OC-91

Synthesis and characterization of a PNA probe targeting the Bcl-2 gene promoter: a promising tool in anticancer treatment

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Among several anti-gene strategies, the use of DNA analogues such as Peptide Nucleic Acids (PNA) represents a promising approach for the modulation of gene transcription. PNAs are mimics of DNA in which the sugar-phosphate backbone is replaced by the N-(2-aminoethyl)glycine moiety. The absence of charges on the PNA backbone allows the formation of PNA/DNA complexes provided with a higher stability than that of the corresponding natural DNA/DNA counterparts [1]. We have recently demonstrated that the PNA complementary to the 7-mer longest loop of the G-quadruplex formed by the 23-mer bcl2midG4 sequence, located 52–30 bp upstream of the P1 promoter of Bcl-2 gene, is able to selectively bind the loop of the structure. The results have shown the ability of the PNA-coated OAd5 oncolytic vectors to load and transfect their PNA cargo with a high efficiency and also the synergistic cytotoxic effect against human A549 and MDA-MB-436 cancer cell lines [2]. We have also demonstrated that the synthesized PNA does not interact with the corresponding duplex. With the aim of improving the target specificity we have investigated whether the length of the chosen PNA sequence could affect the type of interaction with the complementary DNA sequence. We extended the length of the pyrimidine-rich PNA from seven to ten bases complementary to the $N_{10–19}$ tract of the bcl2midG4 sequence target. Additionally, we synthesized the 10-mer PNA-FITC labelled analogue. PAGE, CD and CD melting experiments were performed to investigate the interaction of the PNA and its analogue with the DNA target, in both quadruplex and duplex complexes. Moreover, molecular dynamics simulations were used to investigate the stability and the structural features of the target heterotriplexes. The drugability of the new PNAs was attested by fluorescence microscopy which showed that the FITC-labelled PNA specifically enters the cell nuclei, with no significant fraction being co-localized in the mitochondria or endoplasmic reticulum organelles. Finally, preliminary cytotoxicity assays confirmed the biological activity of the new anti Bcl-2 PNA. Overall, the studies here reported extend our knowledge about the structural properties of DNA_2-PNA heterotriplexes and provide the basis for the development of new PNA-based anticancer agents for the treatment of human cancers expressing high levels of the Bcl-2 protein.

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OC-92

Combined effect of amide protons and second sphere water molecules on the relaxivity of Gd(III)-DO3A-hydroxypropionamide complexes

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Gd(III) complexes with polyaminopolycarboxylic ligands are commonly used as MRI contrast agents (CAs) in the medical diagnosis. In particular, Gd(HP-DO3A) (ProHance®, **Figure 1**), one of the clinically approved MRI CAs, contains two sources of protons for transferring the paramagnetism of the Gd(III) ion to the bulk water, namely the coordinated water molecules and the proton on the coordinated hydroxyl group.[1] The objective of this study was the synthesis of different HPDO3A-like ligands, in which the methyl group in the ordinary arm of HP-DO3A was functionalized with electron-withdrawing amide groups. In particular, we have synthesized (**Figure 1**) HPA-DO3A ligands bearing, a primary, a secondary and a tertiary amide (**1**-**6**) as well as a dimeric $(HPA\text{-}DO3A)_2$ system (**7**).[2] Among the secondary amides, different options on the amidic moiety were also explored, such as hydrazides (**3**), 1,3-dihydroxypropyl (**4**) and methylphosphonic (**5**) functionalization.

As for their application as MRI CAs, the presence of electron-withdrawing amide groups and other hydrophilic groups near the metal centre have three effects: 1) it makes the –OH group in the hydroxypropyl arm more acidic; 2) it introduces an acid-catalyzed prototropic effect and 3) it makes possible the presence of water molecules in the second sphere of hydration. All these effects cause an improvement of the relaxation properties of Gd(HPA-DO3A) complexes (measured by ^{1}H and ^{17}O NMR relaxometry), in particular at acidic pH. Moreover, as these chelates have to be stable for *in vivo* application, the stability constants and the kinetic inertness of Gd-HPA-DO3A complexes were determined by pH-potentiometry and spectrophotometry.

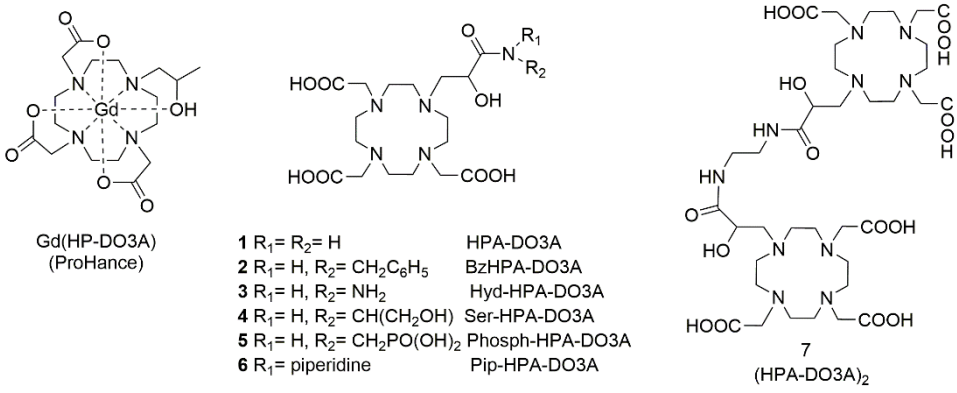

Figure 1: Structures of the ligands involved in this work.

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OC-93

From microalgae to vaccine adjuvant: immunomodulant activity of sulfavants and its correlation with colloidal self-assembly

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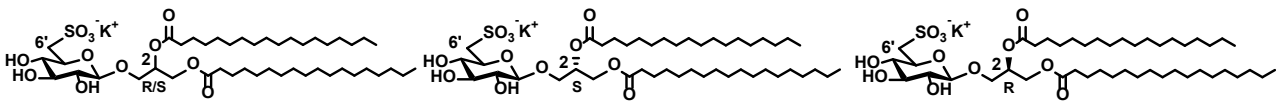
In the last decades, the improved understanding of how innate mechanisms influence the adaptive immunity system has prompted the research of new vaccine adjuvants by a rational design of new chemical entities.

Recently, we have searched for new immunomodulants in extracts of diatoms. This work led to isolation and characterization of α-sulfoquinovosides [1] as possible adjuvant candidates. These algal substances showed a promising activity and their biological optimization by structural modification led to the synthetic analog 1,2-O-distearoyl-3-O-β-D-sulfoquinovosyl glycerol named Sulfavant A. The synthetic product induces maturation of human dendritic cells (DCs) with no expression of inflammatory cytokines and, in vivo, boost of a immune protective response.[1] Later on, two other synthetic analogues of Sulfavant A (named Sulfavant S and Sulfavant R) were synthesized, and they showed the capability to elicit DC maturation at a concentration 1000 times lower than that the progenitor molecule.[2]

Investigation on the colloidal arrangement of Sulfavant A, R and S pointed out the formation of different kind of aggregates for the three molecules (Graph 1). The supramolecular interactions of these aggregates affect the different immunomodulant behavior of these molecules. [2]



Sulfavant A Sulfavant S Sulfavant R

Acknowlegments:
Authors thank European Union “PON Ricerca e Innovazione 2014-2020” for funding a Ph.D

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OC-94

Gold Catalysed Coupling Reactions of Arenediazonium *o*-Benzenedisulfonimides

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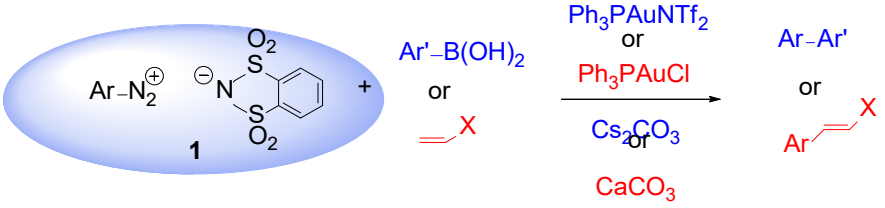
Gold catalysis is considered a fundamental topic in organic synthesis with several applications.[1] The high importance of gold catalysis is attributable to some peculiar qualities of gold which include good commercial availability, remarkable stability, functional groups and oxygen tolerance, tunability, minimal use of additive and excellent chemoselectivity. The use of oxidative gold catalysis as an effective means of facilitating C–C bond-forming reactions has been attracting increasing amount of attention in recent years.[2] The fact that Au (I) and Pd(0) are isoelectronics means that Au (I) species are able to catalyse reactions, including cross-coupling reactions, that are typically promoted by Pd(0). It is worth noting that strong oxidants were normally required in order to facilitate the Au (I)/Au (IIII) transition in the catalytic cycle. Some of our researches have resulted in a large family of dry diazonium salts, the arenediazonium *o*-benzenedisulfonimides **1** (Scheme 1).[3]



Scheme 1: Arenediazonium *o*-Benzenedisulfonimides **1** in gold catalysed Heck and Suzuki couplings

The properties of these compounds mean that they have great potential in numerous synthetic applications. In fact, they are easy to prepare and isolate, they are extremely stable, and they can be stored for an unlimited time. Moreover, they react easily both in water and in organic solvents, and *o*-benzenedisulfonimide can easily be recovered and reused at the end of the reactions.

Interestingly, arenediazonium salts have been recently used as electrophilic reactants in some Au (I) catalysed cross-coupling reactions, usually under fotoredox conditions.[4] In fact, their capacity to undergo to a single-electron reduction under visible light and in the presence of photosensitizers means that they provide aryl radicals which give sequential oxidative additions onto Au (I) species. The subsequent reductive elimination from the resulting Au (III) complexes, produces the desired coupling adducts and regenerates the Au (I) catalyst.

In the light of these, we proposed mild, easy and efficient gold catalysed Heck and Suzuki couplings of arenediazonium *o*-benzenedisulfonimides **1**.[5] The target products were generally obtained in satisfactory yields. It is worth noting the interesting role that the *o*-benzenedisulfonimide anion plays as an electron transfer agent in enabling a radical pathway that does not require the presence of photocatalysts or external oxidants.

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OC-95

A Palladium Iodide – Catalyzed Oxidative Carbonylation Process for the Synthesis of Functionalized Imidazopyridines

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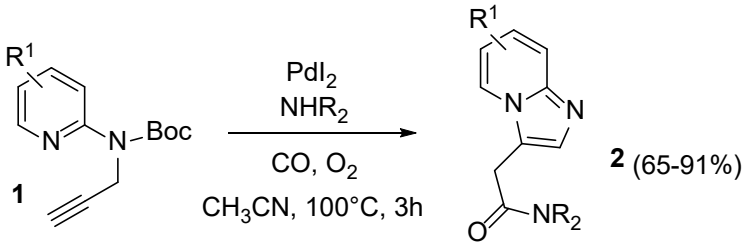
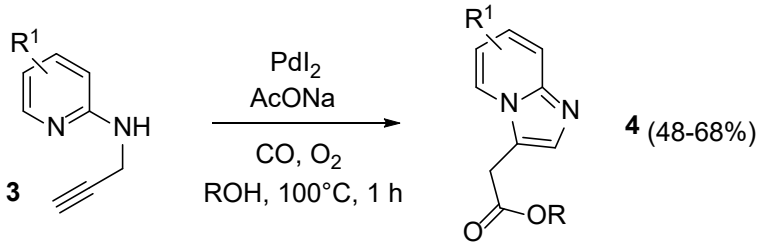
We report a novel PdI_2-catalyzed carbonylative approach to the synthesis of functionalized imidazo[1,2-*a*]pyridines starting from readily available (prop-2-yn-1-yl)pyridin-2-amine derivatives. Imidazo[1,2-*a*]pyridines are an important class of diheterocyclic derivatives, known to display a wide range of pharmaceutical activities (such as anticancer, antimycobacterial, antileishmanial, anticonvulsant, antimicrobial, antiviral, antidiabetic, proton pump inhibitor, and insecticidal activity).[1]

The reaction takes place through the oxidative monocarbonylation of the terminal triple bond with C-H activation,[2] followed by intramolecular conjugated addition and double bond isomerization, to give 2-(imidazo[1,2-*a*]pyridin-3-yl)-*N*,*N*-dialkylacetamides **2** or alkyl 2-(imidazo[1,2-*a*]pyridin-3-yl)acetates **3**, depending on reaction conditions. In particular, amides **2** were obtained starting by *N*-Boc-protected-(prop-2-yn-1-yl)pyridin-2-amines **1** which underwent deprotection in situ and carbonylation when allowed to react with CO, O_2 (20 atm of a 4:1 mixture of carbon monoxide and air) and a secondary amine, in presence of catalytic amount of PdI_2 in conjunction with KI, in CH_3CN at 100° C° for 3 h (Scheme 1).



