of turnover numbers and productivity values.

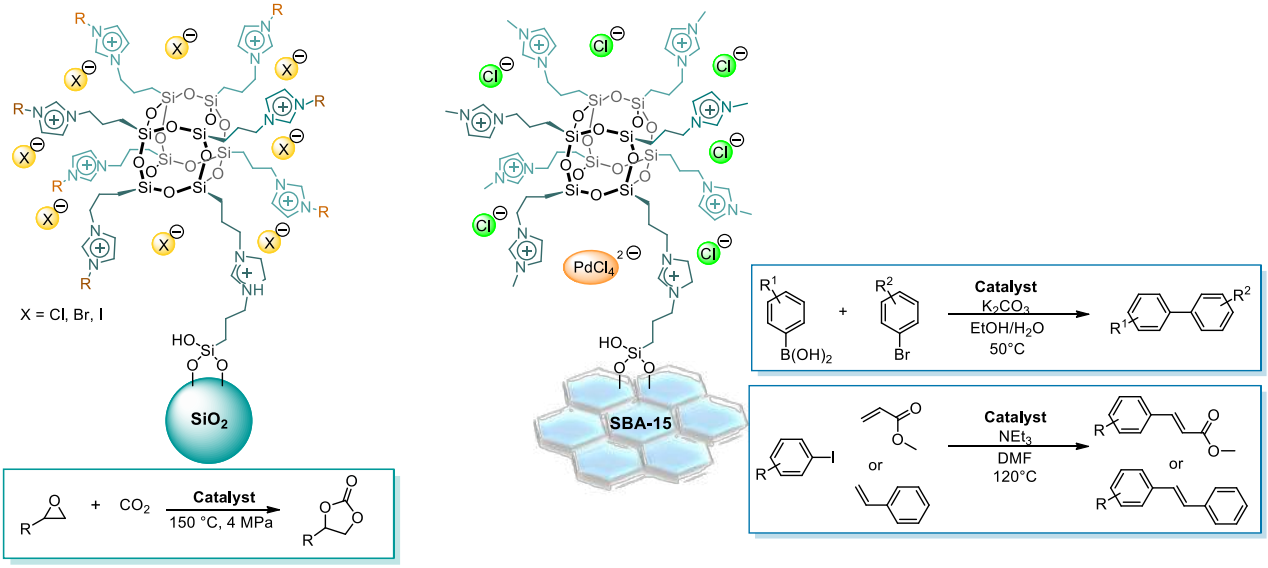

Figure 1: Imidazolium-modified POSS nanocages for catalytic applications.

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A D_2O-promoted labeling of alkenyl C-H bonds through Pd(0)/ carboxylic acid joint catalysis

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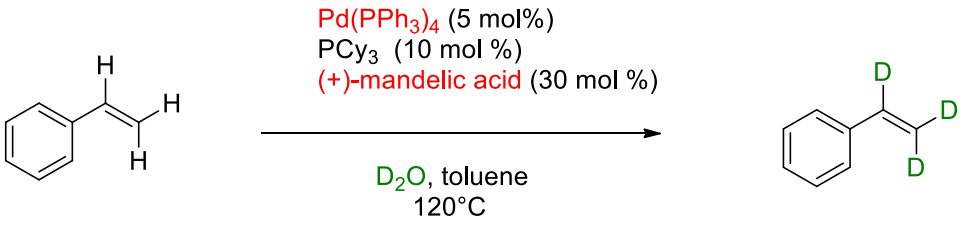
We would like to bring to your attention a poster featuring a simple catalytic method for the extensive labeling of alkenyl C–H bonds by using a palladium(0) complex and a carboxylic acid in the presence of deuterium oxide. The reaction can be useful for making a variety of terminal alkenes and best results has been achieved with aryl-substituted ones. This method could be regarded as a convenient approach for the synthesis of elaborated labeled chemicals from the cheapest and safest source of deuterium.

The process allows to achieve extensive deuterium incorporation using terminal olefins. In particular, an array of vinylarenes could be labeled. The deuteration is extensive at the □□□position and almost complete at the □□. The method displays ample functional group tolerance, including halides, ethers, cyclic carbamates, various N-heterocycles, ferrocenes and steroid derivatives. The practical viability of the reaction is witnessed by its efficacy, which is retained up to a 6-mmol scale.



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Polarclean/water as safer and recoverable medium for the selective C2-arylation of indoles catalyzed by Pd/C

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The direct C–H bond functionalization is nowadays an attractive synthetic strategy both for academia and for industrial scale processes, allowing the establishment of environmentally-benign and economically attractive organic syntheses.[1] In particular, the C–2 selective arylation of indoles has gained special attention giving access to a large class of functionalized heterocycles particularly interesting for medicinal chemistry.[2] During the past decades, the most explored synthetic routes to afford C–2 arylated indoles involved the use of homogeneous catalysts and toxic organic solvents, both for the environment and for human health.[3]

Herein we report our investigation on the use of Polarclean, a new, biodegradable, safer and "industrial waste"-derived solvent as reaction medium for the synthesis of C2-arylated indoles using diaryliodonium salts as arylating agent and commercial Pd/C as catalyst, proving that this approach combined with a purification procedure by recrystallization leads to a significant minimization of the waste production.

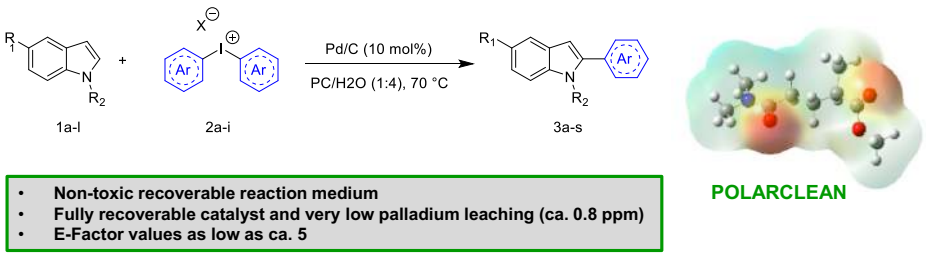

Figure 1: graphical abstract representing the selective Pd/C catalyzed C-2 arylation of indoles using Polarclean reported herein

Aknowledgment

The research leading to these results has received funding from the NMBP-01-2016 Programme of the European Union's Horizon 2020 Framework Programme H2020/2014-2020/ under grant agreement n° [720996]. The Università degli Studi di Perugia and MIUR are acknowledged for financial support to the project AMIS, through the program "Dipartimenti di Eccellenza - 2018-2022". Regione Umbria is acknowledged for funding through "Umbria bo.R.do", P.O.R. Programma Operativo Regionale F.S.E. (Fondo Sociale Europeo) Umbria 2014-2020 Asse III "Istruzione e formazione". Sterling SpA is also thanked for useful suggestions and support

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Antiproliferative effects of synthetic prenylated quinones and thiazinoquinones inspired by marine natural products

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Cancer finds in chemotherapy one of the most applied strategy for its treatment; therefore, the development of novel and improved anticancer agents has become mandatory. In this frame, the sustainable exploitation of marine natural products as starting hits is a precious and still untapped resource. Several classes of marine-derived compounds play specific roles in cell processes through interaction with key cellular target, and among these, quinones are a clinically relevant class of chemotherapeutic agents with anticancer activity. Particularly, many polyprenylated quinones/hydroquinones, known as meroterpenes, provided different anticancer and antimutagenic agents. Structure-activity relationship studies (SARs) on natural and synthetic compounds demonstrated that these effects depend on the length of the prenyl side chain and on the type and position of the substituent groups on the quinone moiety[1]. Taking inspiration from the cytotoxic marine metabolite aplidinone A (**1**, Figure 1), a geranylquinone featuring the 1,1-dioxo-1,4-thiazine ring, prenylated quinones and corresponding thiazinoquinones (**2**-**5**, Figure 1) have been synthesised to broaden the knowledge on the antiproliferative effects of these scaffolds. The adopted syntheses afforded compounds **2**-**5** in high yield by using an efficient and versatile protocol based on commercially available reagents. Therefore, compounds **2**-**5** were included in a pharmacological screening to assess their effects on viability and proliferation of breast adenocarcinoma (MCF-7), pancreas adenocarcinoma (BxPC-3), and bone osteosarcoma (MG-63) cell lines. The geranylquinone **3** resulted the most relevant compound in the series exerting a cytostatic activity through induction of cell cycle arrest with a significant segregation of cells into G0/G1 phase at concentration of 20 μM[2].

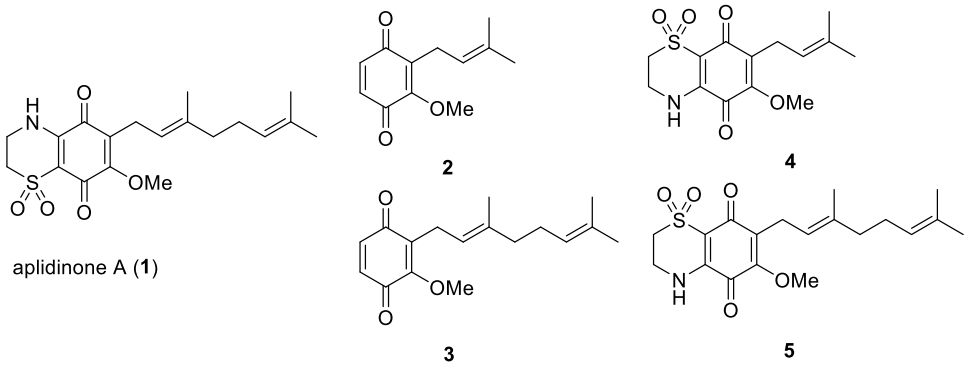

Figure 1: Structure of aplidinone A (**1**) and synthetic prenylated quinones/thiazinoquinones derivatives (**2**-**5**)

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Extraction optimization of hight added value compound from food waste material using supercritical carbon dioxide.

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This work is intended to revaluate food waste material through a green process. The research is based on an experimental design to optimize the extraction process of high added value compounds using supercritical carbon dioxide ($scCO_2$) as a green solvent instead organic solvents. Nowadays, the food industry wastes are estimated to be around 90 million tonnes every year;[1] most of them are converted in energy, however they still contain high added value chemical compounds. The research was conducted next Exenia Group, an Italian company working with $scCO_2$ since 1995. Exenia Group is set on the research and development of new $scCO_2$ industrial applications: from pasteurization to supercritical fluid extraction (SFE). Edible white rice is only 65% of total grain weight, so the milling process produces a lot of by-products. Despite rice bran is a waste in the rice production chain, it contains most of the rice nutrients including bioactive phytochemicals such as γ-oryzanol, well known for is antioxidant, anti-inflammatory and anti-hypercholesterolemic activities and used in pharmaceutics, cosmetics and food industry. [2] Goal of the present research work was the optimization of the extraction process of rice butter which contains γ-oryzanol, a complex mixture of ferulic acid esters of phytosterols and triterpenoids.[2] The extractions were conducted with a semi-industrial $scCO_2$ extractor following a Composite Face-Centered (CCF) design of experiments and a response surface methodology considering 2 factors and 3 variables for a total of eleven experiments. Three repetitions of the central point were performed to evaluate the repeatability of the method. After a first preliminary extractions, we chose to vary the pressure (between 300 and 400 bar) and temperature (between 40 and 60°C), monitoring the yield in γ-oryzanol by a HPLC methodology.[3]

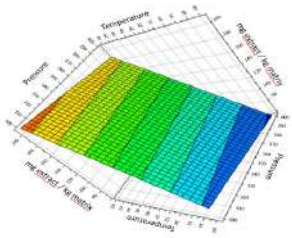

Figure 1: Experimental design surface.

The results show that the extraction yield in γ-oryzanol is more influenced by temperature than pressure (figure 1). Although experiments are still ongoing, the results show that this is a good-performance extraction.

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[4]

Synthetic applications with nucleophilic a-substituted organometallic reagents

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The transfer of a-substituted nucleophilic reagents can accomplish the introduction of halogenated fragments featuring the exact and desired degree of functionalization, in a single step operation[1]. Halogenated carbenoids and silylated carbanions provide an exceptionally powerful tool for performing such transformations in high yields and with excellent chemocontrol. The formation of these nucleophilic species is regulated by sensitive parameters such as temperature conditions, solvent anhydricity and stoichiometric ratios and the right balance of these allows to understand not only the theoretical aspects of the transformation but also the design of new synthetic strategies[2].

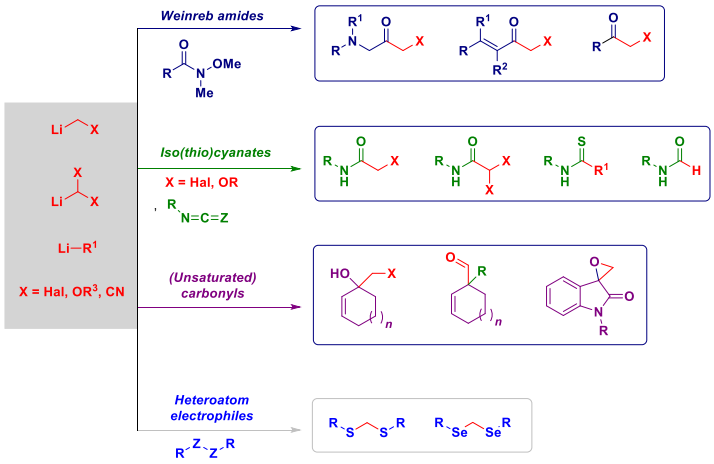

Figure 1: Homologation strategies with various electrophiles.

Here we furnish a detailed overview of the new methodologies developed by Pace's group [3,4,5] for the homologation of various carbon electrophyles with a-substituted organometallic reagents such as lithium and magnesium halocarbenoids.

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2-hydroxycyclobutanone as a key tool for the synthesis of benzofurans and indoles bioactive compounds

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Two new synthetic strategies have been developed: starting from 2-hydroxycyclobutanone and using a bronsted acid as catalyst: the first one uses phenol as a nucleophile, while the second one an analine; doing this highly functionalized benzofurans and indoles have been obtained respectively.[1,2] These new strategies can give access to new molecules and can be used to simplify the synthesis of bioactive compounds and natural products.[3,4]

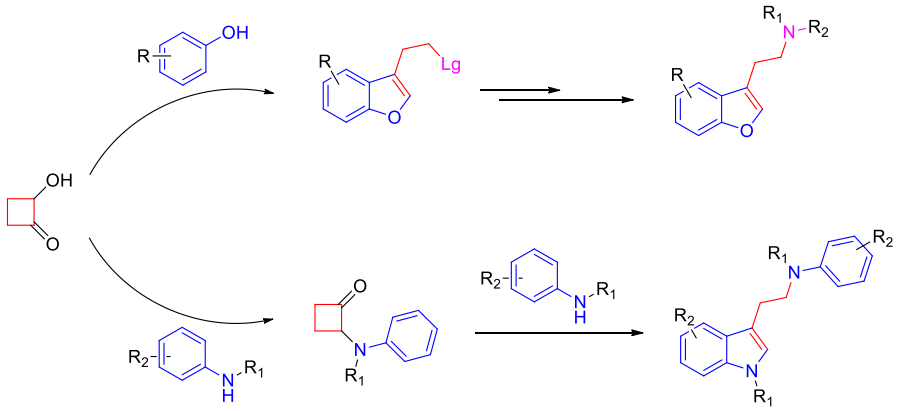

Figure 1: Synthesis of highly functionalized benzofurans and indoles.