Scheme 1

On the other hand, *N*-unsubstituted (prop-2-yn-1-yl)pyridin-2-amines **3** were converted into esters derivatives **4** when the process was carried out in an alcoholic solvent in presence of AcONa as the base and the catalytic system PdI_2/KI, at 100°C for 1 h, under 16 atm di carbon monoxide and 4 atm of air (Scheme 2).



Scheme 2

References:

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OC-96

Allylation of Aldehydes by Dual Photoredox and Nickel Catalysis

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Addition of allyl organometallic reagents to aldehydes, ketones, and imines is a widespread used methodology in organic synthesis.[1] A plethora of organometallic reagents and conditions have been exploited for chemo- and stereo-selective allylation.[2] Normally, organometallic allylating reagents are obtained by redox reactions with metals in low oxidations state and suitable allyl precursors (e.g. allylbromides). Stoichiometric use of metals for preparing the organometallic reagent are therefore necessary and the final work-up of the reaction results in the production of waste.

Recently, the merging of transition metal catalysis and photoredox catalysis has become a hot topic in organic chemistry.[3] Numerous examples of highly effective photocatalytic C(sp^3) cross-coupling reactions were recently reported. Only few examples concerning the addition to polar functional groups, such as carbonyls or imines were described,[4] and no examples of generation of nucleophilic nickel organometallic species were reported yet under the photocatalytic conditions.

In the present work, we have used photoredox synergistic catalysis for obtaining in mild conditions π-allylnickel, as an effective allylating agent of electrophiles. The methodology using inexpensive tertiary amine as sacrificial reductant, avoiding the use of metals such as magnesium, zinc, or manganese in stochiometric amount. The reaction shows broad scope and it is quite tolerant regarding functional groups present.

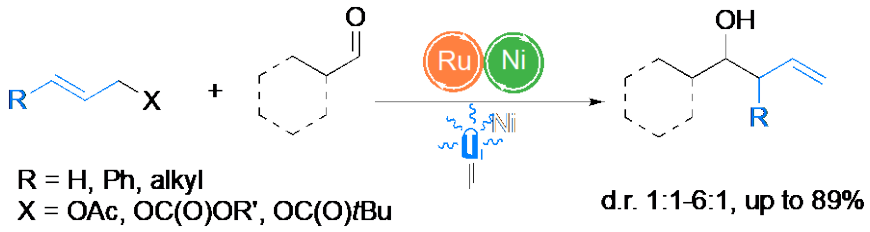

Figure 1.

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OC-97

Sustainable Catalytic Bromination of porphyrins

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Porphyrins represent the most famous compounds in the family of polypyrrolic macrocycles. The richness of properties of this class of molecules, allowed their exploitation in different fields of research, ranging from medicine[1] to catalysis,[2] chemical sensors[3] or as dyes in DSSC.[4] Among the different functionalizations of porphyrin scaffold, bromination represents one of the most important. On one hand, brominated derivatives represent the starting point for further modification of molecular framework achieved by cross coupling methodologies, such as Suzuki, Heck, Stille or Sonogashira reactions; on the other hand introduction of up to 8 bromine on the porphyrins scaffold varies significantly chemical, physical and geometrical properties. Common procedures require NBS or the corrosive and toxic Br_2 as Br source, and $CHCl_3$, CCl_4, o-dichlorobenzene or CH_3OH as solvents. We present a sustainable approach for the bromination of aromatic substrates based on a V(V) catalysed reaction, occurs in a two-phase medium and uses cheap and environmental friendly reagents such as H_2O_2 and KBr.[5] With respect to the classical protocols for porphyrinoids bromination, this approach is based on milder and safer reaction conditions.

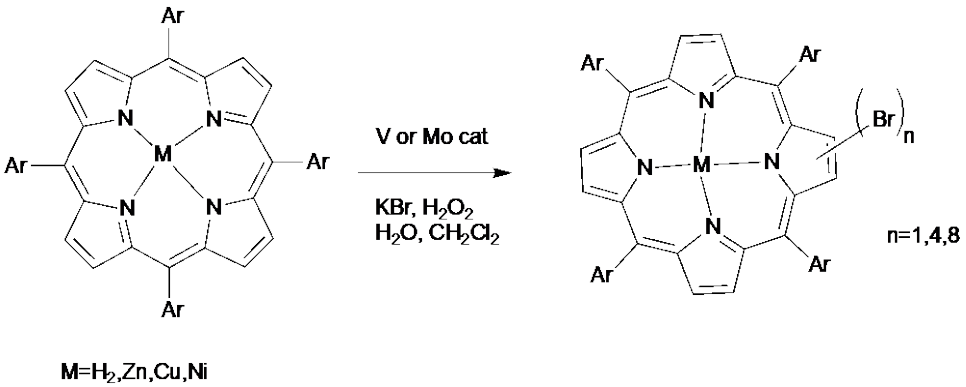

Figure 1: Catalytic Bromination of porphyrins using V or Mo catalysts.

By an accurate tuning of key parameters (H_2O_2 and KBr amount, catalyst), we are able to introduce one to eight Br atoms on β-pyrrolic positions of the porphyrin framework. While with Vanadium good results to obtain partially substituted porphyrins have been gained, the exploitation of the more active Molybdenum catalyst offered a better outcome in the achievement of complete halogenation of peripheral positions.

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OC-98

Pyridyl and quinolyl methanols: applications in metal-free reductions of aromatic nitro compounds

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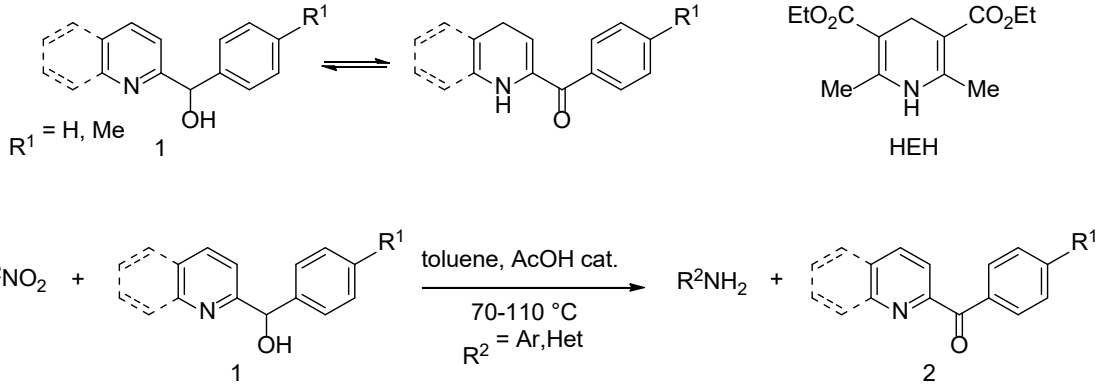
The weak acidity of the 'picoline type' hydrogen atom in 2-pyridyl- and 2-quinolyl-methanols **1** is responsible for their surprising reactivity as hydrogen donor allowing the metal-free reduction of aromatic and heteroaromatic nitro compounds to the corresponding amines.[1]



Scheme 1: Metal-free reduction of R^2NO_2 with compounds **1**

In particular, the quinolyl system shows a higher reactivity with respect to the pyridyl one thank to the low aromaticity of the bicyclic heterocycle. An easier access to the 1,4-dihydroquinoline form allows efficient metal-free reductions of aromatic nitro compounds and activated imines.

Ketones **2**, coming from the oxidation of **1**, can be easily recovered and converted back to **1** by simple reduction, making possible the recycling of the reducing agent and ascribing the process to sustainable friendly reactions.

Moreover, due to the inertness of Hantzsch Ester (HEH) as hydrogen donor towards nitro compounds, carbinols **1** may play a complementary role in the panorama of metal-free reducing agents.

Mechanistic aspects as well as synthetic applications of these new reactions will be properly discussed.

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OC-99

A convenient access to imidazo[1,2-*a*]pyridines and fluorescent polycycles from nitrodienic building-blocks

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When exploiting the reactivity of the versatile nitrodienic building-blocks **1**, originated by the ring-opening of a suitable nitrothiophenic precursor (**2**)[1,2] towards 2-aminopyridine(s), it is possible to obtain a collection of 2-aryl-3-vinylimidazo[1,2-*a*]pyridines (**3**, **4**).

The formation of the final heterocyclic system occurs without the use of a catalyst and in mild condition, thanks to the particular functionalization of the conjugated system, that triggers a cascade process after the initial aza-Michael addition of the 2-aminopyridine on the nitrovinyl moiety.

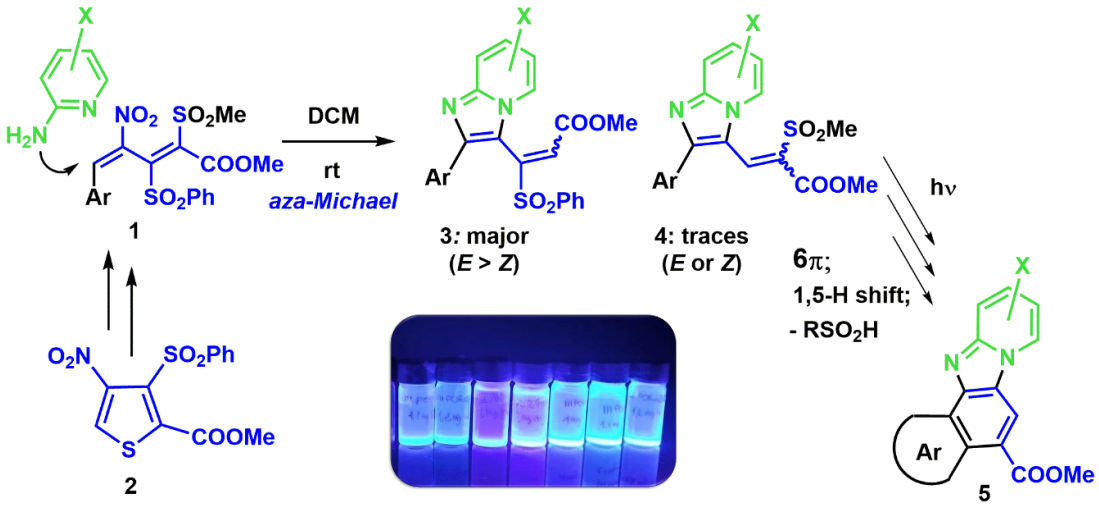

Figure 1: Fluorescence of compounds **5**.

Besides the general interest inherent to the pharmacological properties of imidazo[1,2-*a*]pyridine derivatives,[3] the substituents present in the compounds herein allow an interesting photoinduced electrocyclization reaction, leading to the fluorescent heterocycles **5** with good yields. Latest achievements in the contest of this research project will be presented and discussed.

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OC-100

1,3-Dipolar Cycloaddition of Azides with Substituted Enaminones for Regioselective Synthesis of Trisubstituted 1,2,3-Triazoles.

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1,2,3-Triazole derivatives represent a significant class of unsaturated nitrogen heterocycles that exhibit a number of important biological properties, such as antibacterial, antifungal, anticancer, antiviral, antitubercular, analgesic, anti-inflammatory, anticonvulsant, antidepressant and anti-arrhythmic activities.[1] Moreover, these compounds have also industrial applications as dyes, agrochemicals, corrosion inhibitors, and photostabilizers. In general, the synthetic strategies to obtain substituted triazoles are the catalyzed alkyne-azide cycloaddition or eliminative azide–olefin cycloaddition reaction (EAOC) between azides and olefins.

On the basis of our experience of cycloadditions in non-conventional reaction conditions,[2-4] in this work we present the synthesis of trisubstituted 1,2,3-triazoles, substrates with high molecular diversity, by base mediated 1,3-dipolar cycloaddition between enaminones and azides. After an opportune screening to individue the best Ionic Liquid and base, the synthesis are carried out with variously susbtituted enaminones and azides with excellent yields and in a regioselective manner (**Figure 1**). The final substrates maintain on their skeletal a versatile functional group such as carbonyl, susceptible to successive chemical manipulations.

In addition, theoretical calculations were made to clarify the reaction mechanism.

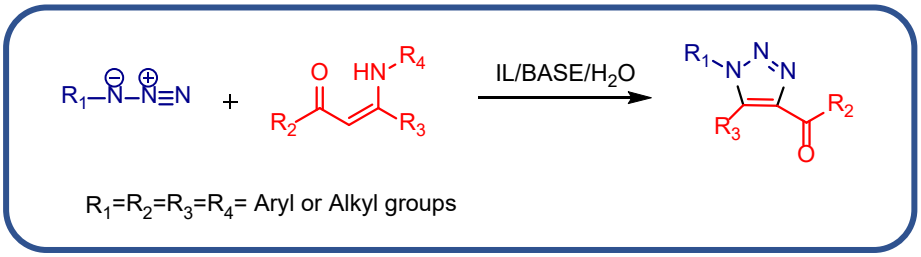

Figure 1: Base mediated 1,3-dipolar cycloaddition to synthesize trisubstituted 1,2,3-triazoles.

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OC-101

Divergent reactivity of *N*-allyl-2-aminophenols in domino reactions exploiting hypervalent iodine(III) reagents

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In recent years, the functionalization of alkenes and alkynes makes use of hypervalent iodine(III) as a tool to reoxidize the transition metal catalysts[1] or to activate directly the unsaturated systems in a metal-free manner.[2]

The use of the *N*-allyl-2-aminophenols as building blocks allows us to report a divergent reactivity easily modulated by the reaction conditions. Indeed, the reaction performed in the presence of Pd(II)-catalyst and of a chiral ligand results in a stereoselective intramolecular alkoxylation through the incorporation of the nucleophile from the oxidating agent (path A).

On the other hand, when the hypervalent iodine was employed in the absence of the metal, a new tricyclic product is observed, arising from an intramolecular Diels-Alder reaction coupled with the transfer of the nucleophile from the iodane (path B).

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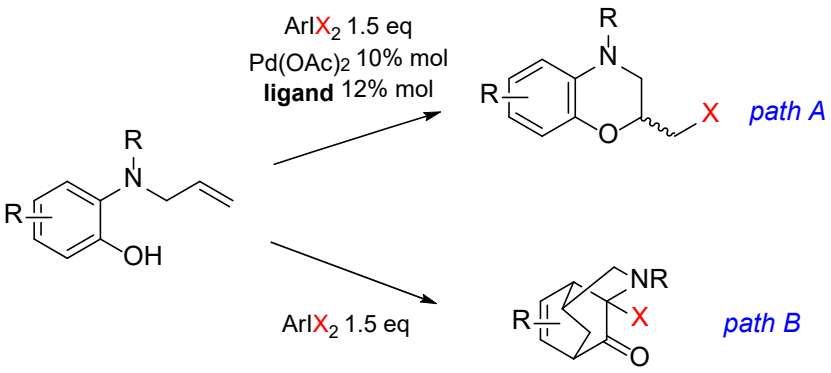

Figure. Hypervalent iodine-promoted a divergent reactivity of *N*-allyl-2-aminophenols.

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OC-102

Synthesis of 1,2,3-Triazole/MWCNT Conjugates for Environmental Application

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Functionalized carbon nanotubes (CNT) have attracted significant attention due to their unique electronic, optical, thermal, mechanical and chemical properties. The ability of these nanomaterials to undergo surface modification allows them to form nanocomposites with a wide range of materials such as polymers, metal nanoparticles and biomolecules.[1] Hybrid materials based on CNT have been developed for sustainable environment and green technology perspectives.

CNTs have been exploited for the development of a polyester-based gelcoat nanocomposite using as nanofiller multi-walled carbon nanotubes (MWCNT) conjugated with a biocidal 1,2,3-triazole to be used as a new eco-friendly antibiofouling coating. Ecotoxicological studies, performed on marine organisms, belonging to different evolutive classes, revealed the great biocidal properties of the synthesized nanocomposites. Differently from other investigated biocidal coatings, the antibiofouling properties of this system are not exerted by releasing drugs or other agents in the environment but simply inhibiting the replication of microorganisms on the nanocomposite surface.[2]

CNTs were also investigated for their ability to remove hazardous substances from aqueous media.[3] Triazole based dendrimers were built directly to the MWCNT surface by click chemistry reactions, affording the MWCNT-TD chelating system (Fig.1a). The Moedritzer-Irani reaction performed on the amine groups of MWCNT-TD afforded the corresponding α-aminophosphonate chelating system MWCNT-TDP. Both nanosystems have been experimentally evaluated for their chelating ability towards Hg(II), Pb(II), Ni(II) and Ca ions by ICP-MS analyses and the complexation mode were investigated by DFT calculations (Fig.1 b).

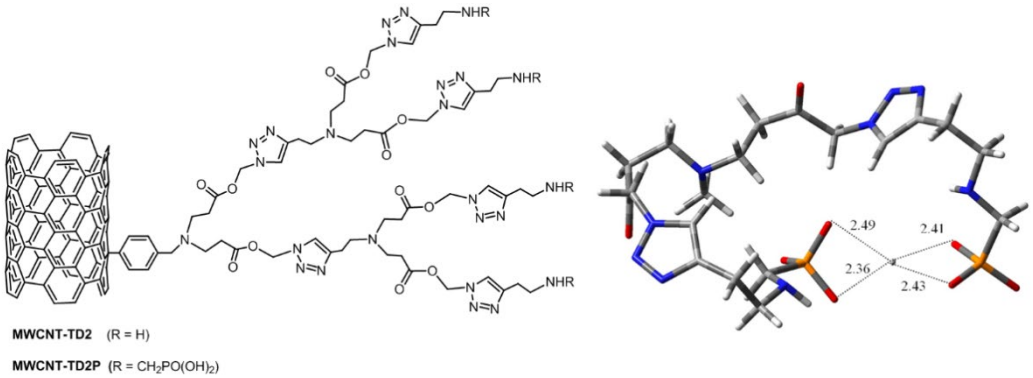

Figure 1: (a) Dendrimer-functionalizedMWCNT; (b) 3D plot of a significantpopulated conformation of MWCNT-DT2P complexation mode.

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[1] C. Vasile, *Materials*, **2018**, *11*, 1834.

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OC-103

Phosphine-catalyzed stereoselective dearomatization of 3-NO_2-indoles with allenoates

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In the last years new powerful methods for the desymmetrization of hetero-aromatic structures have been refined, giving the possibility of moving from simple 2D structure to a more complex chemical 3D space.[1] A current trend in the field encompasses the possibility to expand significantly the chemical diversity accessible via dearomative protocols by means of the so far less explored "dark-side" reactivity of electron-rich arenes.[2] Particularly, in this work the stereoselective phosphino-catalyzed dearomatization of 3-NO_2-indoles will be presented.

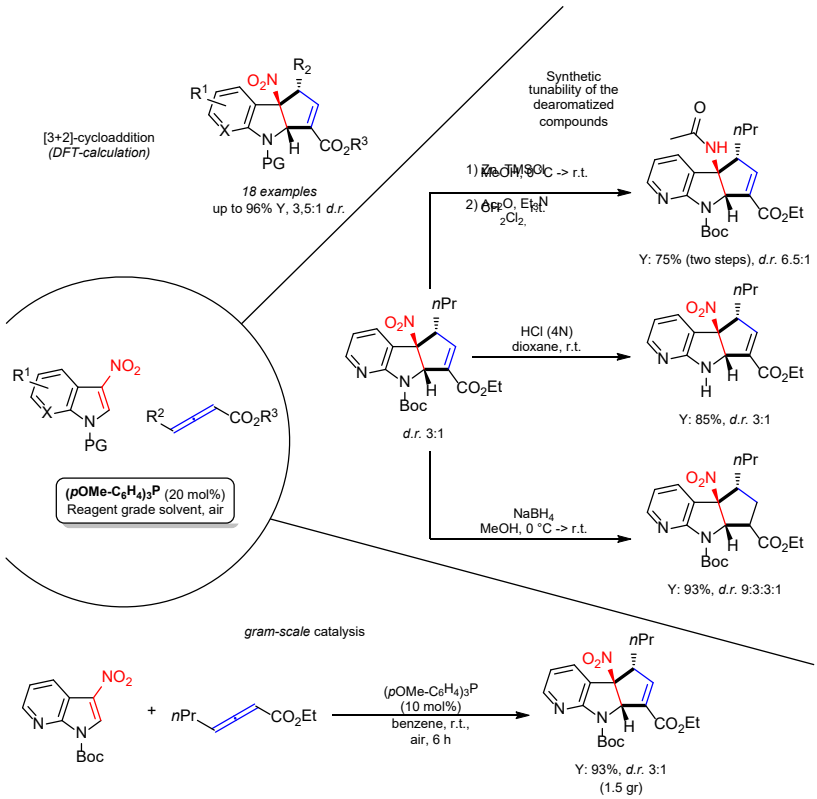

Figure 1

With this new methodology a range of densely functionalized indolines were synthetized in good to excellent yields and particular mild conditions (r.t., air, reagent grade solvent).

The mechanism of the catalytic process has been revealed to be a stepwise [3+2]-cycloaddition by means of computational and labelling studies (Figure 1).

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OC-104

Dicationic Ionic Liquids: Synthesis, Characterization and catalytic Properties

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The addition of a linker between two common ionic liquids' cations leads to a class of organised liquids, known as dicationic ionic liquids,[1,2] which presents remarkable physical and chemical properties.

Several of these compounds have been synthetized, characterized by thermal analysis[3] and various spectroscopic techniques including Thz spectroscopy. Furthermore, DFT studies on minimal neutral clusters (one dication and two anions) have been conducted to rationalize the experimental evidences.