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Turning an old synthesis upside-down: application of direct arylation reactions to the preparation of π-conjugated molecules

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Pd-catalysed cross-coupling reactions are an extremely versatile tool to create new C-C bonds and prepare π-conjugated molecules with potential applications in the field of organic electronics. While most of the metal-catalysed cross-coupling transformations require a (hetero)aromatic halide and an organometallic reagent as reaction partners, the possibility of activating at least one C(sp^2)-H bond of a (hetero)arene makes the direct arylation (DA) reaction stand out, avoiding the use of preformed organometallic compounds. Moreover, DA-reactions usually allow to reduce the number of both synthetic and purification steps and improve the sustainability of the synthetic process.[1]

Starting from these premises, we decide to revise the synthesis of **TTZ5** (Figure 1), an organic photosensitizer especially suitable for applications in high-performance thin-film Dye-Sensitized Solar Cells (DSSCs)[2] and photocatalytic dye-sensitized hydrogen production,[3] through the employment of DA-reactions, to scale up its preparation. Synthetic routes based on different cross-coupling reactions were compared in terms of number of synthetic and purification steps, E-factor and Eco-scale.[4] A new DA-based synthetic protocol was designed for the direct *one-pot* functionalization of a thiazolo[5,4-*d*]thiazole-based core (**TzTz-1** – Figure 1) with electron-rich and electron-poor (hetero)aromatic groups and, then, successfully applied to the preparation of several photosensitizers for thin-film transparent DSSCs, suitable for applications in photovoltaic greenhouses.[5]

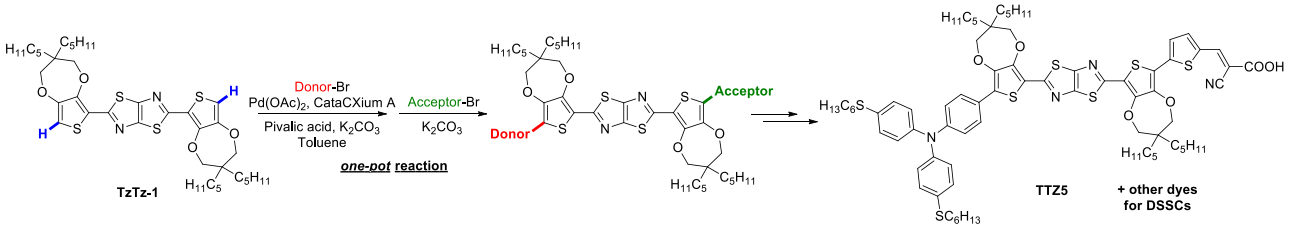

Figure 1: *One-pot* functionalization of **TzTz-1** through DA-reactions.

References:

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Electronic Transport in Crown Ether Based Columnar Liquid Crystals

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Discotic mesogens based on crown ethers and alkoxy substituted triphenylenes were synthesised and investigated. The liquid crystalline properties with and without complexed alkali metal ions were investigated with polarising optical microscopy (POM), differential scanning calorimetry (DSC) and small and wide angle X-ray scattering (SAXS, WAXS). The electronic transport was studied by temperature dependent photoconductivity, the ionic conductivity by impedance spectroscopy.

By adding alkali metal salts with soft anions (iodide, thiocyanate, tetrafluoroborate), a strong increase of the stability and the width of the columnar phases caused by an improved intra-columnar order appeared.

A significant increase of the photoconductivity in the columnar mesophase due to a smaller stacking distance of the π-systems was observed. We expected these materials to be ionic conductors, therefore macroscopically aligned thin films were investigated by dielectric spectroscopy. Contrary to our hypothesis, the existence of channels for cation transport formed by the stacked crown ether moieties in the columns can be excluded. We found the cations being coordinated to strongly to contribute significantly to the conductivity. The observed ionic conductivity is dominated by the movement of the anions through the molten alkyl side chains. Smaller anions move faster than larger ones.

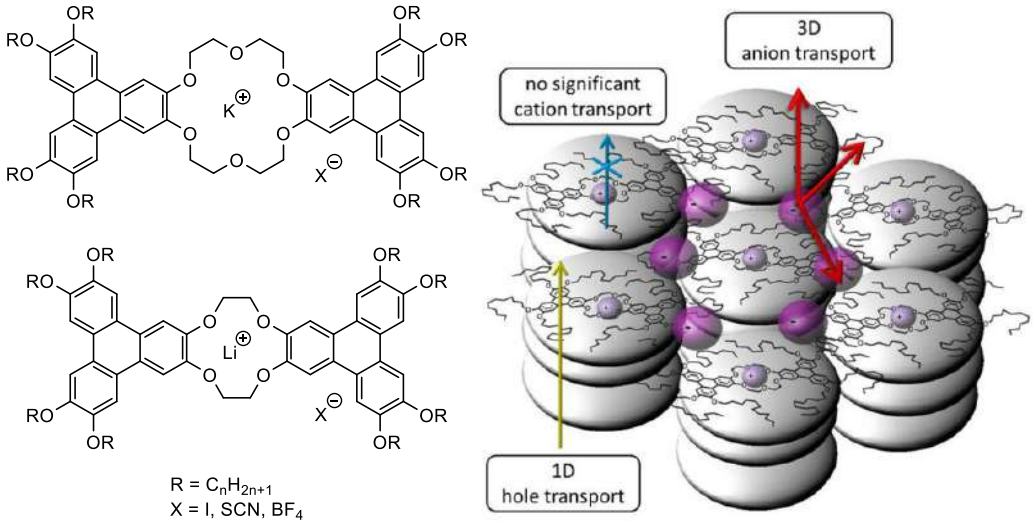

Figure 1: Structures of the investigated liquid crystals with alkali metal salts (left). Schematic representation of the columnar mesophase with the different possibilities for electric conduction (right). Figure taken from ref.[1]

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Fast Heck-Cassar-Sonogashira (HCS) Reactions in Green Solvents

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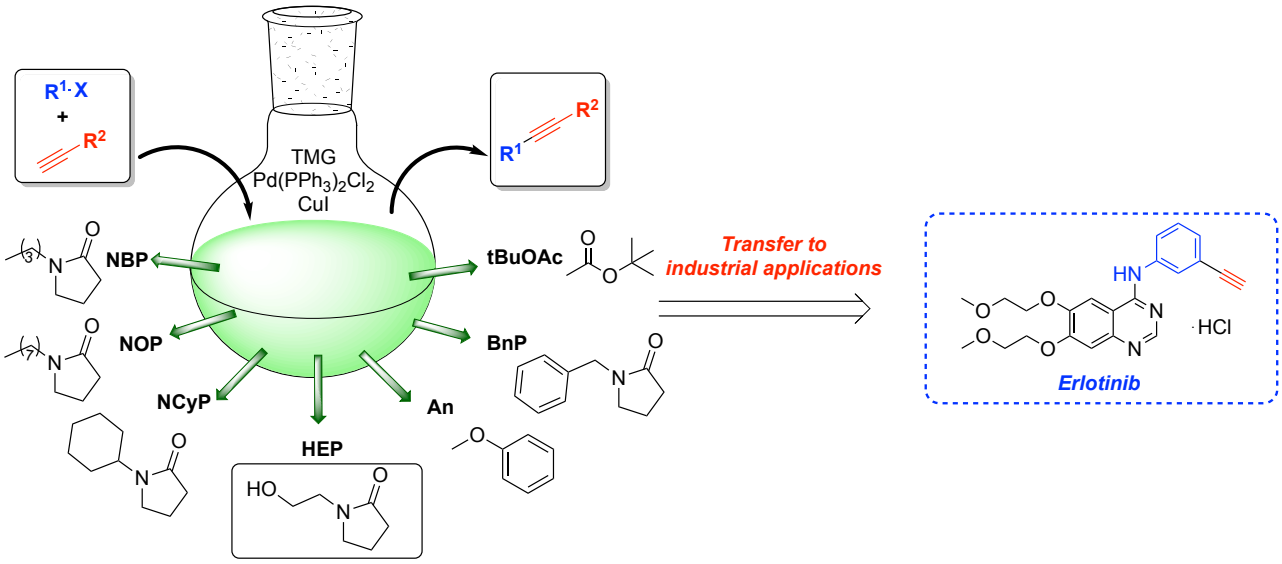

Figure 4: Conditions and green solvents used in HCS cross-coupling reaction.

The replacement of toxic solvents with greener alternatives in cross-coupling reactions has been a very important topic in the last decades. Green solutions in industrial processes to preserve the environment have evolved from an ethic approach to an inevitable necessity. Solvents represent the main source of waste in chemical industrial processes and their selection is critical in Pd-catalyzed cross-couplings, because of their strong influence in the coordination sphere of the metals and their ability to stabilize the catalyst complex. The target of this study was to investigate a fast and efficient protocol to perform Heck-Cassar-Sonogashira cross-coupling in green solvents. The optimized HCS protocol allowed a complete and readily conversion under mild conditions. The best results were achieved with N-Hydroxyethylpyrrolidone (HEP), allowing also a complete recovery of the product because of the migration of the solvent in water. In addition, the methodology was successfully applied to the synthesis of an intermediate of the anticancer drug Erlotinib, demonstrating the versatility of the new green protocol.

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Iron-Catalyzed Regioselective C(sp2)–H Alkenylation of Quinoline *N*-Oxides

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The direct C–H functionalization of quinoline-*N*-oxides represents an interesting synthetic strategy, offering the opportunity to realize dehydrogenative "external oxidant-free" functionalizations, exploiting the inherent ability of the *N*-oxide to reoxidize the catalyst, other than serving as a weakly-coordinating directing group.[1]

More commonly, this processes have been accomplished by using expensive 4d and 5d elements while, especially in recent years there has been a growing interest in the development of efficient catalytic processes based on 3d transition metal.[2] In this perspective, iron represents an ideal choice, as one of the most abundant elements in the earth's crust and being associated with a very low toxicity.[3]

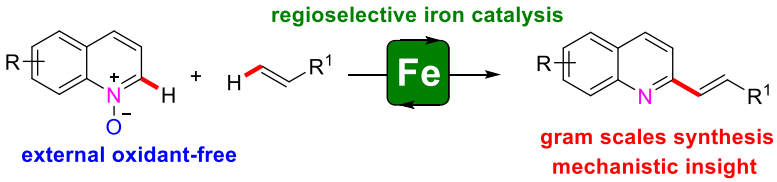

Figure 1: features of iron-catalyzed C–H alkenylation.

In this contribution is presented an efficient and regioselective iron-catalyzed methodology for the C–H alkenylation of quinoline-*N*-oxides. The protocol based on the use of inexpensive and easily accessible $FeSO_4$, showed broad applicability to a wide range of substrates. Experimental and computational investigations provide support to a mechanism based on a facile C–H activation event. Practical utility has been also demonstrated by performing the reaction efficiently on a multi-gram scale.

Acknowledgments: Grateful acknowledgement to project AMIS-"Dipartimenti di Eccelenza 2018-2022" for financial support

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Design and synthesis of hyodeoxycholic acid derivatives as GPBAR1 receptor modulators useful in the treatment of colon inflammation

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In the context of inflammatory diseases, the Inflammatory Bowel Diseases (IBDs), which include Crohn's disease (CD) and ulcerative colitis (UC), represent the most common in the worldwide population. The current treatment of IBD includes FANS, corticosteroids, antibiotics, immunosuppressive and anti-TNF-α agents.[1] However, the limited efficacy of these treatments urges the identification of new therapeutic approaches, as well as the employment of GPBAR1 agonists.[2,3] This receptor has an important role in intestinal homeostasis and inflammation-driven immune disfunction. Previous studies have shown that Gpbar1$^{-/-}$ mice have an altered intestinal morphology with increased permeability and higher susceptibility to develop colitis. In addition, in the immune system, GPBAR1 reduces phagocytic activity and the production of pro-inflammatory cytokines (TNF-α, IL-1α, IL-1β, IL-6 and IL-8). Modification on HDCA scaffold afforded to a small library of hyodeoxycholane analogs, as selective and potent GPBAR1 agonists. Our medicinal chemistry strategy has consisted in the introduction of a nitrile group in the side chain and different alkyl, alkenyl or aromatic substituents at C-6 on HDCA. All compounds synthesized have been tested on GPBAR1 receptor through transactivation assays using the hepatic cell line HepG2.

Our studies identified compound **6** as potent and selective GPBAR1 agonist (EC_{50} = 0.3 μM), exerting minimal activating effects on the latter receptors. GPBAR1 activation, combined with the ability to revert both the expression of inflammatory genes *in vitro* and the inflammatory pattern in TNBS-induced colitis model, indicates compound **6** as a promising lead for the treatment of GPBAR1-related inflammatory bowel disorders.

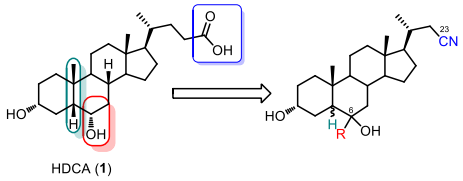

Figure 1: Modifications on HDCA scaffold

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Synthesis of primary and secondary amines catalyzed by metal recyclable nanoparticles

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Aromatic amines are important intermediates and bulk chemicals to produce pharmaceuticals, polymers, herbicides, fine chemicals, and more.1 The catalytic hydrogenation of nitroarenes for the synthesis of anilines uses expensive noble metal-based catalysts, that allow high yields. Unfortunately, the high cost of these catalysts limit their practical use. However, using cheaper metals, such as copper, nickel etc., critical reaction conditions are needed to achieve good yields towards the desired products. 2 Therefore the development of a facile, efficient and low-cost approach to the preparation of aromatic amines remains a great challenge from a synthetic point of view. In this context, herein we report the synthesis of primary and secondary amines by using polymer supported recyclable nickel nanoparticles (Ni-NPs), as the catalyst. The catalyst resulted active and selective towards the formation of primary 3 (Figure 1) and secondary 4 (Figure 2) aromatic amines under mild reaction conditions and it was recyclable for at least five times.

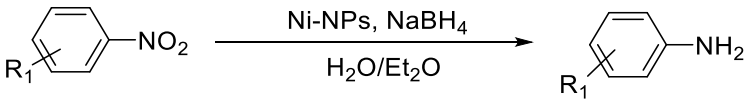

Figure 1: Reductive amination of nitroarenes to anilines.

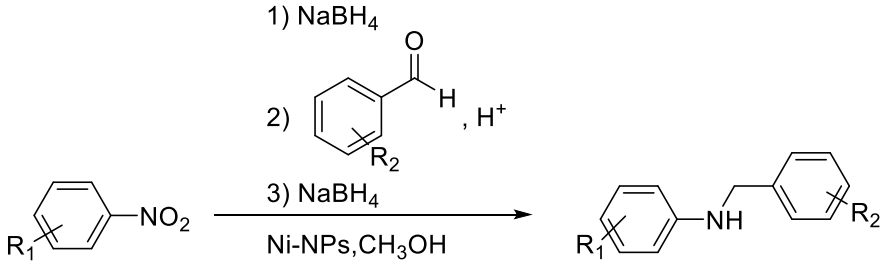

Figure 2: Reductive amination of different aldehydes with nitroaromatics.

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3D printed azo-based membranes for gas permeability

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Three-Dimensional printing (3DP) is an innovative technique, actually used both in industrial and academic fields. The high versatility and user-friendliness, the progressive printers' price knock off and the considerable saving of raw materials are only few advantages of these technologies. Among others, the Digital Light Project (DLP) printer is under investigation to widen the palette of printable formulations, producing innovative functional 3D printed devices. The exploitation of new functional materials, for example temperature-, light- and pH-responsive polymers, is one of the most interesting survey field[1]. Azodyes are typically used in the formulation to confer innovative features due to the ability to undergo *trans/cis* isomerization under light (UV or laser) irradiation[2].