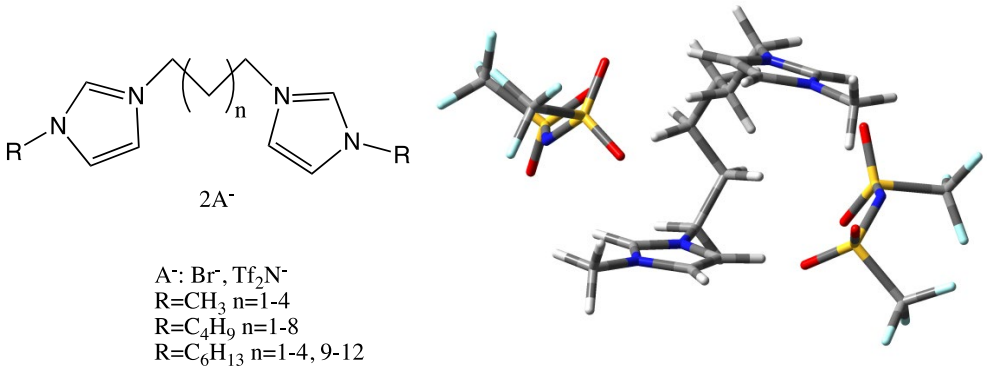

Figure 1: Left: some of the synthetized structures. Right: a DFT structure of a minimal neutral cluster.

Some of these ionic liquids have been used as catalysts for the cycloaddition reaction of CO_2 to epichlorydrin.

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OC-105

Photocatalytic hydrogen production by means of Pt/brookite TiO_2 sensitized with dithienosilole-based organic dyes

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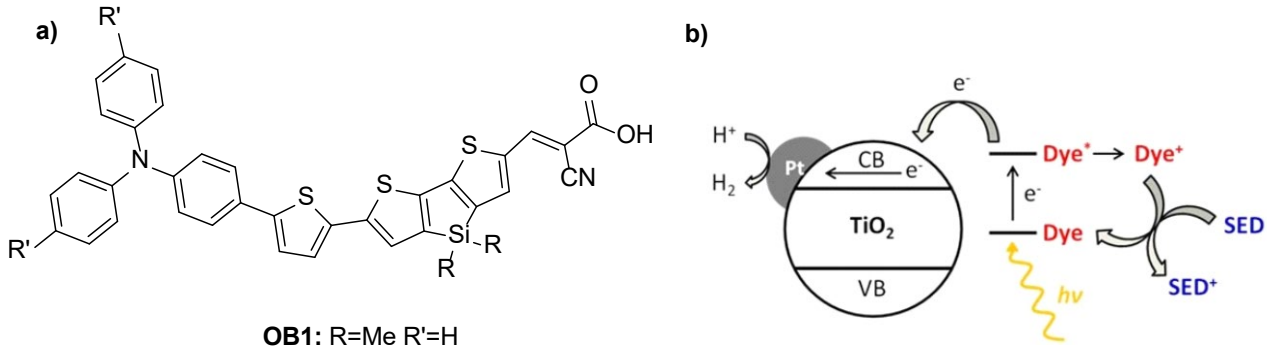
The production of H_2 from sunlight and water is playing an increasingly important role in the production of clean fuels from sustainable and abundant energy sources[1]. In this process, commonly referred as artificial photosynthesis, the role of the sensitizer, is critical for optimizing the harvesting of visible light and triggering the reduction reaction at the catalytic active site. Organometallic sensitizers have mainly been studied so far, however, thanks to recent advances and lower manufacturing costs, metal-free organic sensitizers have recently received increasing importance. On the basis of recent studies, concerning organic molecules applied on photoactivated H_2 production, appeared that those dyes well performing in DSSC are in most cases suitable for hydrogen production. For this reason, we selected a family of organic dyes having a dithienosilole core which are known to lead to high efficiencies in DSSC (10%, 7%)[2] as starting point to synthesize three new dyes (**OB1-3**) to study the influence of structural changes in the photoactivated H_2 evolution process. More in detail, the efficiency of some new organic D-π-A dyes in the H_2 production process has been investigated using the commercially available benchmark TiO_2 (P25) and the best performing dye was also used to sensitize a catalyst based on a different TiO_2 crystalline form, namely brookite/Pt. The aim of this work is to understand the possible correlation between structure and activity of such dyes, in particular the effect of introducing alkyl chains on the scaffold in order to affect several properties such as solubility, aggregation, shielding and wettability of the semiconductor and also the changes induced by the use of a different crystalline form of TiO_2.



OB1: R=Me R'=H
OB2: R=Oct R'=H
OB3: R=Oct R'=OHex

Figure 1: a) dyes synthesized in this work b) dye sensitizer H_2 production working principles

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OC-106

Copper-free methodologies for the multimerization of bioactive iminosugars

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Glycosidases play a pivotal role in a variety of key biological processes. While the design of specific glycosidase inhibitors has attracted the interest of academics and pharmaceutical industry for a long time, only recently several efforts have been devoted to study the impact of the "multivalent effect" (defined as the increase of binding affinity compared to the traditional monovalent ligands) on glycosidase inhibition. A diversity of multivalent systems was synthesized essentially by using iminosugars (nitrogenated glycomimetics) as bioactive units and exploiting the copper-mediated azide–alkyne cycloaddition (CuAAC) reaction.[1] However, given that the cytotoxicity of copper is a potential drawback of the CuAAC approach, the need for alternative procedures is urgent.

In this context, we recently developed two copper-free methodologies for the multimerization of bioactive iminosugars. On one-hand, gold glyconanoparticles (sugar-coated gold nanoparticles, AuGNPs) were employed as novel scaffolds for the preparation of hybrid multivalent architectures decorated with pyrrolizidine (DAB-1)[2] or piperidines (DNJ) iminosugars and their biological activity was investigated towards different target glycosidases (Figure 1A). On the other hand, an innovative approach to multimerize DAB-1 was disclosed. The synthetic strategy involves a highly selective 1,3-dipolar cycloaddition performed onto a cyclic polyhydroxylated nitrone[3] and is able to afford, in principle, a chiral enantiopure polyethylene glycol decorated with several pyrrolidine imminosugar units (Figure 1B). This methodology fully respects the principles of atomic economy and avoids the possible contamination of the final product with copper traces.

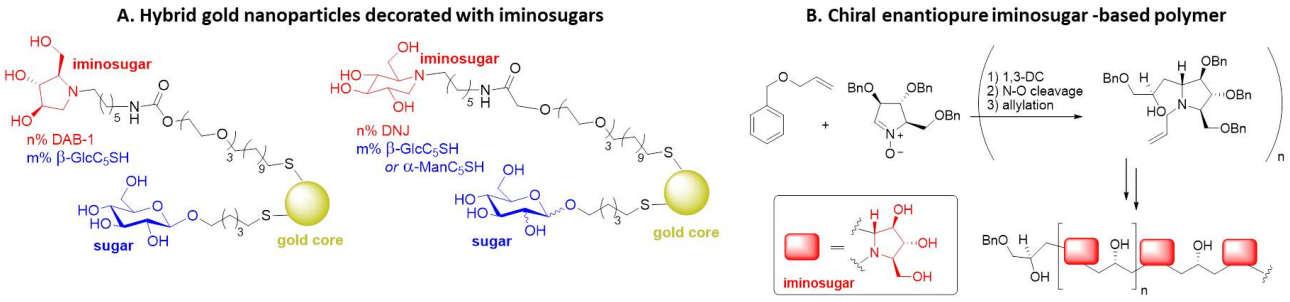

Figure 1: Copper-free methodologies for the preparation of novel multivalent iminosugars.

References:

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OC-107

Non-conventional technologies for copper heterogeneous catalysts production and its applications in organic synthesis

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During the last few years, conventional protocols have been replaced with intensified processes where alternative energy sources are used to achieve higher efficient and more sustainable procedures. Aiming to carry out methods lowering the energy and time consumption enabling technologies such as microwaves, ultrasounds and mechanochemistry have been successfully applied.

The use of truly efficient catalytic reactions is one of the most direct way to pursue green chemistry. In the last decade, copper heterogeneous catalysis gained more and more attention due to important advantages: (1) compared to other transition-metal, copper catalysts are inexpensive, readily available, insensitive to air, and can be easily handled (2) are extremely versatile and effective in different reaction types.

Here in we report the preparation of a new solid supported copper catalyst based on an efficient grafting of β-CD onto the inorganic silica surface.The use of non conventional techniques for the synthesis of this material, as well as for its use in click reactions, has played a very important role in terms of faster and more selective processes.

Moreover, an efficient synthesis of copper nanoparticles has been achieved. Ultrasound is known for its capacity in enhancing particles dispersion and favoring mechanical depassivation. In our study, copper nanoparticles supported over celite proved to be the ideal material for the transfer hydrogenation reaction of nitrobenzene in continuous flow.

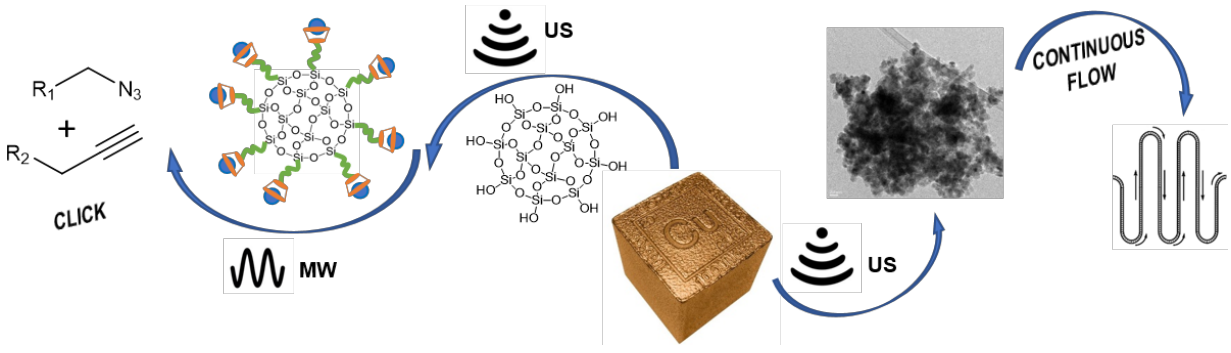

Figure 1: Microwave and ultrasound irradiations in copper heterogeneous catalysis.

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COMUNICAZIONI POSTER
Sessione 1

PC-01

Study of milk proteins' digestibility: characterization of the peptide fraction released and potential impact on allergenicity

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Cow's milk is listed among the main food allergens: with fish, egg, crustacean/shellfish, nuts, peanuts, wheat and soy it is responsible for the 90% of food serious allergic reaction worldwide. The main milk allergens are caseins and the whey proteins α-lactalbumin and β-lactoglobulin. Milk proteins allergy is also the most prevalent allergy for young children with an incidence up to 2-7.5% of the population. One reason of this incidence might be the different protein composition between cow's and human milk, for instance β-lactoglobulin is not present in human milk while it is the main whey protein in cow's milk.

Milk undergoes several technological treatments to guarantee its safety and stability for human consumption. The application of high temperatures might affect milk proteins inducing structural and chemical modifications. The major common modification is the Maillard reaction.[1] This modification is promoted by the high temperatures and occurs between lactose, the main sugar present in milk, and the amino group of lysine residues in proteins. We previously identified modified sites on whey proteins by LC-MS spectrometry.[2] Through LTQ-Orbitrap and UPLC-MS analysis lactosylated residues were identified in the mixtures of peptides produced and compared with the known epitopes reported in literature confirming the presence of some modified lysines in these epitopes.

Recently, we approached further studies, in order to investigate how the digestibility of whey proteins can influence their allergenicity. Adopting the Minekus standard protocol [3] suitable for food, kinetics studies were performed on whey proteins concentrates in order to obtain a digestion LC-MS profile for the whey proteins in their lactosylated forms. In particular we focused our attention on the identification of peptides released during the digestion, which are part of epitopes. In some cases it was found that the presence of the lactose linked to the molecule doesn't be affected by the digestive enzymes. The fact that the molecule remains stable until the end of the intestinal phase, raises the issue of the allergenic risk. Complete studies concerning dynamic simulation of digestion phases and peptide bioavailability and transfer through intestinal membrane phase should be performed, in order to better elucidate the role of this modified epitope.

Finally the chemical synthesis of the modified peptide sequence, identified in the digestion experiments, has been also approached and preliminary results will be showed and discussed.

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PC-02

Design of novel organic hole transport materials for perovskite solar cells

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Hole transport materials (HTMs) based on conductive small organic molecules are crucial components to prepare highly efficient perovskite solar cells (PSCs). Currently, the Spiro-MeOTAD is the most used HTM allowing for a conversion efficiency of 22%. Unfortunately, it has a series of drawbacks that prevent the commercialization of the cells prepared using this material[1]. Therefore, fully organic molecules based on triphenylamine moieties have been proposed as alternative to Spiro-MeOTAD. In this work, the *in silico* design of four new triphenylamine-based HTMs (HTM1-4) is presented. Their electronic and molecular properties have been investigated by means of Density Functional Theory (DFT) and Time Dependent-DFT methods and they have been compared to those of the Spiro-MeOTAD[2] and other triphenylamine-based HTMs, e.g. PTZ2[3], already present in literature (fig.1). Furthermore, a comparison with the experimental characterization of HTM1 is reported. The computed and experimental results suggest that HTM1-4 can be suitable candidates for the construction of potentially efficient PSCs.

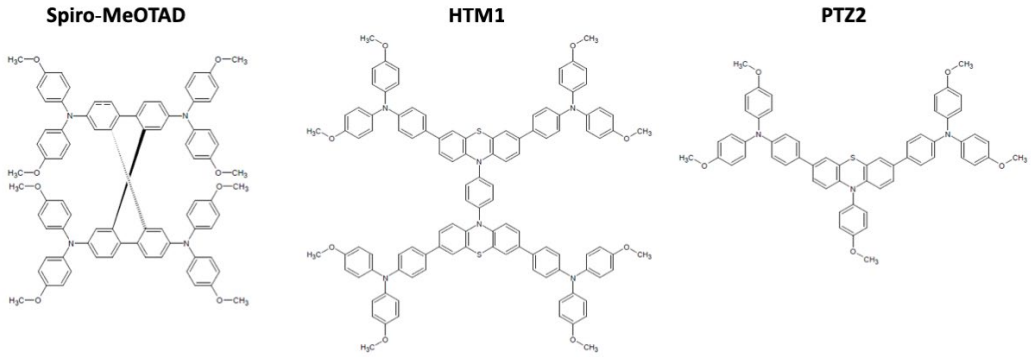

Figure 1: HTM1 molecular structure compared to Spiro-MeOTAD and PTZ2 molecular structures.

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PC-03

Alternative Chemocatalytic Methods for Selective Conversion of Cellulose into Lactic Acid

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Lactic Acid (LA) is a chiral carboxylic acid traditionally used in food industry as acidulant, preservative and emulgator[1]. It has the potential to become a precursor for the synthesis of α-amino acids, opening to the production of proteins from agricultural wastes via chemical routes in the future[2]. In this work, we present alternative methods as microwaves combined with the reactor Q-tube and with ultrasounds to realize the selective hydrothermal conversion of cellulose into LA, under mild reaction conditions in presence of either $ErCl_3$ or grafted on MCM-41 silica surface. We decided to investigate: (i) the best MW/Q-tube conditions to perform the conversion of biomass derived hexoses with $ErCl_3$, which at the best of our knowledge was never performed with this type of reactor, and (ii) the coupling of MW heating with US cellulose pre-treatment for its selective conversion into LA in the presence of heterogeneous catalyst. For all the substrates in both catalysis, lactic acid is the major product, together with lesser amounts of 5-hydroxymethylfurfural, furfural and levulinic acid. The best results in terms of yield and selectivity when Q-tube reactor was used, were reached at 165°C in 30 minutes. Thanks to the US-effect, cellulose MW-assisted conversion into LA with Er^{III}-MCM-41 was possible at 200°C and pressure under the water subcritical conditions with increased operational safety.

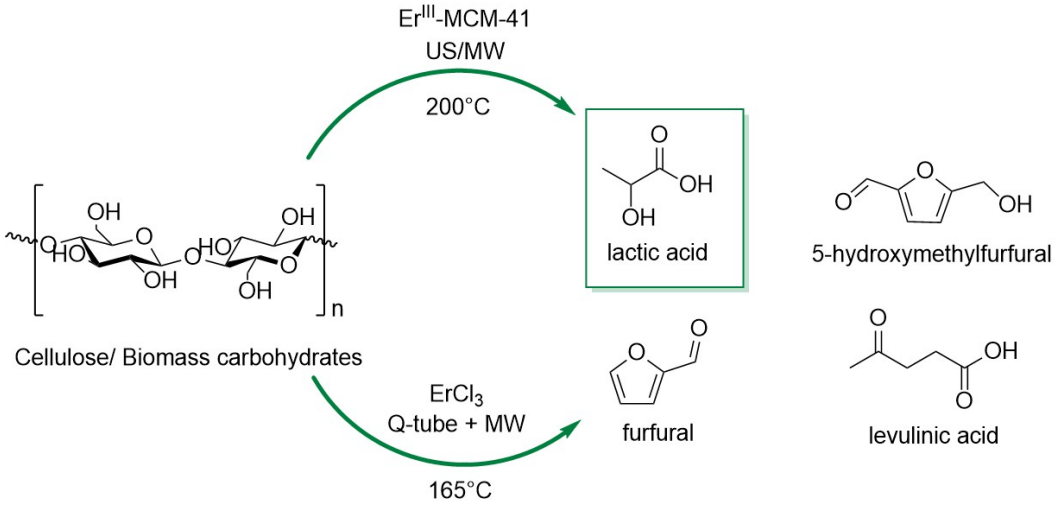

Figure 1: Catalytic hydrothermal conversion of cellulose and biomass carbohydrates.

References:

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PC-04

Natural deep eutectic solvents as an efficient and versatile catalytic system for the Nazarov cyclization

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The Nazarov cyclization (NC) consists in a conrotatory electrocyclization of divinyl ketones to cyclopentenones, catalyzed by Brønsted or Lewis acids, and represents one of the most useful synthetic tools for the preparation of cyclopentenone motifs.[1] However, the reaction has some drawbacks, most prominently the use of strong Brønsted acids which are usually toxic and the use of volatile organic compounds (VOCs) as solvents. To date, advances on more sustainable versions of the NC are limited to very few reports.[2] Natural deep eutectic solvents (NaDES) have recently emerged as a new promising class of green solvents, not only because of their low cost, low toxicity and biodegradability, but also because they can have an active role in promoting organic reactions.[3] Here, we report our study on the Nazarov cyclization performed in acidic deep eutectic solvents, employing non-toxic, naturally occurring carboxylic acids as components of the catalytic system. Various divinyl ketones, bearing different substituents and embedded in heterocycles, have been successfully cyclized, showing the versatility of the methodology.

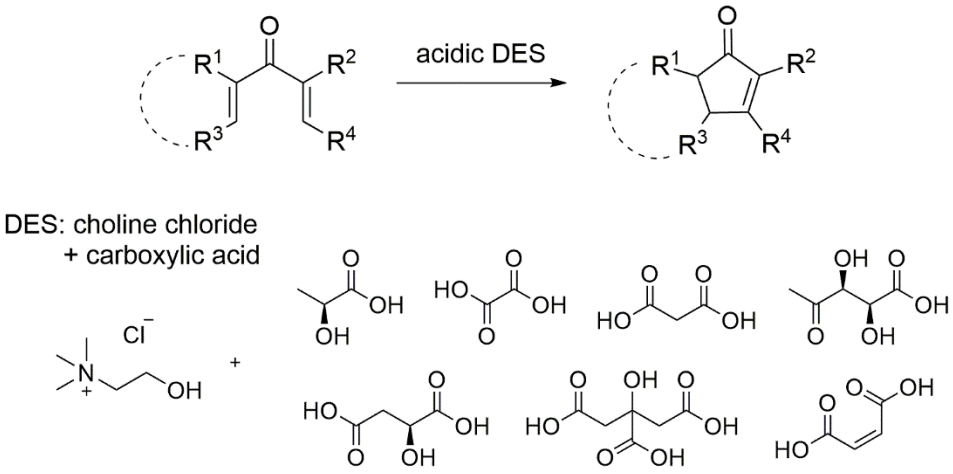

Figure 1: The Nazarov cyclization in acidic deep eutectic solvents.

References:

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PC-05

Synthesis of Indenes by Tandem Gold(I)-Catalyzed Propargyl Claisen Rearrangement/Hydroarylation Reaction

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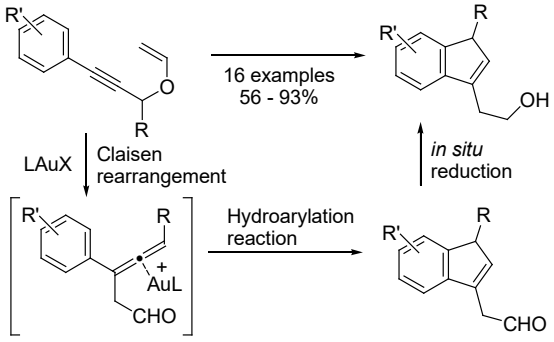
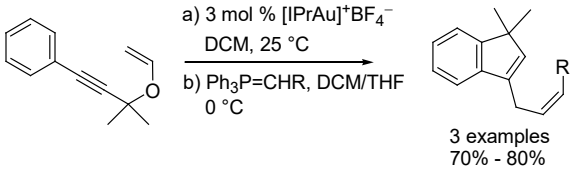
As the indene framework is found in several natural products and it finds application in material science, and in the preparation of ligands for metal complexes, the development of efficient methodologies for the construction of indenes plays an important role for organic synthesis[1]. According to the previous works of our research group[2], we present a tandem gold(I)-catalyzed Claisen rearrangement/hydroarylation reaction of vinyl propargyl ethers[3] which efficiently provides functionalized indenes in good to excellent yields (Scheme 1). The reaction occurs under mild conditions with [IPrAuCl]/$AgBF_4$ as the best catalytic system. A variety of substituents and functional groups present on the substrate are tolerated. The effect of the aryl ring substituents and the results of a DFT computational study suggest that the final hydroarylation is the rate determining step of this cascade process. In order to increment the diversity of the products obtained, further *in situ* chain elongation can be carried out by Wittig olefination of the aldehyde functionality (Scheme 2).



Scheme 1: tandem gold(I)-catalyzed Claisen rearrangement/hydroarylation reaction.



Scheme 2: sequential Au(I)-catalyzed tandem process/Wittig olefination.