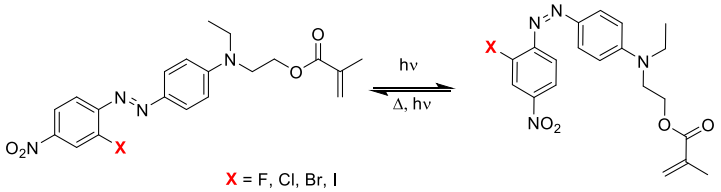

Figure 1: Scaffolds of methacrylated azodyes

In this work we designed, synthetized, and characterized azo benzene methacrylated monomers (Figure 1) with different groups in *ortho* position respect to the azo bridge, exploiting the methacrylic functional group to covalently connect the dye with the polymeric chains. It is well known in literature that the ortho position in the azodyes can interact with the polymeric matrix[3]. We printed azodye-based membranes and we obtained an increase in CO_2 and O_2 permeability respect to the membrane without dyes (taken as reference) as well as a decrease in H_2O permeability. Moreover, under green laser irradiation (532 nm) the gas transmission rate, increases in a reversible and repeatable way. This property can be used to modulate the permeability and the gas selectivity in the final 3D printed device.

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Synthesis of Near Infrared Quaterrylene-based Dyes for Colourless Dye-sensitized Solar Cells

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Photovoltaic cells (PV) based on semiconductor technology techniques are, nowadays, the most efficient systems for solar energy conversion. Dye-Sensitized Solar Cells (DSSCs) represent one of the best performing technologies developed though their performances are not comparable with the well-known silicon-based photovoltaics cells.[1] Building Integrated PhotoVoltaics (BIPV) based on DSSC are a promising application to make DSSC more attractive in the energy production field. An innovative approach resides on the implementation of colourless DSSCs based on NIR sensitizers such as polymethine and rylene dyes.[2,3]

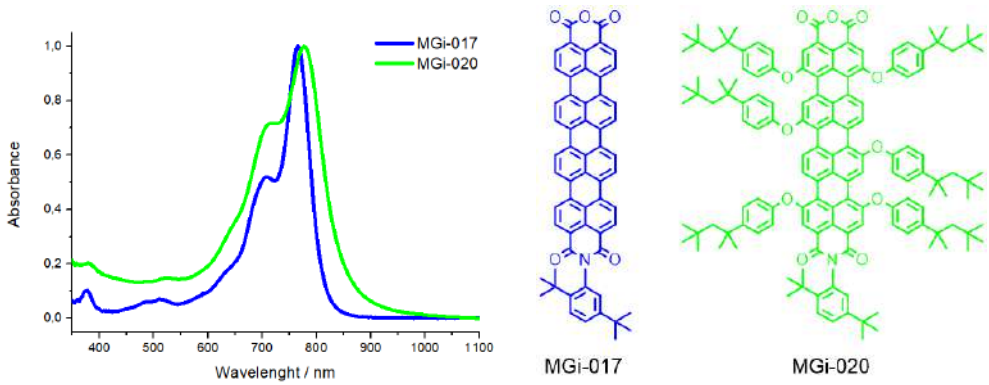

Figure 1: Quaterrylene based-dyes structures and their UV-Visible absorption spectra.

In this work, we present the synthesis of two quaterrylene dyes to evaluate their application as NIR-sensitizers in DSSCs. Different synthetic pathways were explored to functionalize the rylene core to modulate the photophysical and electronical reequipments and to improve the processability properties of the final materials. The overall photophysical and electrochemical properties were investigated. The assemble and study of devices based on quaterrylene dyes is under investigation and the preliminary results will be presented.

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Organocatalysed Michael addition of masked acetaldehyde to nitroalkenes

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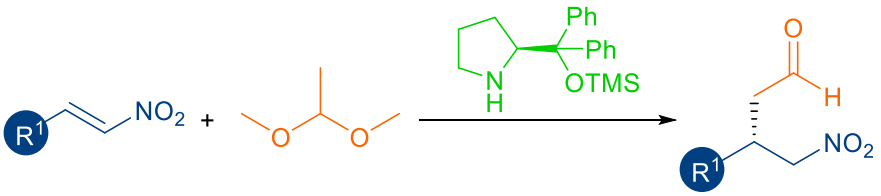
A novel and safe reaction for the enantioselective enamine-catalysed[1] addition of acetaldehyde to nitroalkenes is presented[2,3,4,5]; this protocol makes use of a safe acetaldehyde precursor to access important intermediates to APIs, and allows the use of fewer equivalents of acetaldehyde and lower catalyst loadings. The reaction developed proved to be suitable to be performed on gram-scale and to produce key intermediates for the synthesis of pharmacologically active compounds, such as pregabalin.[6]



- Lower catalytic loading
- No free acetaldehyde
- Lower excess reagents

Figure 1: Enantioselective Michael addition of acetaldehyde dimethyl acetal to nitroalkenes.

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Synthesis of Star-Shaped Alkoxy- and Chloro-Triphenylbenzenes: Suzuki Coupling in the Presence of Halogenated Precursors[1]

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The synthesis of new triphenylbenzenes **2**, representing an extension of known derivatives **1**, including a further substitution pattern and partial substitution with chlorine, is reported (Figure 1). Compounds **2** were obtained by Suzuki-Miyaura cross coupling via two routes, well-established coupling of aryl boronic species **3** (*N*-methyliminodiacetic acid (MIDA) boronates) and 1,3,5-tribromobenzene **5** (route A) or alternatively, aryl bromides **4** and 1,3,5-trisboronic benzene **6** (pinacole boronate) (route B). Their liquid crystalline behaviour was investigated by DSC, POM and SAXS/WAXS (Figure 1, right).

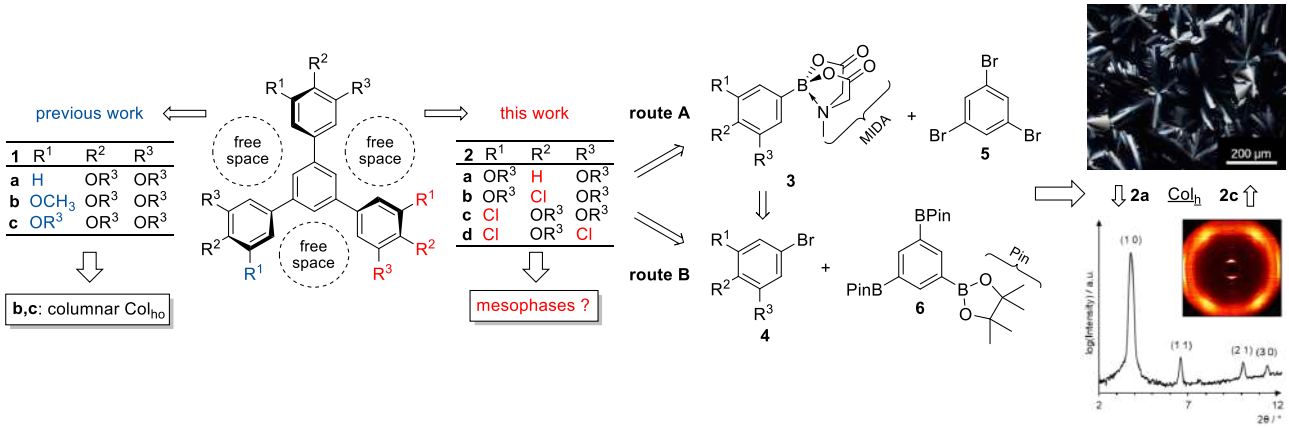

Figure 1: Known (**1**) and new (**2**) triphenylbenzenes (left). Retrosynthesis of **2** via two different routes (middle). Col$_h$ phases of **2a** and **2c** (right). Figure taken and edited from ref. [1].

On route A, the presence of additional halogens can lead to further couplings and thus to undesired by-products. By switching the synthesis to route B, couplings take only place on the core and further conversion is prevented, leading to a simpler purification and an increase in the overall yield. While for triphenylbenzenes **2a** and **2c** Col$_h$ phases were observed, the position (**2b**) or amount (**2d**) of chlorine in the other molecules did not seem to be sufficient to form stable mesophases. Based on SAXS results, a helical packing model was proposed for **2a** and **2c**. Additionally, inhibition of crystallisation was observed when chlorine was involved in the molecular structure, which is mainly attributed to the size and polarity of the atom.

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Synthesis of a new Theranostic Agent Containing Boron and Biotin for BNCT/MRI Applications

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BNCT (Boron Neutron Capture Therapy) is a binary therapy for the treatment of cancer, especially of malignant brain tumours, based on the capture of epithermal neutrons (0,025 eV) by ^{10}B nuclei that have been selectively delivered to the tumour cells. In order to be effective, BNCT requires 20-30 μg of ^{10}B per g of tumour, therefore *in vivo* visualization of ^{10}B distribution is important.[1] To monitor the path and the selective localization of the boronated agent at the tumour site, MRI (Magnetic Resonance Imaging) technique together with Gd(III)-DOTA complex are employed. To ensure high selectivity at the tumour site, the streptavidin-biotin complex can be applied. Streptavidin is a protein that recognizes and selectively binds biotin with a very high affinity. The boronated agent binds the streptavidin which can also bind itself to a biotinylated antibody that selectively recognizes the tumoral cells. Then it can undergo irradiation for BNCT therapy. In this work it is reported the synthesis of a new theranostic (therapeutic and diagnostic) agent for BNCT/MRI applications which contains a carborane unit (dicarba-*closo*-dodecaborane) assuring a high payload of ^{10}B atoms (figure 1). In order to obtain a multifunctional agent, one of the carbon atom of the cage is employed to functionalize the theranostic with a biotin molecule and a six carbon atoms spacer exploited as binding site for streptavidin. The other carbon is functionalized with a very efficient contrast agent such as Gd(III)-DOTA complex.

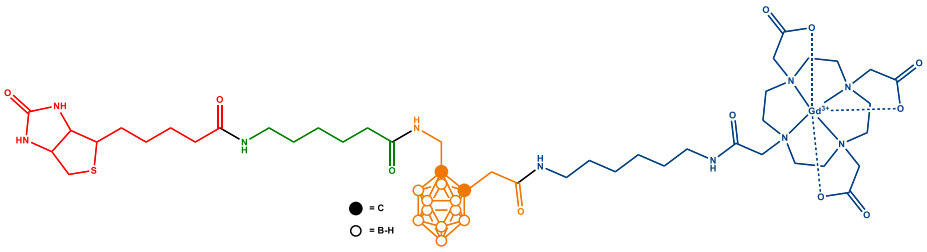

Figure 1: Structure of the theranostic agent. The moieties are shown in different colours: in red the biotin molecule, in green the spacer, in orange the carborane cage and in blue the Gd(III)-DOTA complex.

The synthesis of the carborane cage starts from an alkyne with two orthogonal protecting groups which undergoes dehydrogenative insertion reaction with decaborane.[2] The carborane is then functionalized with the biotin and the Gd(III)-DOTA complex, previously synthesized. *In* vitro and *in vivo* tests will be carried out in order to test its efficiency as antitumor agent.

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Iodolactonization of 3-Alkynylthiophene-2-Carboxylic and 3-Alkynylpicolinic Acids for the Synthesis of Fused Heterocycles

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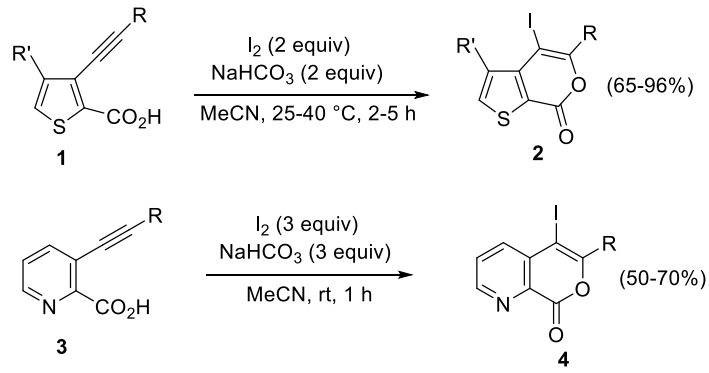
Iodocyclization of suitably functionalized alkynes represents an important tool in organic synthesis, since it allows the formation of iodine-containing heterocycles that can be further diversified by subsequent cross-coupling reactions [1].

In this contribution, we report on the iodolactonization of 3-alkynylthiophene-2-carboxylic acids **1** and 3-alkynylpicolinic acids **3** to give thienopyranones **2** and pyranopyridinones **4**, respectively, from regioselective *6-endo-dig* annulation (Scheme 1).



Scheme 1

Reactions take place in CH_3CN under mild conditions (25-40°C) the presence of I_2 as the iodine source and $NaHCO_3$ as the base, to afford the products in fair to excellent isolated yields.

To assess the synthetic potentiality of the newly prepared iodothienopyranones **2**, some paradigmatic cross-coupling reactions were also performed, such as the Sonogashira and the Suzuki reactions. Fair to good yields of the corresponding coupling products were obtained with all iodothienopyranones tested, using different terminal alkynes or arylboronic acids as the coupling partners.

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"Blackness" is an index of redox complexity in melanin polymers

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Melanins, a characteristic group of insoluble phenolic polymers found widespread in Nature from humans to mammals, plants and fungi, display typical dark colorations and an outstanding combination of optoelectronic, free radical, antioxidant and semiconductor-like properties that raise considerable interest for manifold applications in materials science and biomedicine.[1] Besides traditional model polymers from DOPA or DHI, a valuable yet little investigated platform for inquiring into the origin of melanin chromophore is provided by synthetic fungal allomelanin (mycomelanin) mimics produced by oxidative polymerization of 1,8-dihydroxynaphthalene (1,8-DHN) and related precursors. Studies of 1,8-DHN polymers have shown a deep black color associated with an unusually intense EPR signal and potent antioxidant effects, far exceeding those of the nitrogenous eumelanin from DHI. Studies of the structure, properties and mechanism of formation of 1,8-DHN mycomelanin led to the identification of the main oligomer intermediates, displaying the 2,2'-, 2,4', and 4,4'-coupling patterns, a chemistry reflecting the reactivity of transient phenoxyl radical intermediates.[2] Disclosed herein is the first experimental evidence for a direct correlation between the broadband visible light absorption ("blackness") and the coexistence of reduced and oxidized substructures in a set of model polymers from isomeric dihydroxynaphthalenes structurally related to fungal melanin from 1,8-dihydroxynaphthalene.[3] Excellent linear plots (r^2 = 0.97 and 0.94) were determined between the integrals of featureless absorbance curves over the 400-800 nm range, the electron spin density values in the EPR spectra and the width of selected oligomer peak clusters in the MALDI-MS spectra. Blackness, which is shown to be strongly interrelated with electron spin density, is thus proposed herein as a robust index of redox inhomogeneity and electron complexity reflecting the shift of oligomer populations toward highest oxidation states.

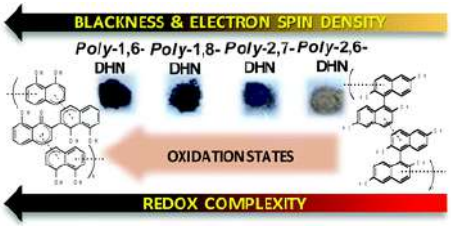

Figure 1: representation of the correlation between blackness and redox state disorder in melanin polymers.

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Oxidative palladium-catalyzed cyclization/azidation of unactivated alkenes using hydrogen peroxide and sodium azide

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Vicinal difunctionalization reactions of unactivated alkenes have recently received great interest in organic chemistry as a fruitful way to access to more complex molecules. Using this methodology, transition metal-catalyzed intramolecular/intermolecular procedures have been applied to obtain differently functionalized cyclic compounds.[1] In this context, reaction involving the introduction of an azido group are rather rare despite organoazides are versatile intermediates in organic synthesis valuable for a wide range of applications. In this limited range of literature examples, copper salts have been typically used for cyclization/azidation procedures.[2]

Among the strategies successfully employed for the difunctionalization of olefins, palladium-catalyzed reactions in oxidative conditions have a relevant role,[3] but methodologies involving the introduction of an azido group in intra and intermolecular procedures are lacking.