References:

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PC-06

PdI_2-Catalyzed Carbonylative Approach to Benzothiophene Derivatives from (2-Alkynyl)(methylthio)benzenes

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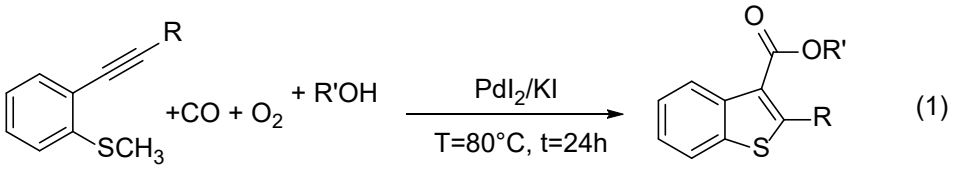
It is known that carbonylation reactions are particularly efficient and convenient processes for the direct synthesis of carbonylated heterocycles[1]

In the present communication we report that benzothiophene derivatives **2** can be conveniently synthesized by palladium-catalyzed intramolecular carbonylative heterocyclization of (2-alkynyl)(methylthio)benzenes **1** (Eq.1).

Benzothiophenes are an important classes of *S*-heterocycles in pharmaceutical science. They are used in a variety of drugs, pesticides and biologically active compounds[2].



1

R=Alkyl, aryl
R'= Me, Et, *i*-Pr

2

(50-77%)

Reactions are carried out at 80 ° C, in alcoholic solvents (R'=Me, Et, *i*-Pr,), in the presence of PdI_2 (1 mol%) in conjunction with KI (20 mol%) and under 40 atm of a 1: 4 mixture of CO / air. Benzothiophene derivatives **2** are obtained in good yields (50-77%).

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PC-07

Hybrid ionogels as potential antioxidant agents

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The addition of natural antioxidant into polymeric materials has been proven fundamental to prevent or retard the oxidation of polymeric materials. However, the incorporation of these low molecular weight antioxidants results hard due to their low volatility, low efficiency and low chemical or photo-chemical stability. To overcome these issues, some anti-oxidant species have been physically adsorbed on carbon nanotubes (CNT) exerting an extremely high radical scavenging activity on the polymeric material.[1]

Nevertheless, the obtainment of homogenous dispersions of CNT in a matrix is still challenging, for this reason we focused on the incorporation of functionalized carbon nanotubes on supramolecular gel matrix. It is well known that supramolecular gels are formed by low molecular weight molecules able to self-assemble through supramolecular interactions (hydrogen bonding, π–π stacking, van der Waals interactions) forming a 3D network in which a solvent is trapped. These soft materials can host several nanomaterials and, thanks to additional interactions between gelator molecules and nanomaterials, the resulting hybrid gels show improved properties. For example, it has been recently demonstrated that some nitrogen carbon nanodots were able to favor the gel formation and that the gelatinous matrix retained or improved carbon nanodots properties, showing a notable antiradical activity.[2]

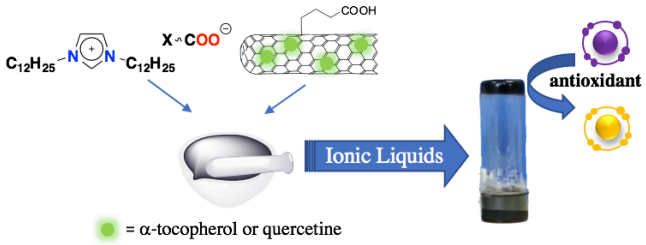

Figure 1. Schematic representation of gelators and CNTs used to form hybrid gels.

In the present study, the influence of CNTs on the gelling ability of some carboxylate imidazolium gelators in ionic liquid solutions has been investigated. Hybrid gels properties such as critical gelation concentration, gel-sol temperature, morphology, rheology and self-repairing ability after disruption have been studied as function of gelator and solvent nature as well as in dependence of the different functionalization of CNTs. Hybrid gels exerted excellent radical scavenging activity, in addition, a small amount of gel can be incorporated in polymeric films warranting homogeneous dispersion of CNTs and good anti-oxidant properties of the film.

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PC-08

Gluconic acid for eco-friendly Ionic Liquids: chemical and biological investigations.

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Ionic liquids (ILs) are employed in several fields thanks to their well-known properties. For a long time, ILs were considered the "green" alternative to conventional organic solvents.[1] However, the increasing attention on environmental health led to consider different ILs structures and alternative synthetic pathways. Considering the tunability of IL structures, new synthetic approaches with natural sources as starting materials were taken into account.[2] Here, new eco-friendly ILs were synthesised using gluconic acid. The structures carry gluconic moiety on the cation or as the anion (Figure 1). Hence, several OH groups decrease toxicity and shape a high coordinative site.

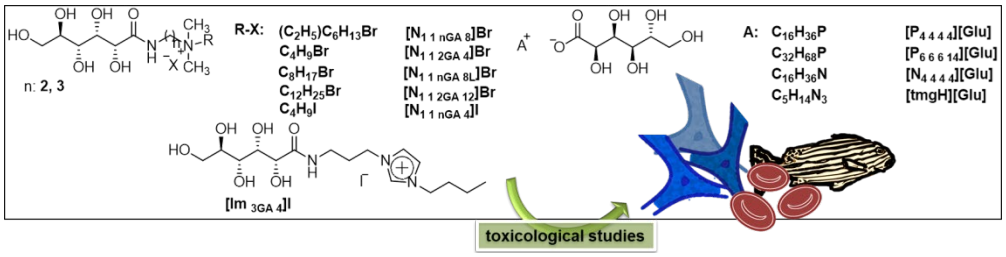

Figure 1: Structures of ILs synthesised and characterised in this work.

These new organic salts were fully characterised from a physico-chemical point of view. However, also, the study of their impact on the ecosystem health was performed. To this aim, three different cancer cell lines, Hela, HTC and MCF7 cells, were chosen to assess cytotoxicity effects of ILs.[3] Moreover, haemolysis investigations were carried out to consider the effect on human blood cells. Finally, Zebrafisha organisms were used as an aquatic model for ILs toxicity.[4] Indeed, the response by living organisms in an aquatic ecosystem gives additional information for dispose of ILs. In the aim of a sustainable approach, these ILs have been designed and analysed to achieve good materials with low environmental impact.

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PC-09

Conversion of carbohydrates into 5-HMF in Deep Eutectic Solvents under mild reaction conditions

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Faced by pressing challenges like the depletion of fossil fuels, researchers are putting intense focus on the replacement of current feedstocks with renewable and sustainable sources, like lignocellulosic biomass, for the obtainment of industrially relevant chemicals.[1] To this aim, in agreement with the principles of Green Chemistry, the use of environmentally friendly and safe solvents, as well as mild reaction conditions are factors of paramount importance. In this context, the latest development is represented by Deep Eutectic Solvents (DES).[2] These are mixtures which, at a particular composition, display a definite melting point, lower than those of each individual component. Oftentimes they are composed of cheap and naturally occurring components and their preparation requires only a mixing process, without any synthetic of purification step.[3] In the framework of our interest in biomass valorisation in non-conventional solvents,[4,5] we studied the conversion of fructose and sucrose, into the chemical platform 5-hydroxymethylfurfural (5-HMF). The reactions were promoted by the resin Amberlyst 15, in a wide range of DES differing for the nature of the hydrogen bonding donating and accepting components (Figure 1).

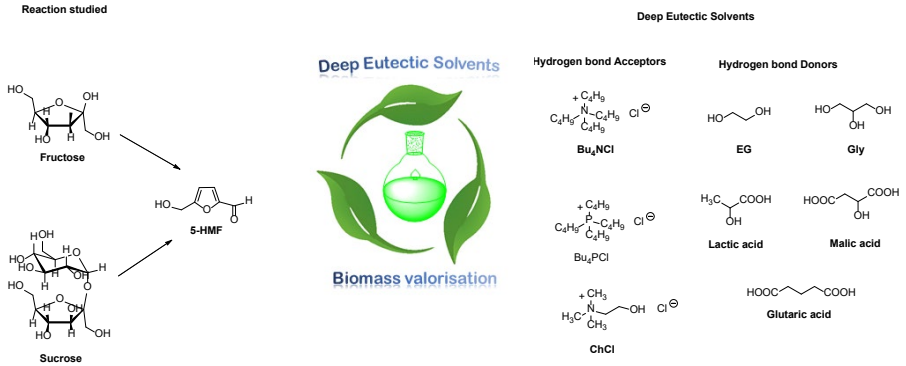

Figure 1: Reaction studied and DES used.

From our study, we found that coupling Amberlyst 15 with carboxylic acid-based DES allowed us to obtain high yields of 5-HMF under the relatively low temperature of 60 °C for fructose and 80 °C for sucrose, which are competitive with what reported in literature, but without using strong acids or transition metal salts as catalysts. The structure of the hydrogen bond donor dramatically affects the reaction outcome. Finally, we also investigated the recyclability of the best-performing DES.

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PC-10

Zinc oxide nanoparticles supported on halloysite nanotubes for environmental remediation

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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.[1,2]

Functionalized halloysite constitutes a valuable support for metal nanoparticles, promoting catalytic applications with tunable properties. The peculiar tubular shape of HNTs favors the dispersion and surface availability of the supported metal nanoparticles that are active in the catalytic path. Moreover, the presence of an empty lumen opens new perspectives for the production of nanoarchitectures with synergistic catalytic effects, due to the increase in local concentrations and confinement.

Among the various alternative catalysts, zinc oxide received much attention due to its cheap, non-toxic, thermally stable, and amphoteric properties.

Herein we report the synthesis and characterization of a novel catalyst based on zinc oxide nanoparticles supported on halloysite nanotubes. The new material has been thoroughly investigated by means of several techniques. To evaluate the feasibility of the hybrid as a catalyst we studied the photodegradation of several organic dyes, chosen as pollutant models, using different experimental conditions. We also performed some recycling experiments to assess the stability of the material obtained.

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PC-11

Visible-Light-Driven Synthesis of Tetrahydropyridazines from γ-δ Unsaturated *N*-Tosylhydrazones

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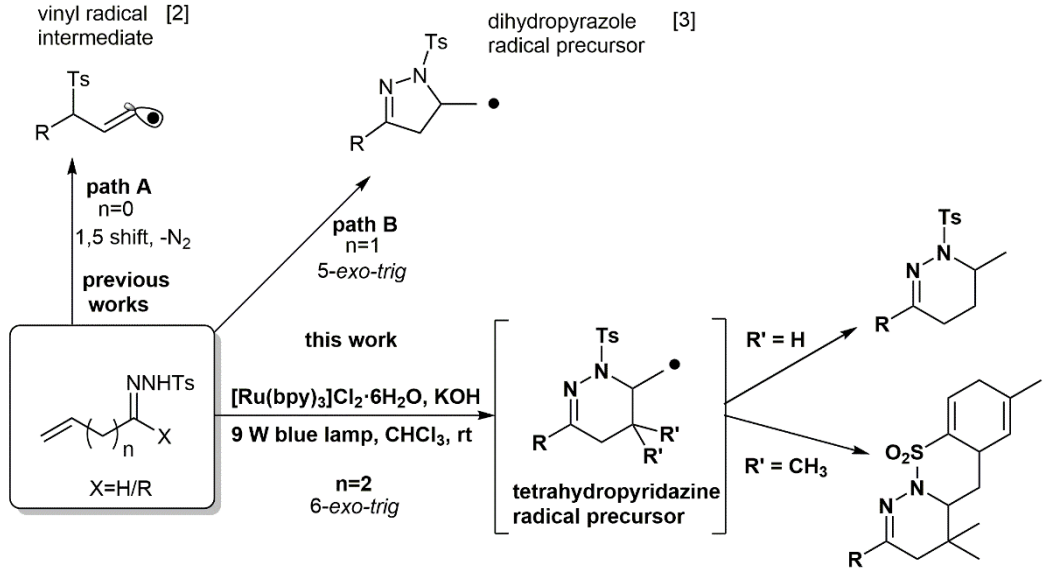
Tetrahydropyridazines are six-membered aza-heterocycles which has proven to be biologically active. Many synthetic routes have been explored for their synthesis, such as the condensation of 1,4-keto carboxylic acid with hydrazine, followed by reduction, Diels–Alder reactions of 1,2-diaza-1,3-dienes with olefins and rearrangement reactions[1]. Thanks to the previous experiences of our group with photocatalytic generation of highly reactive radical species from tosylhydrazones, we envisaged the possibility of an alternative visible light-mediated synthesis of these heterocycles.