Following our interest in a research line on the transition metal-catalyzed domino reactions for the difunctionalization of alkenes, we investigated a new palladium(II)-catalyzed procedure to obtain azidomethyl substituted heterocycles through amino and oxyazidation reactions. The process occurs in the presence of NaN_3 as source of azide ions and hydrogen peroxide as oxidizing agent to involve a Pd(IV)-complex, which is the key intermediate of the process.

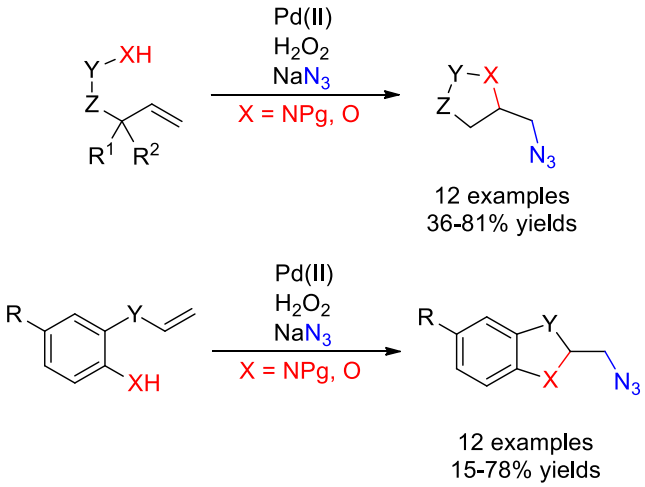

Figure 1: Palladium-catalyzed cyclization/azidation procedures.

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Synthesis of Symmetrical β-Nitro Alcohols *via* Tandem Nef-Henry Reactions Promoted by Vitamin B2

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Chemistry related to nitro compounds is still noteworthy since this functional group shows a rewarding versatility in medicinal chemistry[1] and more broadly for its possibility to be converted into other moieties.[2] In particular, since their discovery, at the end of 19th century, both Nef and Henry reactions have been exploited to convert nitro compounds into corresponding carbonyl or carboxylic groups or to install new carbon-carbon bonds, respectively.[3] Moreover, in the last decade, the importance of new research in tandem procedures has been well depicted by Nicolaou and co-workers pointing out how these processes are crucial in designing synthetic strategies.[4]

Herein, we report a new methodology for the synthesis of symmetrical β-nitro alcohols promoted by Riboflavin (vitamin B2) which consist in a first conversion of the nitro compound to the corresponding aldehyde which is then coupled to a Henry reaction. The methodology works well with differently substituted primary nitro compounds, while secondary nitroalkanes fail to afford the expected nitro alcohol.

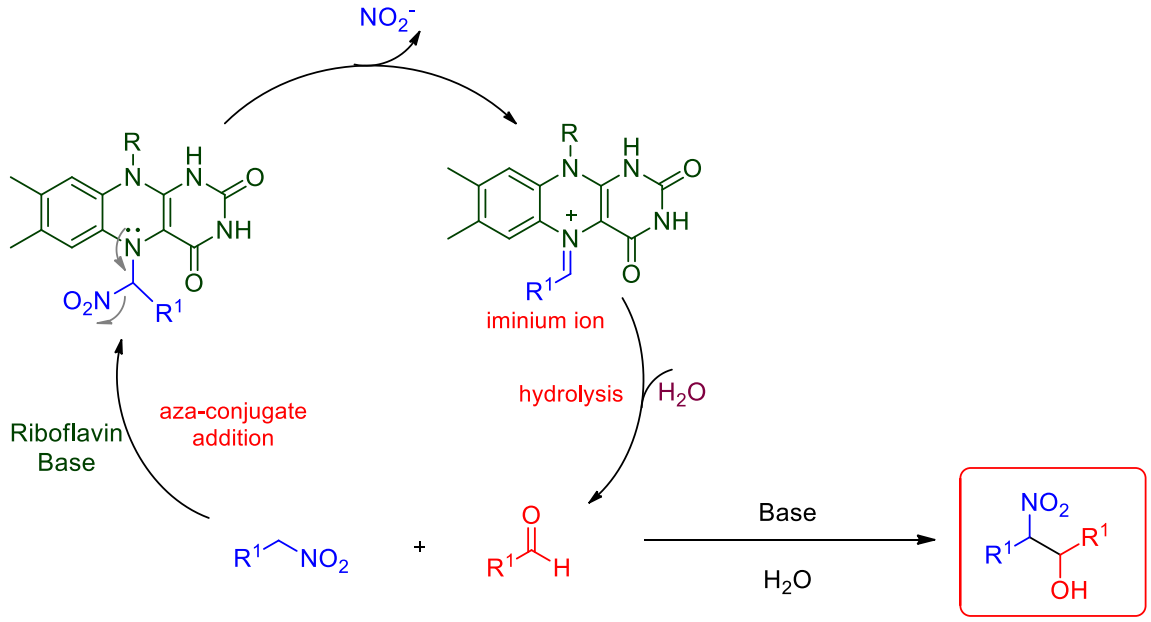

Figure 1: Examples of vitamin B2 promoted synthesis of nitro alcohols.

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C_4-C_3 ring contraction of 2-hydroxyketones: photochemical synthesis of hydroxycyclobutanones, mechanistic studies and synthetic applications.

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The four member ring 2-hydroxycyclobutanone, has been reacted with indoles[1a], anilines[1b] and thiols[1c] through a nucleophilic addition-C_4-C_3 ring contraction reaction furnishing the corresponding cyclopropylcarbaldehyde and/or ketones derivatives in satisfactory yields and broad scope.

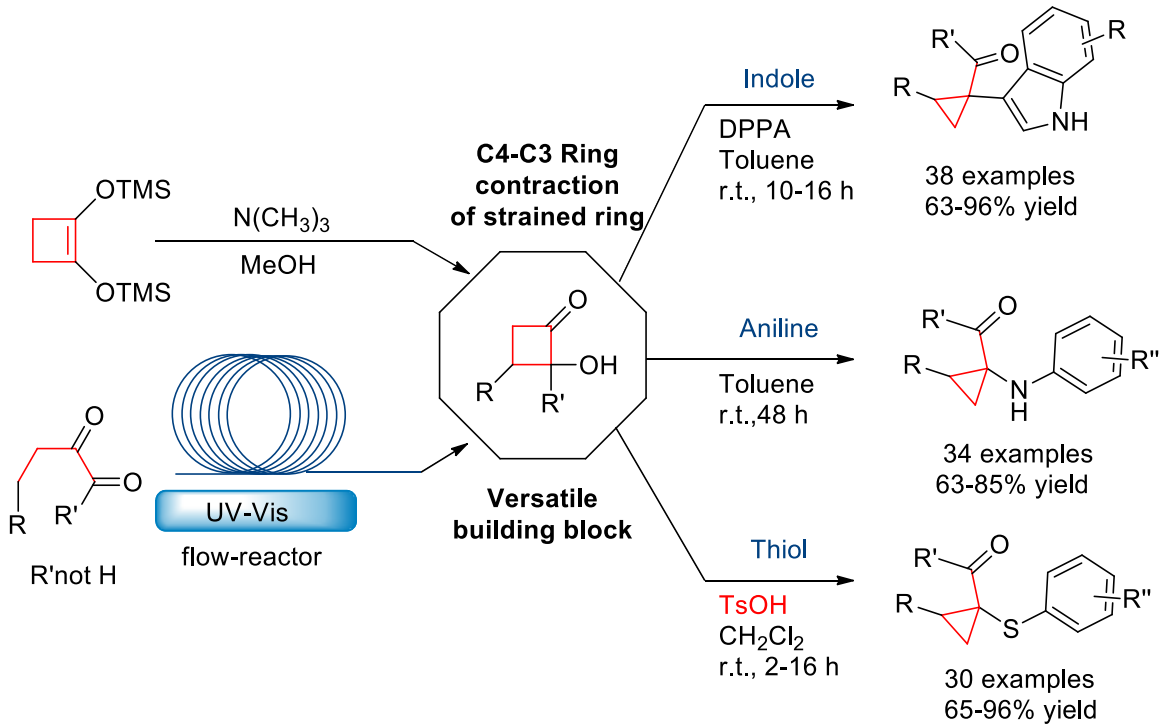

Figure 1: Synthesis and C_4-C_3 contractions of 2-hydroxyciclobutanones.

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New strategies for the multistep semi-synthesis of Oleocanthal and Ligstroside

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Literature describes Oleocanthal (OC) as the major phenolic compound in extra-virgin olive oil with broad functional and health benefits through its capacity to interact with different specific disease targets, such as cancer, inflammation, and neurodegenerative and cardiovascular diseases[1]. Numerous studies demonstrated that OC inhibits inflammation in the same way as ibuprofen; moreover, is substantially more potent on equimolar concentrations[2]. The attention toward the OC's synthesis derives from the drawback to find an effective way to extract it. At the best of our knowledge, in literature a rapid and effective synthetic pathway has not been developed yet; but recently, Sarikaki and co-workers have developed a new biomimetic synthesis of oleocanthal, oleacein and their analogues starting from oleuropein[3]. We want to suggest a synthetic green strategy modifying the known strategy with more sustainable methods. This new pathway allows to obtain as intermediate the Ligstroside, one of two main olive secoiridoids. In the Figure 1 is reported the synthetic strategy formulated by our group. At the moment we have been able to obtain only the Ligstroside, obtaining an overall yield of 10%. OC can be obtain applying microwave aqueous Krapcho decarboxylation according to Costanzo et al[4].

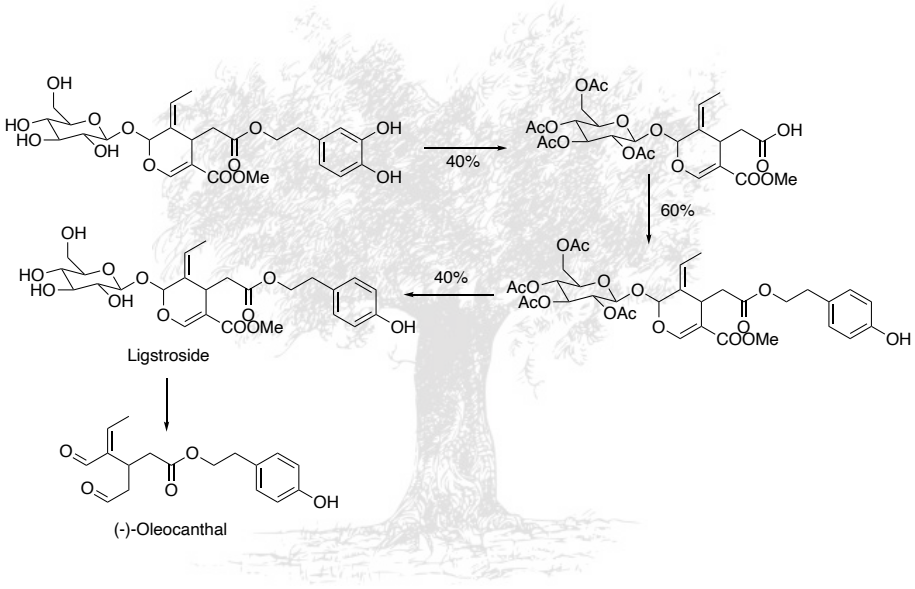

Figure 1: Strategy of synthesis of Oleocanthal and Ligstroside.

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A new stereoselective entry to chiral carbocycle-fused uracils

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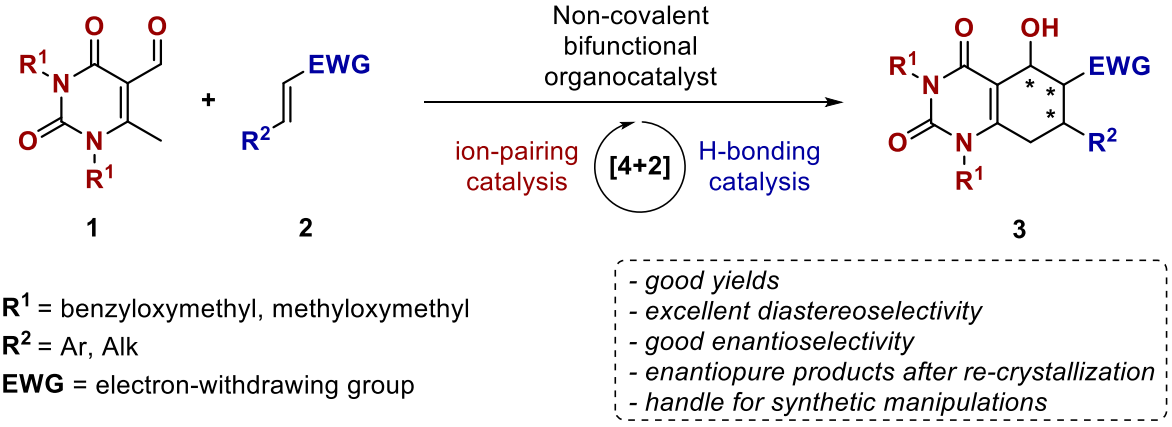
Uracil derivatives rich in functional groups represent attractive molecules in the field of medicinal chemistry-oriented synthesis, exhibiting biological activities especially as antivirals.[1] However, these heterocycles are often flattened and C(sp^2)-rich rings. Accordingly, three-dimensional and chiral C(sp^3)-rich fused uracil derivatives containing one or more stereocentres constitute particularly interesting novel chemotypes. Vinylogous reactions constitute a potent tool for the selective functionalization of remote C(sp^3)-H bonds.[2] Thus, the combination of the vinylogy concept with asymmetric chemical methods for the synthesis of nonracemic carbocycle-fused uracils paves the way to a new exploration area.

In this context, recent discoveries showed the unprecedented reactivity of pro-nucleophilic uracil-based carbaldehydes of type **1** (Scheme 2) which were able to react with enals after covalent activation by a secondary amine organocatalyst via the intermediacy of an in situ-formed ortho-quinomethane dienamine.[3]

In this presentation a new asymmetric, vinylogous [4+2] cycloaddition between pronucleophiles of type **1** and an activated double bond acceptor **2** is highlighted. By using suitable non-covalent bifunctional organocatalysts, a new series of highly functionalized, enantioenriched fused uracil heterocycles with three contiguous stereocentres **3** have been obtained (Scheme 2).



Scheme 2. Graphical abstract of the [4+2] cycloaddition reaction for the synthesis of uracil-based heterocycles

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Learning new biological functions for organic molecules with computers.

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Allosteric drugs have been attracting increasing interest over the last few years. In this context, it is common practice to use high-throughput screening for the discovery of non-natural allosteric drugs. While the discovery stage is supported by a growing amount of biological information and increasing computing power, major challenges still remain in selecting allosteric ligands and predicting their effect on the target protein's function. Indeed, allosteric compounds can act both as inhibitors and activators of biological responses. Computational approaches to the problem have focused on variations on the theme of molecular docking coupled to molecular dynamics with the aim of recovering information on the (long-range) modulation typical of allosteric proteins.

Here, we present a protocol that combines docking-based screening, information on the conformational dynamics of the protein and Machine Learning (ML) to classify ligands of the molecular chaperon Hsp90 as activators or inhibitors. To this end, we develop a classifier of activation/inhibition of Hsp90 allosteric ligands that is trained on data from a panel of ensemble docking results. The dataset for this study is built from a database of 133 known Hsp90 ligands.

Three different ML methods are compared with the best performing algorithm achieving an average balanced accuracy of 0.90 (over 10-fold cross-validation) in correctly separating inhibitors from activators. A comparison with a direct classification of the chemical properties of ligands suggests that the ML prediction is not dependent on the similarity among the molecular structures, but recovers hidden similarities in functional effects of different ligands.

Supercritical CO_2 and Green Extraction methods for Added Value Products: Carotenoids, Chlorophylls and Phycocyanin from Spirulina Microalgae

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Nowadays, the blue-green microalgae of the genus Arthrospira, commonly known as Spirulina, are commercially grown all around the world for their nutritional properties. The popularity of Spirulina as a food supplement is mainly due to its high protein content (up to about 70% by dry weight) and its richness in minerals, vitamins and provitamins, phytochemicals, essential amino acids, fibres and pigments [1]. Among them, carotenoids, chlorophylls and phycocyanins are of high relevance as food and feed dyes. In particular, phycocyanin has been widely considered as a precious protein target because of its rare intense-blue colour, due to the presence of linear tetrapyrrole chromophores, covalently bound to cysteine residues via thioether bonds. Its protein-based structure is arranged in αβ protomers associated into trimers $(\alpha\beta)_3$ and hexamers $(\alpha\beta)_6$. Its absorption in the visible region (λ_{max}=620 nm) and its natural fluorescence account for its application as marker in the medical field. The presence of the protein in the algae, carrying specific chromophores, is able to enhance the absorption range in the visible spectrum of light, facilitating the photosynthesis.
Different strategies were developed for the isolation and purification of phycocyanin in the last decade, all of them however discarding the residual pigment fraction [2].

This study suggests an integrated and “green” extraction chain that only leads to phycocyanin at the end. The body of the strategy involves two consecutive steps of extraction of carotenoids and chlorophylls through supercritical-CO_2, a well-recognised “green” extraction method, before phycocyanin extraction [3].
The biomass residue, exhausted in terms of carotenoids and chlorophylls, is finally extracted in water to yield phycocyanin. On the basis of recent and past literature on the topic, a strategy to yield the blue pigment with high purity was developed, keeping an eye on the scalability of the overall process in terms of cost and time consumption. Consecutive steps were carried out in order to enhance the phycocyanin purity, including electrocoagulation, dialysis and protein salting-out. These processes yielded 250 mg g^{-1} of phycocyanin (by dry Spirulina weight). A potentially scalable strategy to obtain the blue pigment with high purity (A_{620}/A_{280} = 2.2) was set up. The practical application of the extracted blue phycocyanin pigment as a cotton-based tissue colorant was also experimented.

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Systematic Investigation of the Antioxidant Properties of Agri-food Byproducts and Characterization of the Effects of Hydrolytic Treatments

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We report herein the results of a systematic evaluation of the antioxidant properties of a series of plant-derived byproducts, selected among those produced in largest amounts by the agri-food industry, which represent a cheap, sustainable and easily available source of phenolic compounds, such as lignins and tannins.[1,2] In particular, 2,2-diphenyl-1-picrylhydrazyl (DPPH) and ferric reducing/antioxidant power (FRAP) assays indicated the superior activity of pomegranate peels and seeds, grape pomace and pecan nut shell. The effects of an acid hydrolytic treatment previously applied to other agri-food wastes to improve the antioxidant properties[3,4] were also evaluated. An increase in the antioxidant potency was observed for most of the waste materials following this treatment, with the exception of the condensed tannin-rich pecan nut shell and grape pomace. UV-Vis and HPLC investigation of the soluble fractions coupled with the results from IR analysis and chemical degradation approaches on the whole materials allowed to conclude that the improvement of the antioxidant properties was due not only to removal of non-active components (mainly carbohydrates), but also to structural modifications of the phenolic compounds.[5] Parallel experiments run on natural and bioinspired model phenolic polymers suggested that these structural modifications positively impacted on the antioxidant properties of lignins and hydrolyzable tannins, enhancing their H-atom and electron donor properties, whereas significant degradation of condensed tannin moieties occurred, likely responsible for the lowering of the reducing power observed for grape pomace and pecan nut shell. These results put the basis for a rational exploitation and manipulation of agri-food byproducts for application as antioxidant additives in functional materials.

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Heterogeneous systems based on CNFs and imidazolium salts as catalyst for CO_2 conversion.

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Growing concerns about the environmental impact of carbon dioxide emissions from fuel combustion and other human activities have prompted the scientific community to look for ways to store or, preferably, reuse this molecule. One of the reactions that aims to reuse CO_2 is the reaction with epoxides, high internal energy molecules that can make the process thermodynamically favourable.[1] The high energy input required for the transformation of carbon dioxide can be further reduced through the coordination of the epoxide oxygen with a metal centre acting as Lewis acid or through the formation of hydrogen bonds.[2] Recently, heterogeneous catalytic systems based on supported ionic liquid phases with halide counterions represent a promising class of materials. Halide plays a crucial role as an active nucleophilic species and promotes the opening of the epoxy ring, followed by the insertion of CO_2.[1] As a result, a salt based on bisvinylimidazolium bromide has been synthesised and subsequently polymerised on carbon nanoforms (CNFs) as supports (Figure 1). The materials obtained showed good catalytic activity towards the above-mentioned reaction and moreover their recyclability was also tested.

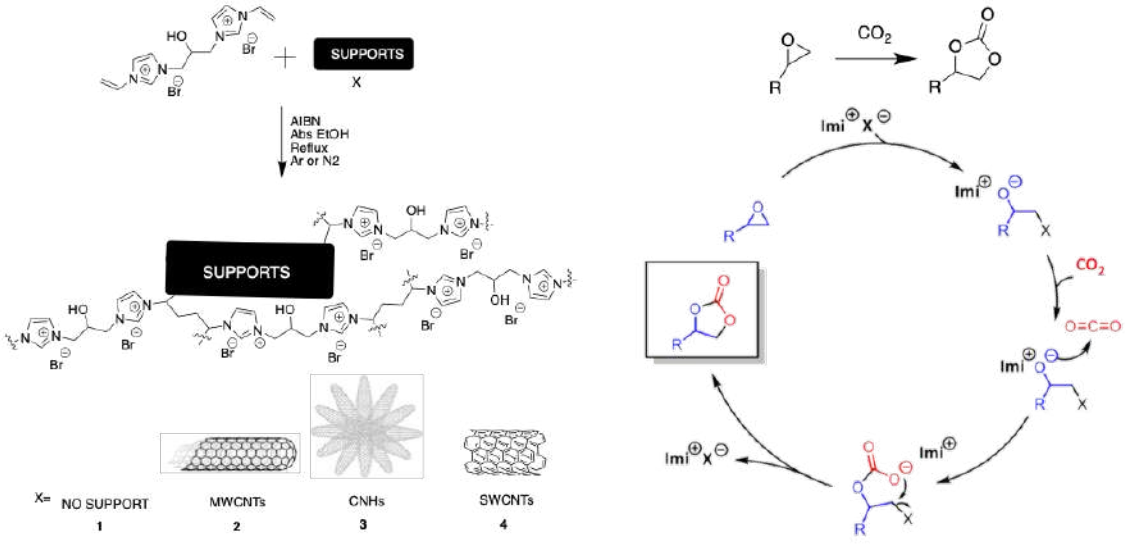

Figure 1: Synthesis of materials and mechanism of the reaction between epoxides and CO_2.

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Development of the synthesis process

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Amides represent the fundamental linking unit in peptides and proteins, consequently, their synthesis is one of the most studied processes in organic chemistry. The industrial amidations are involved in bulk chemical in polymer synthesis, and pharmaceutical production.[1] The conversion of esters into amides under mild conditions without metal catalysts or coupling reagents is a very interesting approach from the industrial point of view, since esters are stable and inexpensive compounds that are abundant in nature.[2] Sulphonamides constitute a class of useful compounds in the pharmaceutical fields. The sulphonamide group can be used to prepare nonsteroidal anti-flammatory drugs (FANS) that are used in the treatment of inflammatory disorders.[3]

The aim of this project is the development of a new synthetic process commissioned by a costumer* concerning the production of an API* (pharmaceutical active ingredient) that contains a sulphonamide group.

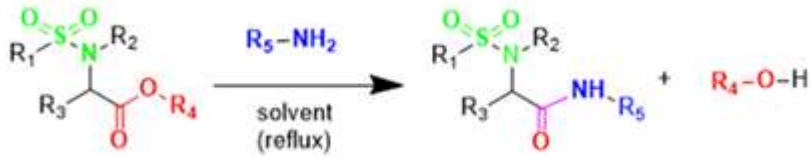

Figure 1: Synthetic route to API by the costumers*

The most important parameters were studied and identified in order to carry out an efficient and sustainable scale up. The crucial parameters are temperature, reaction-time, boiling points, amounts and solvents. Special attention was devoted to safety aspects of the synthesis reaction by the use of calorimetric instruments.

(*The details concerning compounds, methods, customers, documents and patents are protected by trade secret).

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Valorization of agro-industrial fermentation residues: biotransformation of ginger active molecules

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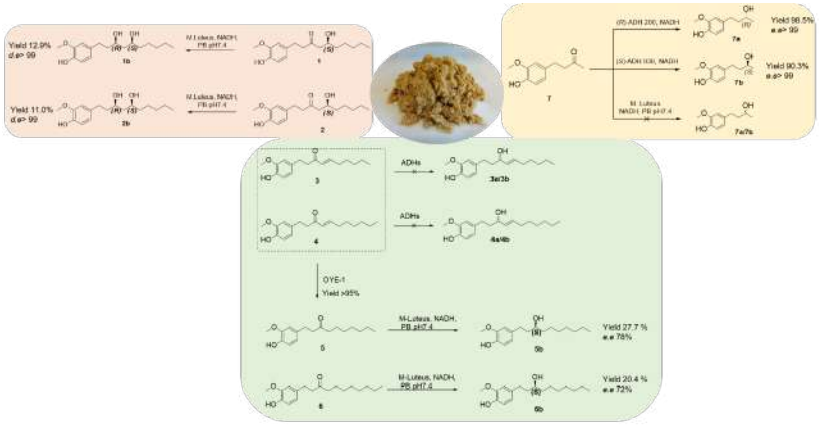
The ginger rhizome is a primary ingredient of oriental food, beverage, and herbal medicine catching on Western Countries meals. In 2016 the food sector processed 3.3 million tonnes of ginger generating a pulp waste that was mostly destined to agricultural field, biorefinery, papermaking etc.[1] The ginger pulp waste still contains an oleoresin rich in gingerol-like compounds, such as gingerols and shogaols, bioactive components with recognized anti-inflammatory and anticancer properties.[2,3] As an alternative valorisation strategy, the recovery of the main ginger waste components and their biotransformation to generate a small library of optically enriched derivatives was herein investigated. The oleoresin was first extracted from a fermented ginger biomass originating from a local farm. The conventional extraction confirmed the presence of still 30% gingerol-like compounds with unaltered chemical profile as characterized and quantified by UPLC-TUV and GC-MS. Then the enantioselective reduction of prochiral carbonyl moiety of pure isolated 6-gingerol (**1**), 8-gingerol (**2**), 6-shogaol (**3**), 8-shogaol (**4**), 6-paradol (**5**), 8-paradol (**6**) and zingerone (**7**) by different alcohol dehydrogenases (ADHs)[4] was investigated. From our preliminary results, no ketone reduction was observed for **3** and **4**. As far as the other substrates concern, only the ADH from *Micrococcus luteus* and engineered ADHs from Evoxx led to chiral alcohols with good to excellent diastereo- and enantiomeric excess (*d.e* and *e.e*) (Figure 1).



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Gold(I)-catalysed divergent reactivity of furans with *N*-oxides

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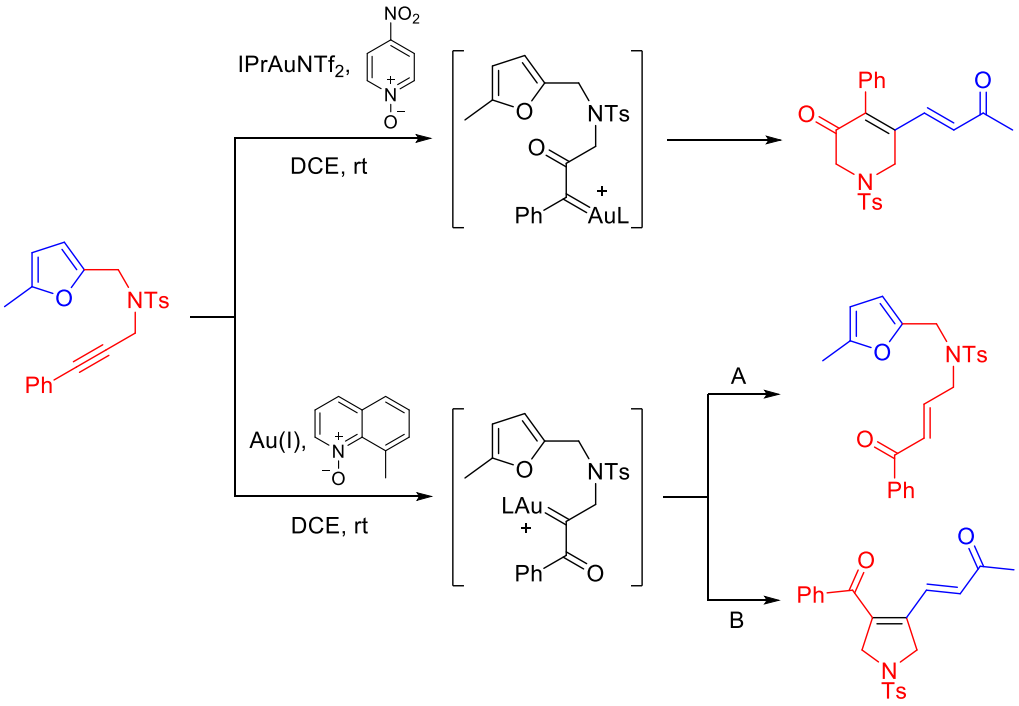
Since the beginnings of modern gold catalysis, furans have played a central role both as substrates and products of gold-promoted transformations. Hashmi's phenol synthesis from furan-tethered alkynes ("furan-ynes") represented one of the very first examples of π-activation of triple bonds by virtue of a gold catalyst.[1] The versatility of furans under gold-catalysed conditions is particularly enhanced by their peculiar attitude to easily undergo ring opening in the reaction mechanism, thus enriching the plethora of synthetic possibilities. On this basis, we wanted to investigate the reactivity of furans tethered to a reactive α-oxo gold carbenes species, generated by reaction of an alkyne moiety with a *N*-oxide species in the presence of a gold catalyst (Scheme 1).[2] Our results show that three different products are possible, and the selectivity of the reaction can be controlled by the choice of the gold catalyst and of the *N*-oxide.[3]



Scheme 1: Reactivity of α-oxo gold carbenes generated from furan-ynes.
A) Au(I) = MorDalPhosAu(NCMe)SbF_6; B) Au(I) = IPrAuNTf_2.

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CB-TE2A-Anhydride: a novel approach for one of the most stable copper chelators

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In bifunctional compounds (BFC), chelating properties of cyclam derivatives, able to chelate in a stable way Copper (II), are well known. In particular the Cu-CB-TE2A complex has shown high stability, efficient complexation and a very low *in vivo* transchelation[1]. In radiopharmaceutical context this chelator, which retains a radioactive metal inside, is linked to a biologically active molecule (probe) by an activator of the carboxylic function while the remaining acid functions are protected with orthogonal protector groups. The drastic conditions for deprotection, often, did not allow the use of a wide range of probes, which are already limited by the high temperatures necessary for copper chelation. In this work, a new synthetic pathway for the synthesis of a new chelator containing the CB-TE2A core is shown.

The multistep synthesis of the chelating agent is quite complex. Compared to the classic synthetic routes[2], we have been able to significantly reduce reaction times and increase yields. The totally deprotected chelator produced undergoes an intramolecular cyclization reaction to form a cyclic anhydride (Figure 1).

Our aim is to synthesize a new chelator that having a CB-TE2A-like core, able to bind to biologically active molecules without further purification in order to be used as a probe for PET trials. The final step that leads to the formation of cyclic anhydride is now under development. Finally, coupling tests will be carried out with various selected molecules to better understand the reactivity of this new compound.