Our group has described the first example of a visible-light-driven transformation of α,β-unsaturated sulfonylhydrazones leading to a vinyl radical intermediate (path A, Scheme 1)[2], while a previous work reported how β,γ-unsaturated sulfonylhydrazones undergo hydroamination reaction to generate a dihydropyrazoles radical precursor (path B, Scheme 1)[3]. We report how the further shift of the unsaturation to the γ-δ position lead to the formation of a tetrahydropyridazine radical precursor under photocatalytic conditions (this work, Scheme 1). Thus, we propose the first example of a photocatalytic synthesis of tetrahydropyridazines and tetrahydropyridazine-based complex structures through an eco-sustainable process and mild reaction conditions.



Scheme 1: Reactivity of different unsaturated *N*-tosylhydrazones.

References:

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PC-12

Synthesis and EPR investigation of a new stable diradical macrocycle

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N-Oxyl compounds represent a versatile class of stable organic radicals with unique properties and reactivity. The diverse chemistry of these compounds has enabled the use of nitroxides in applications covering many fields of chemistry.[1] An interesting possibility is incorporating radicals in the molecular components of a synthetic molecular machine and using electron paramagnetic resonance (EPR) spectroscopy to investigate changes in the magnetic properties as the device operates. Rotaxanes containing nitroxide units have been described in the literature[2] by us, and in these cases the paramagnetic unit was used as spin probe and linked to the macrocycle or to the thread without participating to the recognition process. Recently, we prepared the first example of a nitroxide-containing bistable rotaxane **2** (Figure 1) in which the N-O• radical acts not only as EPR probe for the shuttling process, but is also directly involved in the recognition process of a molecular site.[3] In the reported [2]rotaxane, the wheel consists of a 2,5-dimethyl-2,5-diphenylpyrrolidine-N-oxyl radical bound to a crown ether fragment at the *meta* positions of both aromatic rings (**1,** Figure 1). In this context, the presence of radical centres provide unusual functional addition to the diversity of templates available for assembling rotaxanes. For this reason we explored the possibility to introduce a second paramagnetic centre into a crown ether macrocycle in order to investigate the spectral communication changes between the two radicals arising from the complexation and the movements of the wheel occurring in a molecular machine upon an external input.

In the present contribution we report the synthesis of the diradical crown ether **3** and the EPR studies of the molecular assemblies of this new macrocycle with cationic organic guests.

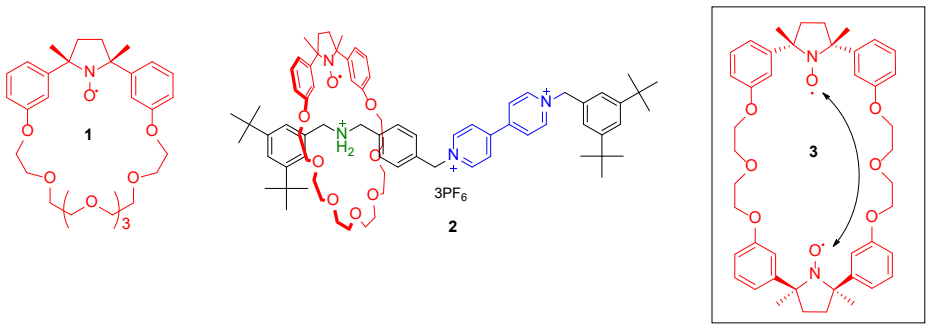

Figure 1: Structures of macrocycles **1**, **3** and rotaxane **2**.

References:

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PC-13

Regio- and diastereoselective organo-zinc promoted arylation of *trans* 2,3-diaryloxiranes by arylboronic acids: stereoselective access to *trans* 2,3-diphenyl-2,3-dihydrobenzofuran.

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The 2,3-dihydrobenzofuran ring-system constitutes the core skeleton of numerous biologically active compounds, as resveratrol oligomers. Among them 2,3-diaryl-2,3-dihydrobenzofurans are the main dimers.[1] *Orto*-oxo substituted *trans* 2,3-diaryloxiranes, prepared taking advantage of the Corey-Chaykovsky reaction between the suitable *o*-substituted benzaldehyde and benzylidene sulfur ylide[2], proved suitable starting materials for the first stereoselective access to *trans* 2,3-diphenyl-2,3-dihydrobenzofuran (Figure 1). The epoxides were regio- and stereoselectively opened by phenyl zinc reagent, which was obtained *in situ* from phenylboronic acid via a facile B-Zn exchange. Deprotection reactions of *orto*-oxo substituted affording the corresponding hydroxyphenols and the last Mitsunobu type cyclization with Ph_3P/DEAD afforded in high yield *trans* 2,3-diphenyl-2,3-dihydrobenzofuran. The use of enantioenriched starting diaryloxiranes resulted in no loss of stereochemical integrity in the final *trans* 2,3-dihydrobenzofuran, which was characterized for the first time in enantioenriched form[3].

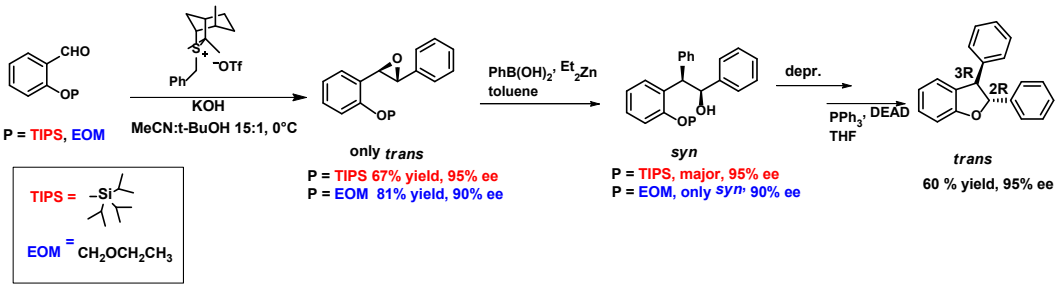

Figure 1

The reaction proved to be quite general using different aryl boronic acids as nucleophilic source and *orto*-ethoxymethoxy substituted *trans* 2,3-diaryloxirane as electrophilic acceptor. In particular, different *syn* aryl alcohols[4] **A** were prepared in good yields Scope and limitations of the method for the preparation of functionalized *trans* 2,3-diaryl-2,3-dihydrobenzofurans **B** (Figure 2) and mechanistic issues on ring-opening reaction will be discussed.

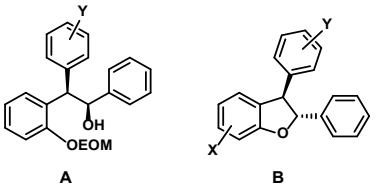

Figura 2

References:

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PC-14

Green and Mild Friedel-Crafts Benzylation of Arenes and Heteroarenes Under *On Water* Conditions

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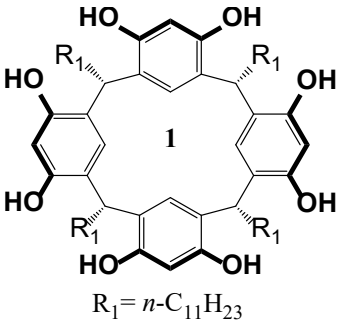
Among the most exploited reactions for the industrial synthesis of fine chemicals and pharmaceutical compounds, Friedel-Crafts[1] alkylation, and particularly benzylation, of arenes and heteroarenes plays a major role[2]. Usually, metal-transition based catalysts are employed on industrial scale, with issues related to the sustainability and costs of the catalysts[3]. A greener approach involves the use of *on water* conditions[4]. It is known that under *on water* conditions hydrophobic effect[5] drives catalyst and reactants to aggregate, leading to an amplification of secondary interactions, with amazing outcomes in catalysis[6,7]. In the present communication, we will show that under *on water* conditions, *C*-undecyl-resorcin[4]arene **1** is able to catalyse Friedel-Crafts benzylation of several arenes and heteroarenes[8] (Figure 1).



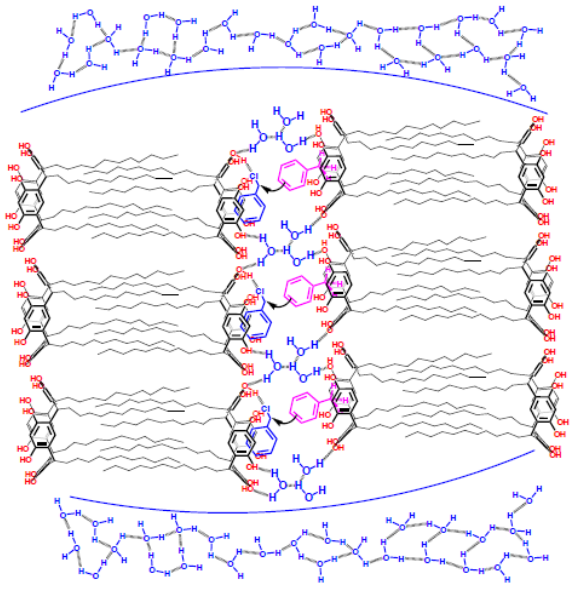


Figure 1. Left, Friedel-Crafts benzylation of arenes and heteroarenes promoted by resorcin[4]arene **1** under *on water* conditions; right, bilayer motif proposed as a model of the 3D packing of **1** in the solid state.

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PC-15

From HIV protease inhibitors to anticancer agents: diversity-oriented synthesis of new compounds with double biological activity

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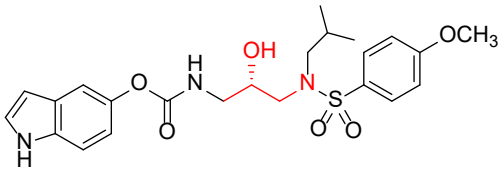
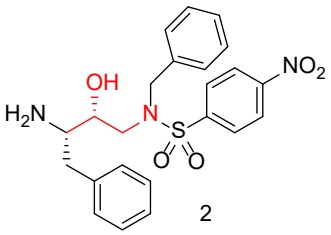
Cancer is a complex disease and the main cause of death in developed countries. The success of some HIV protease inhibitors in treating HIV-related Kaposi's sarcoma proved the feasibility of developing approved anti-HIV drugs for cancer therapeutics.[1] Furthermore, the emergence of drug resistance prompts to produce novel substances with lower side effects and higher efficacy, especially if a double biological activity is possible. In a previous work we synthesized compound **1**, bearing an hydroxyethylaminic *core* linked to an heterocycle moiety, which showed both its biological activity against HIV protease[2] and its cytotoxicity on HepG2 cell lines[3]. Moreover, compound **2**, recently described in literature,[4] which contains the free amino group in the hydroxyethylamine moiety, has proved to be important for anti-proliferative activity. Stimulated by the success of these molecules as antitumor agents, we prepared a library of compounds of general structure **A** and **B**, and tested their potential broad spectrum activities. The synthesis and biological results will be discussed.