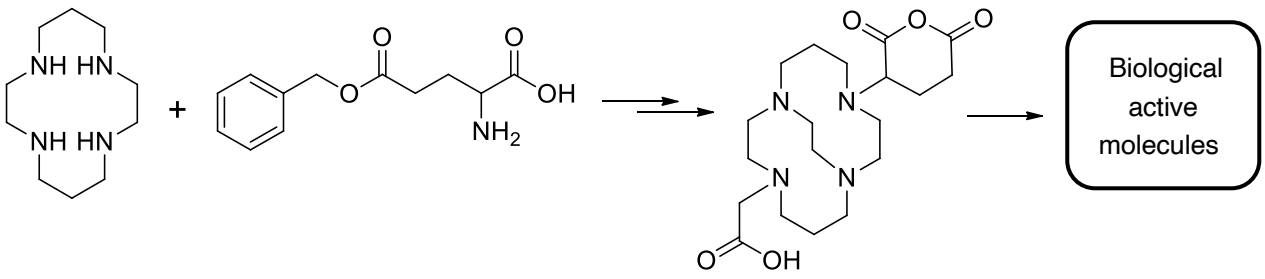

Figure 1: simplified reaction scheme

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Functionalization of CB[6] to sequester CO_2 as a supramolecular nanosponge

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This work aims to develop a new supramolecular system capable of adsorbing a significant amount of carbon dioxide. This system was developed starting from cucurbit[6]uril, which was initially functionalized by inserting 12 OH groups, with a reaction already present in the literature,[1] and subsequently functionalized with 12 chains of 1-(ethyl)-3-methyl-1*H*-imidazole-3-ium bromide (Figure 1).

The presence of the positively charged imidazole groups made possible the formation of cationic-dipole interactions between the positively charged side chain of a functionalized CB[6] and the carbonyl dipole of another functionalized CB[6]. This network of interactions led to the formation of further interstices, in addition to the cavities of the macrocycles, which transformed the system into a supramolecular nanosponge. The evidence of the formation of a supramolecular nanosponge is proven to adsorb a quantity of CO_2 about 8 times higher than the non-functionalized CB[6]. Also, the amount of CO_2 adsorbed is higher than that of zeolite BEA currently used in the industrial sector to adsorb volatile organic compounds (VOCs) and nitrogen oxides. The added value of this new system compared to the zeolite BEA are the much milder reaction conditions required for the synthesis.[2]

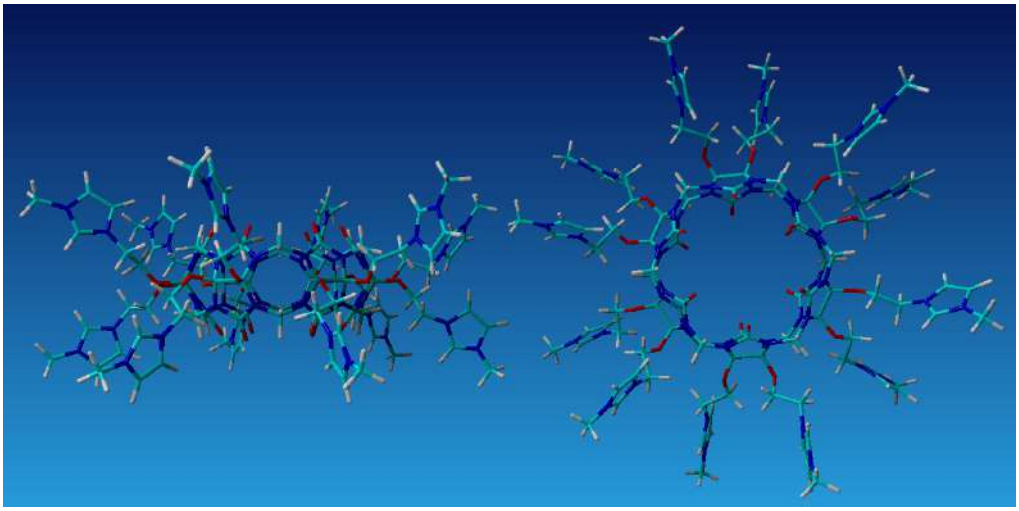

Figure 1: CB[6] functionalized with 12 ionic liquids, side, and top view.

References:

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Exploring secondary π-interactions in NHC-Au(I) complexes and their catalytic influence

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In organometallic catalytic reactions the direct bonds between organo-ligand and metal centre plays a pivotal role over the modulation of the overall catalytic activity. Differently, secondary interactions are usually neglected due to difficult predictions as well as rationalization.[1]

Gold(I) complexes are frequently targeted for these investigations due to their innate affinity for π-system. In particular, Buchwald's phosphine-based Au(I) complexes shown an evident Aryl-Au(I) π-interaction (Figure 1), which has been shown to strongly impact the catalytic effect.[2]

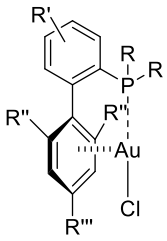

Figure 1: π-interaction between Au(I) and phenyl ring

In this oral presentation will be presented and discussed the synthesis of new C1-symmetric *N*-heterocyclic carbenes (NHCs) based on ImPy crores (Figure 2), which feature similar spatial arrangement with respect to the Buchwald type ligands. The focus of this project is to outline the electronic influence brought by oligo-aryl moiety at C5-position of imidazopyridine core.

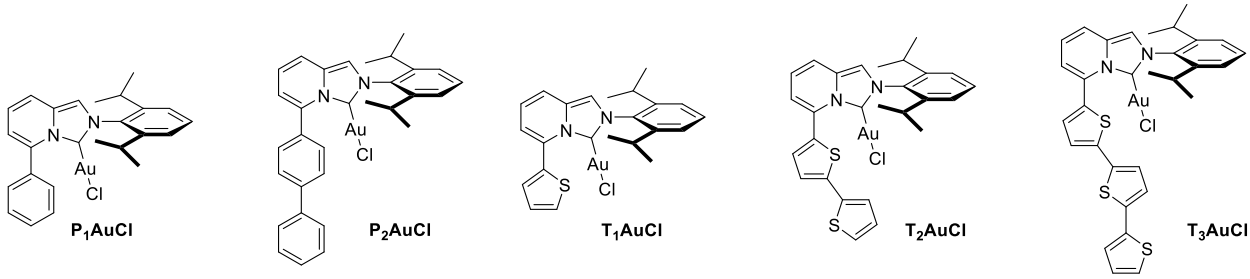

Figure 2: synthetized NHC-Au complexes

These Au(I) complexes have been fully characterized via crystallographic and photophysical analysis and have been employed in different catalytic reactions (e.g. dearomative reaction of naphthols and indoles, hydroamination, cycloisomeration of 1,6 enynes).

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Synthesis of Oxazinobenzimidazolone derivatives by $ZnCl_2$-promoted cyclization

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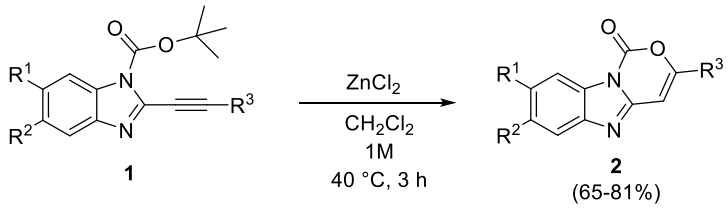
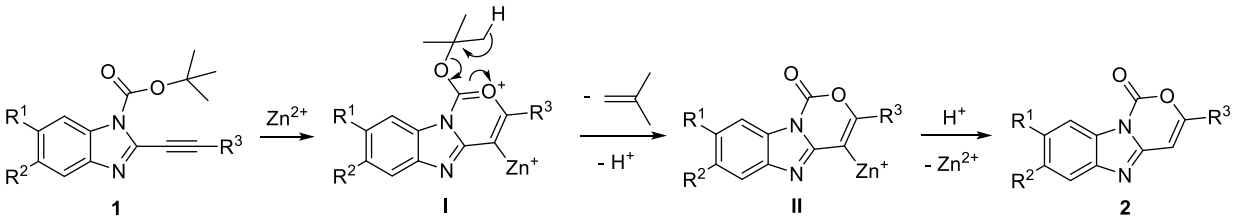
1,3-Oxazinan-2-one derivatives are an important class of heterocyclic derivatives, which possess remarkable biological activities, including antibacterial,[1] anticancer,[2] and antidiabetic activity.[3]

In this contribution, we report a new approach to oxazinobenzimidazolones **2** based on $ZnCl_2$-promoted cyclization of *N*-Boc-protected alkynylbenzimidazoles **1**. Reactions were carried out in presence of 1.5 equiv of $ZnCl_2$, in anhydrous CH_2Cl_2 at 40°C for 3 h, and products **2** were obtained in good to excellent isolated yields (65-81%, Scheme 1).



Scheme 1. $ZnCl_2$-promoted cyclization of alkynylbenzimidazoles **1** to oxazinobenzimidazolones **2**.

A mechanistic hypothesis for this $ZnCl_2$-promoted cyclization involves the intramolecular 6-*endo-dig* nucleophilic attack of the carbamate oxygen to coordinated triple bond to give a the cationic vinylzinc intermediate **I**, followed by β-H elimination with formation of isobutene and complex **II**. The latter eventually undergoes protonolysis to afford oxazinobenzimidazolone **2** (Scheme 2).



Scheme 2. Mechanistic hypothesis for the $ZnCl_2$-promoted cyclization of **1** to give **2**.

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A journey from thermally-tunable synthesis to spectroscopy of phenylmethanimine in gas-phase and solution

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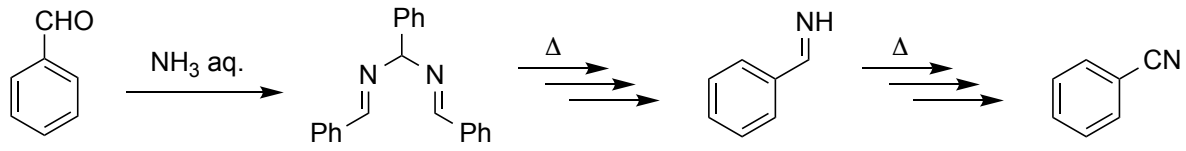
Phenylmethanimine is an aromatic imine with a twofold relevance in chemistry: organic synthesis and astrochemistry. Our group has recently exploited a multidisciplinary approach to tackle both aspects, through the identification of simple procedures to generate imine-intermediates in the gas phase and in solution.[1] The combination of this formation pathway – based on the thermal decomposition of hydrobenzamide – with a state-of-the-art computational characterization of phenylmethanimine, enabled us to detect this elusive species by means of rotational spectroscopy. Both *E* and *Z* isomers have been accurately characterized, thus providing a reliable basis to guide future astronomical observations. A further characterization has been carried out by nuclear magnetic resonance spectroscopy, showing the feasibility of our generation strategy even in solution. The temperature dependence as well as possible mechanisms of the thermolysis process have been examined.



Scheme 5: Synthesis and thermal decomposition of hydrobenzamide.

This work is a prerequisite for the possible radioastronomical detection of these species in the interstellar medium, relying on accurate rotational rest frequencies. First, in view of the strong chemical connection between benzonitrile and phenylmethanimine, an astronomical search in the region Taurus Molecular Cloud (TMC-1) is suggested.[2] Finally, owing to the thorough analysis of rotational and NMR spectra at different temperatures, a possible mechanism of phenylmethanimine formation by thermal tuning of hydrobenzamide, in which water is thought to play a crucial role, is also proposed.

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Synthesis of 3,4,5-trisubstituted isoxazole derivatives as FXR agonists

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The Farnesoid X nuclear receptor (FXR) is a widely studied target, expressed by the liver, gallbladder, intestine and by the kidneys, for its involvement in numerous physio pathological aspects of human organism. FXR is considered the sensor for bile acids which are its endogenous ligands[1], such as chenodeoxycholic acid. FXR activation regulates the bile acids homeostasis both suppressing their synthesis and reuptake and increasing their urinary excretion.[2] Furthermore, FXR plays a functional role in the regulation of glucidic and lipidic metabolism, exerts a considerable antinflammatory activity in enterohepatic tissues and thus it represents a validated target for the treatment of liver diseases, such as cholestasis, liver fibrosis, steatohepatitis (NASH), diabetes as well as obesity and metabolic syndrome. The growing interest towards this receptor inspired the synthesis of several small molecules characterized by different scaffolds ranging from steroidal to heterocyclic derivatives. The most potent FXR-selective known ligand with a non-steroidal core is GW4064,[3] an isoxazole derivative, whose use was limited by its reduced bioavailability and stilbene-mediated photo-instability. Our goal was the identification of new isoxazole derivatives as FXR-selective agonists that could overcome the limits shown by GW4064, with the application of traditional medicinal chemistry methods. In this work, we present the development of a wide set of molecules, in which several modifications were introduced at the C-3, C-4 and C-5 positions of the isoxazole ring that remained unvaried together with the acid terminal portion as in GW4064. The pharmacological characterization of this molecular library brought to the identification of several FXR agonists endowed with improved pharmacokinetics and with nanomolar potency in transactivation and SRC-1 recruitment essays, and thus potentially suitable for the treatment of liver diseases.

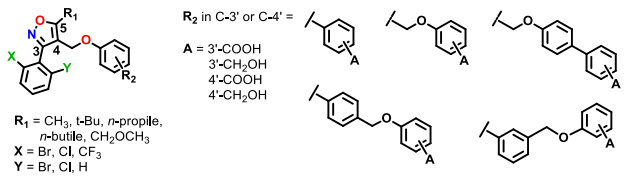

Figure 1: GW4064 derivatives

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Boc-protection on L-DOPA: an easy way to enhance underwater adhesion

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Mussels' ability to adhere to surfaces underwater is a trendy topic for the scientific community in recent years. It is widely believed that L-DOPA (3,4-dihydroxyphenyl-L-alanine), and especially its catechol moiety, plays a pivotal role in the adhesion process, involving hydrogen bonding, metal-oxide coordination, cation-π and hydrophobic interactions.[1] For this reason, L-DOPA is usually incorporated in materials and copolymers to improve their adhesive strength.[2]

In this work, two materials composed of a single-molecule with excellent underwater adhesive properties are presented. The synthetic process is simple, since it only consists in successive protection reactions starting from L-DOPA. The two compounds Boc_2-L-DOPA-OMe **1**, an inseparable mixture of two regioisomers, and Boc_3-L-DOPA-OMe **2** are represented in **Fig.1a**. Films of these molecules are prepared by casting and the adhesiveness is triggered in contact with an aqueous media, as these materials are non-adhesive in the dry phase. Their adhesive strength, expressed as normal force (**Fig. 1b**), is comparable to the adhesive strength of polymers containing L-DOPA.[3]

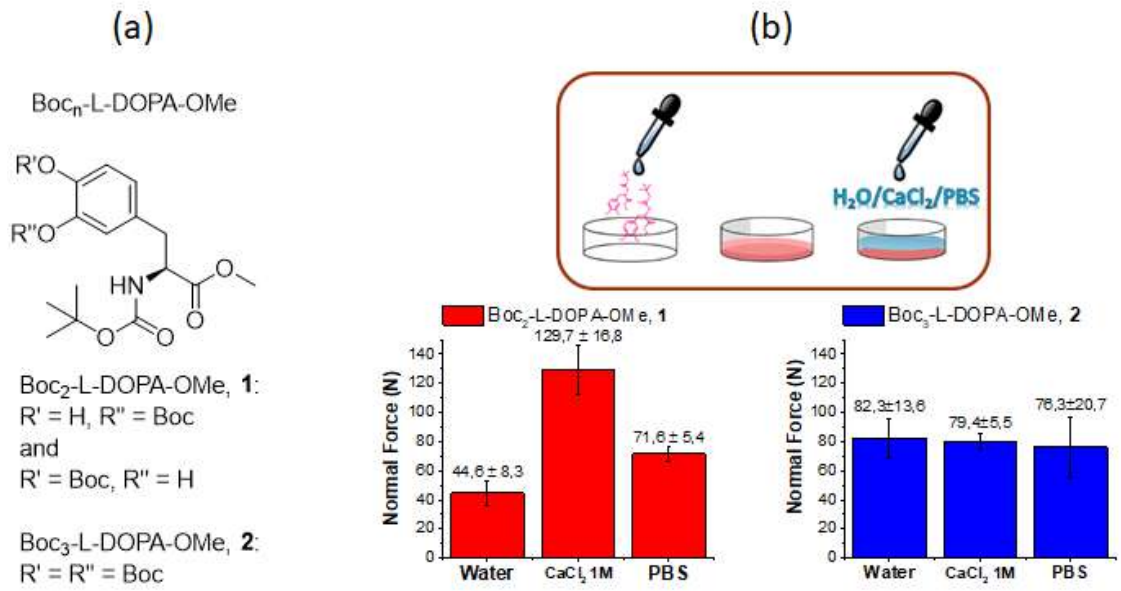

Fig. 1. (a) The chemical structure of the molecules synthesised, with Boc = t-butyloxycarbonyl; (b, up) the deposition of the compounds and the successive wetting with an aqueous media produces a very strong adhesive material; (b, down) the normal force registered with an Instron reported for each media.

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Structure to function investigation in NIR dyes for bilayer membrane imaging

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Near infra-red (NIR) emissive probes have recently attracted interest for bioimaging applications.[1] NIR dyes are characterized by red-shifted absorption and emission wavelengths, remarkable brightness, low photodegradation, while allowing deep tissue penetration, limited biological photodamage and autofluorescence.[2] Although various fluorophores have been synthetized and commercialized for selective staining of important biological structures, a regular innovation in the design of more performing probes for complex and dynamic supramolecular assemblies, such the bilayer membrane, is required.[3] NIR dyes have been recently introduced for the visualization and investigation of the biological membrane providing exceptional brightness and selectivity.[4]

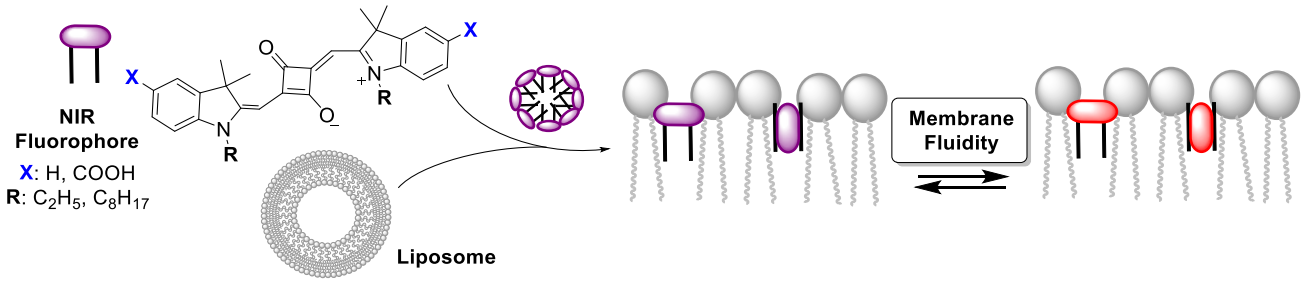

Figure. Schematic representation of the NIR dye staining of lipid bilayer membranes

In the present work, we have synthetized symmetric and asymmetric NIR squaraine, decorated with carboxylic groups on the chromophore and different lengths hydrocarbon chains on the quaternary nitrogen. The formers facilitate the solubilization in physiological media and lock the fluorophores on the outer side of the amphiphilic bilayers, while the latter have been varied to investigate their interactions with the hydrophobic moieties of the membranes. The kinetic of the insertion into large unilamellar vesicles (LUVs) bilayer membranes, the emission signal variations as function of the membrane phases have been studied in correlation to the probe molecular structures to provide key information for the optimization of new NIR probes for application in bioimaging.

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Double Carbonylative Cyclization for the Synthesis of Thienofuranone Derivatives

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After recent studies on the inhibitory activity of molecules with a furofuranone core, which showed an important antiproliferative activity on various human breast cancer cell lines[1], the possibility of synthesizing thienofuranone molecules has been investigated, also considering that no examples are currently known of synthetic approached for this type of heterobicyclic compounds.

In the present work, we report a general synthesis of thienofuranone derivatives **2** based on a PdI_2/KI-catalyzed oxidative *S*-cyclization-cyclocarbonylation process (Eq. 1)

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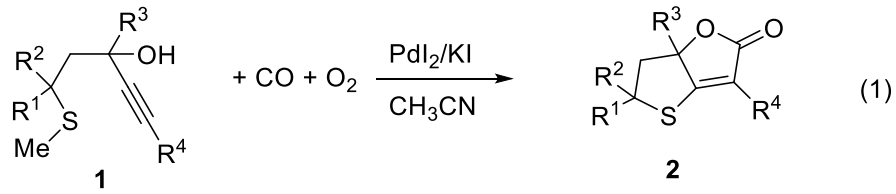

1

2

R^1, R^2, R^3= H, Me
R^4= Aryl, Alkyl

(55%-81%)

Figure 1

The protection of the thiol group with a methyl group in the substrates is of fundamental importance, as it avoids the possible formation of disulfide bonds under oxidative conditions. The methyl group on sulfur is, in fact, easily removed under the reaction conditions by the iodide anion to give methyl iodide, which in its turn convert into MeOH by reaction with water.

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Palladium-catalyzed C(sp3)-H activation for the sustainable intramolecular α-arylation of aryl-amides

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Nowadays, sustainability and environmental impact are among the most important aspects of any chemical reaction. Tools, such as heterogeneous catalysts, safe reaction media and flow chemistry have been proven effective for the development and achievement of green sustainable synthetic protocols[1]. In recent years, our research group has been particularly focused on the application of these tools on C–H activation strategies, especially those giving access to biologically and pharmaceutically valuable molecules[2]. Herein, we present the results of our ongoing work on an intramolecular C(sp3)–H activation reaction for the synthesis of oxindoles.

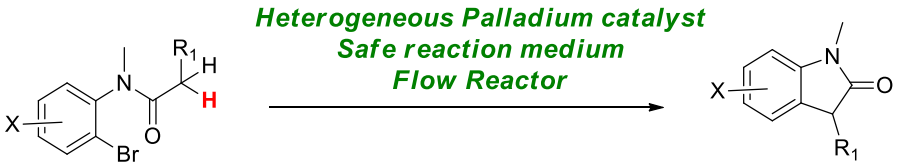

Figure 1: Reaction scheme.

Oxindole scaffolds are found in many biologically active molecules and many synthetic routes have been suggested for their synthesis[3]. In this work, a recyclable heterogeneous palladium catalyst is used, acheiving high conversion and selectivity in a safe reaction medium. A flow reactor will be designed and realized in order to further minimze waste production.

The Università degli Studi di Perugia and MIUR are acknowledged for financial support to the project AMIS, through the program “Dipartimenti di Eccellenza - 2018-2022”.

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Biosurfactants: chemoenzymatic synthesis of fatty acid esters of O-alkyl glucosides

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Sugar fatty acid esters (SFAEs), usually called sugar esters, are non-ionic surfactants which are characterized by excellent emulsifying, stabilizing and detergency properties. SFAEs are widely used in many market sectors (*i.e.* food, detergent, cosmetic and pharmaceutical industry); depending on carbon chain length and nature of the sugar head group, SFAEs cover a wide range of hydrophilic-lipophilic balance (HLB). SFAEs have many advantages over petrochemical-derived surfactants as they are neither harmful to the environment nor skin irritants; in addition, they are fully biodegradable. More interestingly, they can be produced from renewable resources.[1]

Chemical synthesis of SFAEs requires harsh reaction conditions which result, in most cases, in complex mixtures of monoesters, di- or triester isomers, and by-products. Enzyme-based synthesis is an alternative strategy that can overcome the above mentioned drawbacks: enzymatic reactions occur under milder conditions and are characterized by regio-, stereo- and chemoselectivity. Sugar fatty acid esters can be prepared, indeed, through an esterification reaction between a sugar ($C_n(H_2O)_n$) and a fatty acid (RCO_2H) catalysed by a lipase.[2]

However, reaction conditions for enzymatic esterification have to be tuned carefully. In particular, the selection of the solvent is the most critical issue due to the striking different solubility of sugars and fatty acids, as well as to the need to conjugate reagents solubility with enzyme activity and stability. Therefore, although the use of solvent represents a straightforward strategy, difficulties in obtaining high concentration of both reactants within a single phase are such that the overall yield is generally poor.[3,4] To overcome this constrain, the sugar moiety was chemically modified into a less polar derivative, followed by solvent-free esterification with molten fatty acids.

Thus, using glucose as the model substrate, an isomeric mixture of butyl glucosides was prepared by an *O*-glucosylation reaction with 1-butanol in the presence of Amberlyst® 15, a strongly acidic cation exchange resin. In parallel, butyl-*β*-glucopyranose was obtained using *β*-glucosidase from bitter almond as a catalyst. Resulting modified sugars have been submitted to lipase-catalysed esterification with molten fatty acids to obtain SFAEs, whose emulsifying properties are under evaluation.

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CJ-15,208/cEM1 hybrids, novel members of the Trp-Containing Non Cationizable Opioid Peptides (TrpCoNCOPs) class

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Despite of the relevant undesired side effects that can limit their clinical use, the agonists of K-opioid receptor (KOR) represent an interesting alternative to the opiates as analgesics and therapeutics for drug abuse. Functionally selective KOR agonists may activate G protein pathway-specific mediated signaling, that produces antinociception, over β-arrestin2 signaling, which contributes to the adverse effects. In the present study, we discuss a library of cyclic TrpCoNCOPs designed as hybrids of the naturally occurring mixed KOR/MOR ligand CJ-15,208[1], which showed agonist activity in vivo, and the MOR agonist cEM1[2], previously synthesized in our lab, characterized by a D-configured tryptophan, the most relevant pharmacophore, as determined by mol. docking.

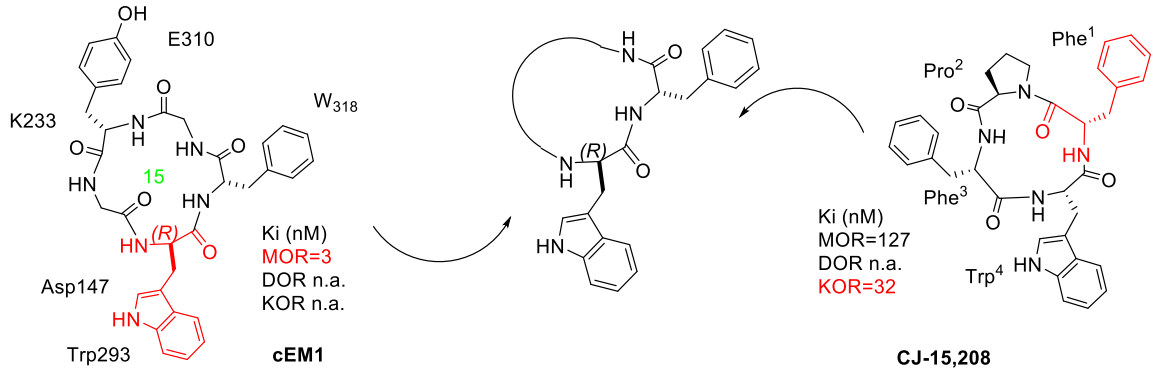

Figure 1: Structures of cEM1, c[Gly-D-Trp-Phe-Gly-Tyr], and CJ-15,208, c[Phe-Trp-Phe-Pro]. Both compounds contributed to create the library of compounds showed in this study.

We prepared 12-,13-, and 14-membered cyclotetrapeptides containing the D-Trp-Phe motif, by introducing α-,β- or γ-amino acids. We evaluated the affinity for the opioid receptors by competition binding experiments; it resulted that the D-Trp-Phe sequence represents a general pharmacophoric motif for the opioid receptors, while the rest of the sequence can drive the selectivity against one specific opioid receptor. In particular, the compound LOR17 c[Phe-Gly-βAla-D-Trp], is a selective, G protein biased KOR agonist, as determined by the cAMP inhibition test. ERK1/2, p38MAPK phosphorylation, and astrocyte cell proliferation were also studied in HEK-293 cells expressing hKOR, U87-MG glioblastoma cells, and primary human astrocytes. Furthermore, we found that compound RDM1135, c[Phe-Gly-GABA-D-Trp], showed nM affinity and high selectivity for KOR, while RDM1127, c[Phe-βAla-β-Ala-D-Trp], resulted to be a KOR antagonist with sub nM affinity.

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Feature-based molecular networking for the fast detection of novel compounds from the old sponge *Stylissa caribica*

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Marine organisms represent the most prolific source of chemically diverse natural products, showing a wide variety of pharmacological properties. A central issue in natural product research is the fast identification of novel natural products from complex extracts, containing hundreds or thousands of different compounds, including primary metabolites, contaminants and known natural substances. LC-HRMS is the analytical technique of choice for analysis of complex extracts, but it provides huge amounts of data that are hard to be examined manually.

Feature-based molecular networking is a modern bioinformatic tool that can be used for efficient analysis of LC-HRMS data. Molecular networking allows the automated identification of structural similarity between metabolites, which are inferred from the relatedness of their MS^2 spectra. In the recent feature-based implementation, molecular networking can also handle the chromatographic features of each compound.[1] The value of features-based molecular networking in natural product discovery has been demonstrated with the isolation of stylissamide L, a new proline-rich cyclic heptapeptide from the extracts of the thoroughly investigated marine sponge *Stylissa caribica*, known to be very rich in cyclic peptides and a wide array of brominated pyrrole-imidazole alkaloids. Structure of stylissamide L, including the cis/trans geometry of the three proline residues, was determined by extensive NMR studies while the L configuration of the seven amino acid residues was assigned performing Marfey's methodology.[2] The accurate analysis of all molecular networking clusters, in search of new natural compounds and their resulting isolation is in progress.

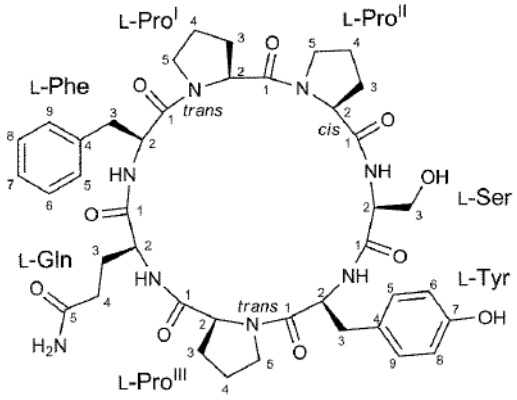

Figure 1. Structure of stylissamide L (**1**).

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Alkoxy-Bromo-Azulenes Displaying Ambient Temperature Smectic E Phases

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Azulenes and crystal-smectic E-phases (SmE) both have recently raised attention in the field of organic electronics.[1–3] The unique electronic properties of the azulene moiety has not been combined with the self-assembly of soft-crystalline phases yet. Therefore, a convenient synthesis of 6-alkoxy-2-bromoazulenes, forming ambient temperature SmE-phases, was developed.[4] Investigations by differential scanning calorimetry, polarising optical microscopy and X-ray diffraction provided insight into the arrangement of this well ordered smectic phase. Comparison of experimental data and quantum chemical calculations of 6-alkoxy-2-bromoazulene with the 'inverted' 2-alkoxy-6-bromoazulene revealed large differences in polarity, which affected optical and mesomorphic properties, and provided insight into structure-property relationships enabling the design of novel thin-film devices.

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Design and synthesis of new potential inhibitors of proteins relevant to cancer insurgence.

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In the last years, several studies have reported the importance of prostaglandin E2 (PGE2) in the evolvement and progression of inflammatory and tumor diseases.[1]The identification of novel inhibitors of eicosanoids biosynthesis with unexplored scaffolds is of great demand to develop a next-generation of anti-inflammatory drugs.

In this poster, we report the identification of new inhibitors of several enzymes involved in the progression of inflammation. Following a multidisciplinary protocol that involves virtual combinatorial screening, chemical synthesis, and validation of the biological activities we afforded to the identification of 1,2,4-oxadiazole hits, able to bind 5-lipoxygenase-activating protein (FLAP) and to inhibit dually microsomal prostaglandin E2 synthase-1 (mPGES-1) and 5-lipoxygenase (5-LO). 1,2,4-oxadiazoles represent a versatile "privileged scaffold" in drug discovery, due to the possibility of modifying and opportunely decorating the nucleus.[2] These promising outcomes pave the way toward a medicinal chemistry optimization campaign of the disclosed hits.

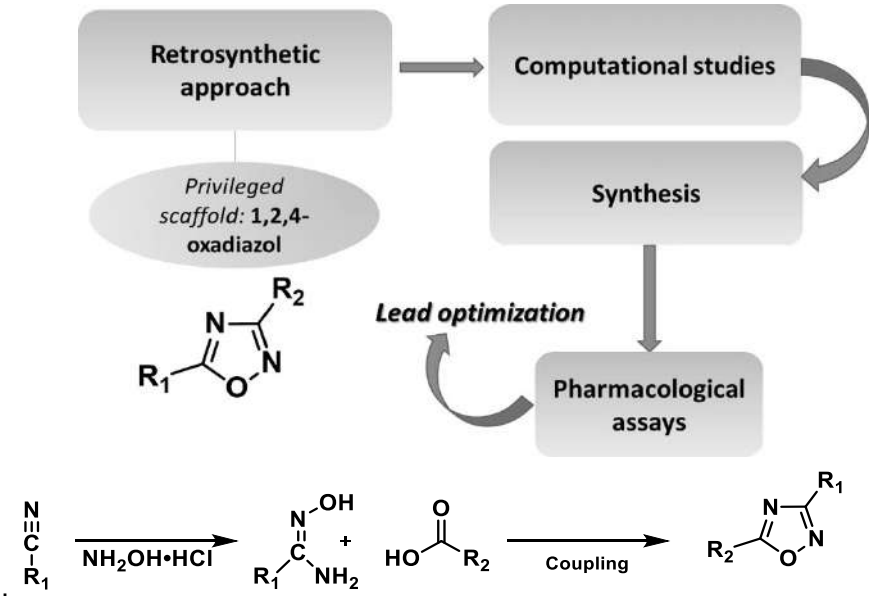

Figure 1: *Multidisciplinary approach and schematic synthetic protocol.*

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Tailor-made Heterogeneous and Recoverable Palladium Catalyst to access Regioselective C–H Alkenylation of Quinoline N–oxides

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The methods for the direct transformation of the C–H bonds are in constant development, proving to be a handy tool in material science and the synthesis of natural products and pharmaceuticals.[1] Many C–H functionalization protocols have been realized exploiting the ability of functional groups to create weak interactions with C–H bonds positioned in their vicinity.[2] In this context, N–Oxide functionality is intriguing, due to its ability in controlling regioselectivity,[3] and the possibility to exploit this functionality as an internal oxidant. Despite recent progress realized with heterogeneous or heterogenized catalytic systems the palladium-catalyzed C-2 selective C–H functionalization of quinoline N– oxide moiety has been solely restricted to the use of homogeneous catalysts. Within our research program devoted to the design and definition of recoverable catalytic systems for C–H activation reactions,[4] we have developed the first recoverable heterogeneous catalyst for the C-2 selective alkenylation of quinoline N–oxide.

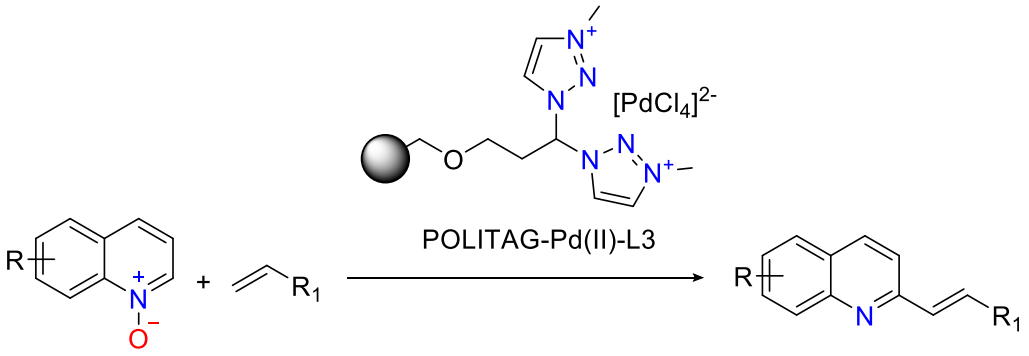

Figure 1: Reaction Scheme

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Aminocatalysis performed by supramolecular fibrils

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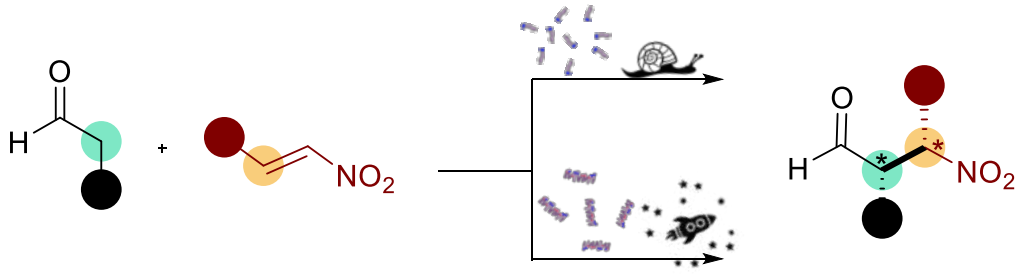
Asymmetric aminocatalysis has seen an incredible growth since the beginning of the last millennium [1]. A considerable variety of aminocatalysed reactions were discovered in the following years underlining the great power of this synthetic technology [2]. Industrial R&D routinely screens organocatalysis as a technology platform; however, its full applicability is sometimes hampered by the relatively high catalytic loading.

By exploiting supramolecular interactions, we present small organocatalyst that are able to self-assemble. These more complex and structured architectures display enhanced catalytic activity with respect to their monomeric counterparts.

This proof of concept was demonstrated and is currently studied for the evolution of new and more active catalysts.



Scheme 1: general reaction performed by fibril-catalyst

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Palladium Iodide-Catalyzed Oxidative Carbonylation of Alkyne Substrates Bearing a Sulfurated Nucleophile: A Multicomponent Approach to Thiophene-3-Carboxylic Esters

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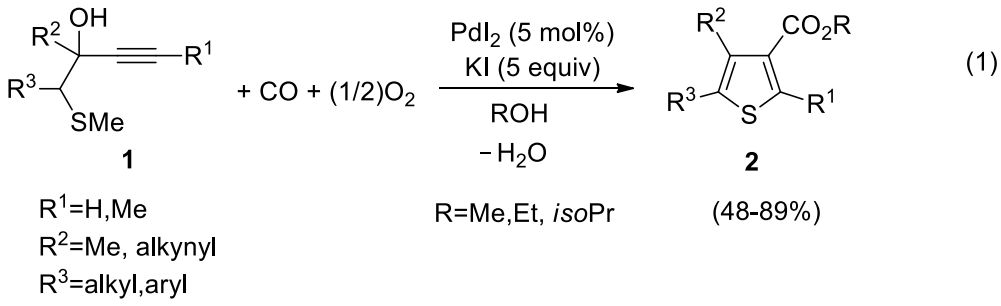
The PdI_2/KI-catalyzed oxidative carbonylation of acetylenes suitably substituted with a nucleophilic group –YH (Y = O, NR) has proved to be a powerful methodology for the construction of functionalized heterocycles in a multicomponent fashion starting from simple building blocks [1].

In this contribution, we report on the PdI_2/KI-catalyzed carbonylative *S*-cyclization of 1-(methylthio)-3-yn-2-ols carried out under oxidative conditions to yield thiophene-3-carboxylic esters **2** as shown in Eq. 1.



To avoid the possible oxidation of a free thiol group, a methylthio group as sulfur nucleophile was used in the substrate, considering that the methyl group on sulfur could be removed under the reaction conditions by reaction with the iodide anion to give methyl iodide. Reactions were performed in alcohols, as external nucleophile and solvents, and under 40 atm of a 4:1 mixture of CO-air. This new synthetic transformation could be successfully applied to the synthesis of different types of thiophene derivatives **2** which are known to possess important pharmacological activities [2].

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KuQuinone Redox Species: A multifaceted investigation

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Comprehension of electrochemical properties of complex quinones is a fascinating topic in chemistry. Indeed, quinoid systems are essential in many biological systems,[1] in energy storage devices[2] and in many other fields.[3] The quinones key role in the aforementioned applications is mainly due to their easy and highly customizable redox chemistry. The solvent, the nature of the supporting electrolyte, the inter- or intramolecular hydrogen bond as well as the presence of acidic additives are just a few factors that can stabilize the quinones redox species and thus modulate their redox properties. Our interest in quinones chemistry started few years ago,[4–8] when we first reported a one-pot synthesis of a new class of polycyclic quinoid compounds, called KuQuinones (KuQs). Such molecules have been used as harvesting material in photoelectrochemical devices[5–7] exploiting their intriguing spectroscopic and electrochemical properties. Hence, in order to deeply understand the nature of KuQuinone redox species involved in the observed electron transfer processes electrochemical and spectro-electrochemical investigation is necessary. In this contribution, a detailed study of KuQuinones redox behaviour, also in the presence of hydrogen bond donor species, will be presented.

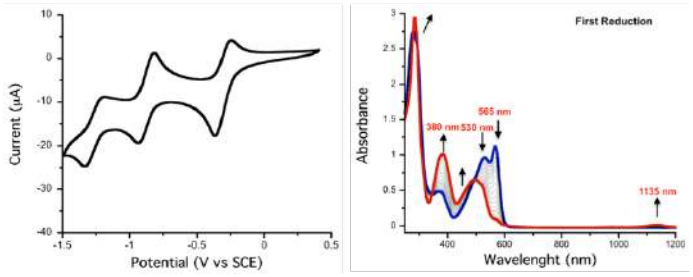

Figure 1: (left) Cyclic voltammetry of KuQEt in CH_2Cl_2/TBAP 0.1 M. (right) UV-vis-NIR spectroelectrochemical of KuQEt during the first reduction process in CH_2Cl_2/TBAP 0.3 M.

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Design and synthesis of fluorescent molecularly imprinted polymers for the recognition of chlorogenic acid

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Phenolic compounds are secondary metabolites frequently found in plants: due to the relevant bioactivity, their identification and quantification in agro-food matrices is a fundamental issue in the field of quality control of food and food supplements.[1] 5-O-caffeoylquinic acid (known as chlorogenic acid CGA) is one of the main phenolic compounds found in coffee, and the interest in developing new methodologies for its identification is due to its high dietary intake as well as to its many properties beneficial for human health.[2] A very promising method to measure this analyte is that of using biosensors, such as fluorescent molecularly imprinted polymers (*f*MIPs), biomimetic recognition elements synthesized through the imprinting technique by performing the polymerization process in the presence of the template and then removing it from the polymer to obtain cavities that should selectively recognize the target molecule. The first two polymers were synthesized through radical polymerization using in both cases 4-vinylpiridine (4VP) as the functional monomer, a reduced mimic of CGA as template, a naphthalimide derivative as fluorescent functional monomer but changing the crosslinker which was in one case N,N'-methylenebisacrylamide (MBA) and ethylene glycol dimethacrylate (EGDMA) in the other (figure 1). Preliminary studies were performed such as UV-visible and fluorescence characterization. It was possible to observe that the polymer having the MBA crosslinker performs better, exhibiting quenching of its intrinsic fluorescence upon binding of the target molecule CGA. Two other *f*MIPs and the corresponding non-imprinted polymers (NIPs) were synthesized using in both cases 4-VP as functional monomer and a fluorescein-based co-monomer, but using divinylbenzene (DVB) and CGA as crosslinker and template respectively in one case, EGDMA and reduced-CGA in the other.[3] Preliminary rebinding tests were performed through HPLC, thus demonstrating that both MIPs have a higher rebinding ability with respect to the corresponding NIPs. As for fluorescence characterization of these polymers, further work will be done in order to find the best conditions for stabilizing them, thus obtaining regular fluorescence behavior upon addition of target molecule. Since the preliminary results seem to be promising, further characterization of the *f*MIPs will be performed, and the final aim of the project will be that of synthesizing different biosensors targeting natural compounds for the validation of a multisensory platform that should be used for real samples analysis.

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Thermal stability of DNA in hydrated imidazolium-based ionic liquids

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In the last decade, ionic liquids (ILs) are drawing great attention thanks to their distinctive properties including negligible vapour pressure, good thermal and chemical stability and high ionic conductivity. More recently, ILs have become appealing as new and highly efficient solvents or co-solvents in the studies of stability, activity and other properties of several bio-molecules (e.g. saccharides, peptides and nucleic acid).[1] DNA is generally stable in aqueous solution, although changes in temperature, pH, and solvent properties can disrupt its typical helix structure, leading to denaturation. Several studies have reported the effect of various classes of ILs on the solvation properties, stability and packing of DNA improving its long term and thermal stability.

Specifically, we have focused on the use of imidazolium based ILs for improving the thermal stabilization of DNA.[2] Temperature of melting transition of DNA is the parameter directly related to the separation of the strands that leads to the destruction of helix structure. Its value can be usually determined in temperature dependent experiments of Circular Dicroism and UV-absorbance. UV-Raman Resonance (UVRR) spectroscopy takes the advantage of a selective focus on the thermal responses of specific nucleobases in the structure of DNA occurring along the complex unfolding process of DNA (Figure). In particular, the excitation wavelength at 250 nm provides a strong enhancement in the Raman spectra of specific vibrational signals that are sensitive markers of the breaking of H-bonds and uncoupling of guanine base. As main results, we have found that i) both the cation and anion of ILs play a relevant role in stabilizing the DNA and ii) the greatest thermal stabilization is produced by short-chain imidazolium cations (9 K in presence of [EMIM]Cl).

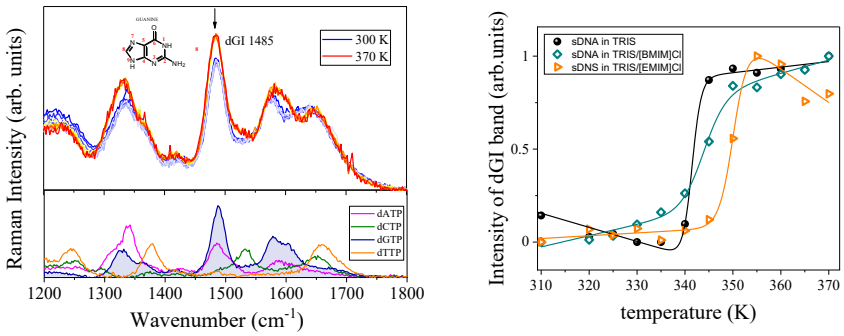

Figure: temperature evolution of UVRR spectra of salmon DNA in TRIS buffer (left, top); UVRR spectra of nucleotides for assignment of main vibrational signals in the spectrum of sDNA (left, bottom); temperature-dependence of the intensity obtained for the dGI band for sDNA in absence and presence of ILs (right).

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Riccardo Moro	UniTO	P39
Giada Moroni	UniBO	F01
Rita Nasti	UniMI	P40
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Thank you

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