Previous works



1



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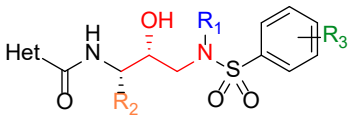
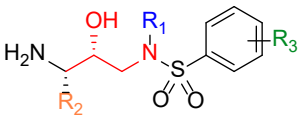


A



B

R1=H, iBu, Bn
R2=H, Ph
R3=4-OMe, 3,4-diOMe, 4-NO2

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PC-16

New Molecules as Translational Readthrough Promoters of Nonsense Mutations: Rescuing the CFTR Protein

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The presence of a nonsense mutation in the DNA frame encoding for a functional protein is one of the causes of severe genetic disease. In particular for Cystic fibrosis (CF), about 10% of CF patients worldwide possess a nonsense mutation in the CFTR gene, causing the absence of the CFTR protein expression and a more severe form of the disease.

Pharmaceutical approaches targeting the specific genetic defect have been faced and heterocyclic scaffolds rule the personalized medicinal approach, as proved by many studies in the CF field. In this context, a potential treatment approaching the genetic nonsense mutation is to promote translational readthrough of premature termination codons (PTCs) by translational readthrough promoters.

PTC124, also known as Ataluren, was launched by PTC Therapeutics to promote the readthrough of premature but not normal termination codons in HEK293 cells.[1]

We reported a rationale for Ataluren promoted readthrough of PTCs by computational approach and GFP-reporter cell-based assay[2] and the observed enhancement of readthrough activity by some Ataluren derivatives.[3,4,5] Moreover, recently we further investigated the possible targets for readthrough promoters.[6]

By using an integrated approach consisting of computational screening, synthesis and biological tests, we identified new small molecules showing high readthrough activity. We evaluated quantitatively the CFTR rescue after treatment with our derivatives in CF model systems and in cells expressing a *nonsense*-CFTR-mRNA.

References:

[1] E. M. Welch, E. R. Barton, J. Zhuo, Y. Tomizawa, W. J. Friesen, P. Trifillis, S. Paushkin, M. Patel, C. R. Trotta, S. Hwang, R. G. Wilde, G. Karp, J. Takasugi, G. Chen, S. Jones, H. Ren, Y.-C. Moon, D. Corson, A. A. Turpoff, J. A. Campbell, M. M. Conn, A. Khan, N. G. Almstead, J. Hedrick, A. Mollin, N. Risher, M. Weetall, S. Yeh, A. A. Branstrom, J. M. Colacino, J. Babiak, W. D. Ju, S. Hirawat, V. J. Northcutt, L. L. Miller, P. Spatrick, F. He, M. Kawana, H. Feng, A. Jacobson, S. W. Peltz, H. L. Sweeney, *Nature* **2007**, *447*, 87-91.

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PC-17

A novel procedure for rapid and accurated quantification of amino functionalities bonded to solid porous matrices

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Recently, solid porous matrices functionalized with amino groups have found wide use in the field of CO_2 capture and storage technologies[1] as well as in separation science for chromatographic applications. In fact, they are profitably used as stationary phases for HILIC (Hydrophilic Interaction Liquid Chromatography) separations[2], which allow the effective resolution of interesting compound classes (e.g. mixtures of mono- or oligo-saccharides). In this study, we developed a new method to quantify the density of basic sites on solid matrices (in particular amino groups). The procedure is fast and easy, and not destructive towards the analyzed material. The approach is based on the preventive salification of the basic groups linked to the solid by 3,5-dinitrobenzoic acid (DNBA). Quantification of the basic functionalities is then performed by an UV-spectrophotometric retro-titration of the salified solid matrix (or, alternatively, by reverse phase HPLC approach), resorting to a preventive either acid or basic displacement of DNBA from the solid material.

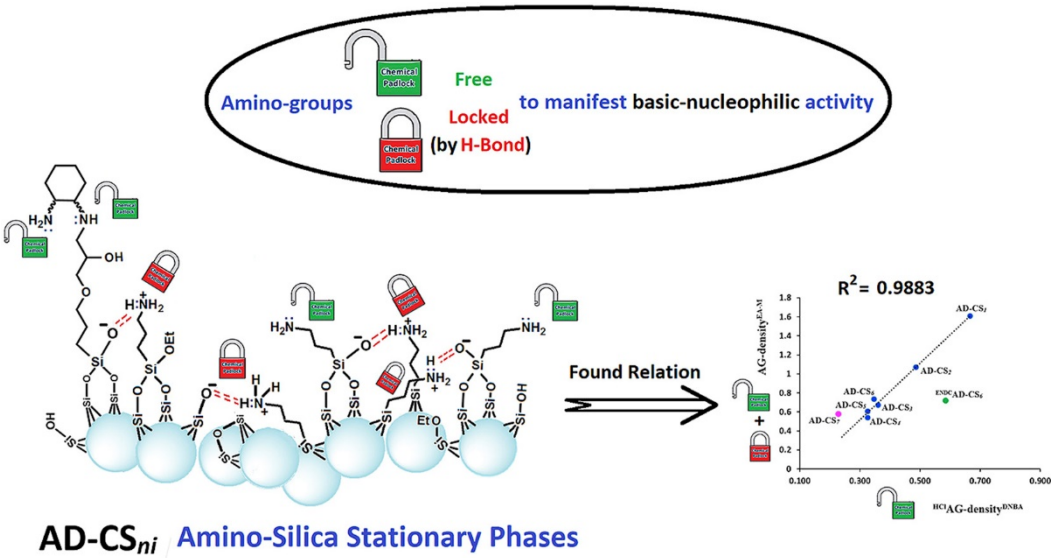

Figure 1: Left side: schematic representation of amino functionalities bonded to amino-silica stationary phases. Right side: plot of the linear correlation found between density values of basic sites chemically bonded to the surface of the AD-CS$_{ni}$ silica samples determined by means of the EA-M and DNBA-M methods, the last one based on final acid displacement of DNBA.

References:

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PC-18

Synthesis of new Water Reducer Plasticizers for concrete, gypsum and clay

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Plasticizers are interesting chemicals admixtures used in materials engineering to improve both fresh concrete, gypsum and clay workability and mechanical properties of hardened materials. Their main function is to decrease the amount of needed mixing water and to control the setting time without losing fluidity of the pastes, which results in higher strength and better durability of final materials. Polymeric additives can cause dispersion of matrix particles due to their structure: indeed, plasticizers combine electrostatic repulsion effect of charged groups on their backbone and the steric hindrance effect of the linked side-chains. [1]

In the late twenties the first-generation additives were developed from by-products obtained from the paper firm. Due their important applications in engineering field, research has been focused on the development of new and more performing plasticizers such as naphthalene/melamine sulfonate derivatives and polycarboxylate esters/ethers, which represent the second and third generation of additives.[2]

Dispersants gave an important and fundamental improvement in materials engineering during the 40 last years, however there is a serious environmental problem related to their use.[3] In order to avoid that pollution problem, we propose to direct our research towards the development of new eco-sustainable and biodegradable superplasticizers from backbone based on cyclodextrins, polysaccharides and modified polycarboxylic derivatives as green alternatives to the existing petrochemical products.

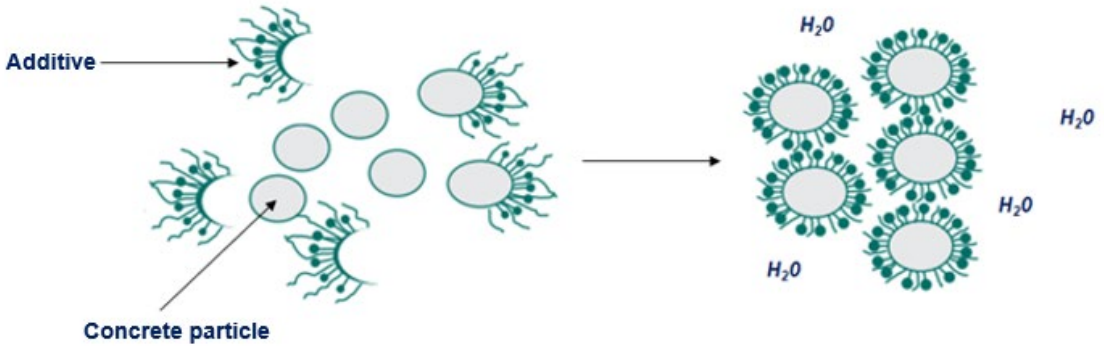

Figure 1: Action mechanism of plasticizers.

References:

[1] L. Shenghua, L. Jingjing, Z. Qingfang, H. Ling, S. Ting, *Ind. Eng. Chem. Res.* **2014**, *53*, 3908-3916.
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PC-19

Boron-functionalized benzodithiophenes

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Tricoordinate boron-functionalized molecules, such as triarylboranes, have recently emerged as a powerful new class of electron acceptors with great potential for application in optoelectronic n-type materials.[1,2] This electron-accepting ability is the result of the p−π* conjugation between the empty p orbital of boron atom and the π* orbital of the π-conjugated framework. Furthermore, aromatic organo-boron systems often show fluorescence emission in the visible range of the electromagnetic spectrum. In recent years many examples of boron-functionalized molecules have been reported but, given their unique n-type semiconducting features, the design of new structures is still an attractive and relevant research topic.

We present the synthesis of new triarylboranes **1**–**4** containing linear or angular benzodithiophene (BDT) as core molecule and bearing one or two dimesityl boryl groups (Figure 1).

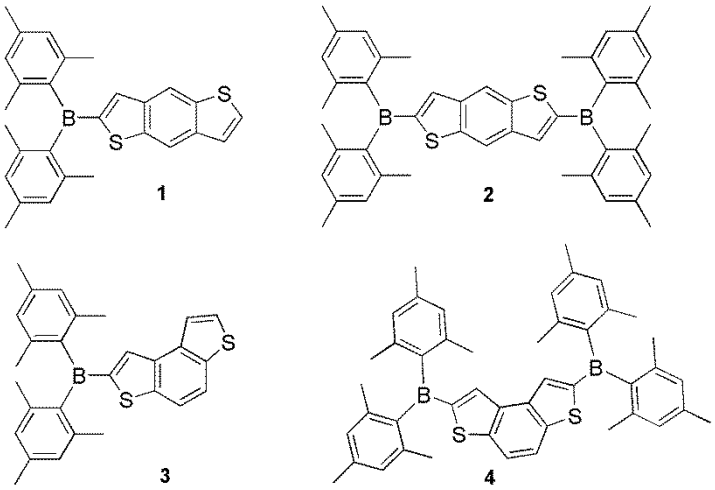

Figure 1. New BDT-based triarylboranes.

Photophysical and electrochemical studies were carried out to evaluate the potential of structures **1**–**4** as building blocks of materials for optoelectronic applications. In particular, compound **2** was selected as the most promising candidate since it shows good luminescence performances (λ_{max} = 470 nm; Φ = 0.57), redox properties and capability to detect fluoride anions.

References:

[1] E. Von Grotthus, A. John, T. Kaese, M. Wagner, *Asian J. Org. Chem.* **2018**, *7*, 37-53.
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PC-21

Development of new beta-lactam-based integrin ligands: Synthesis and Applications

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Integrins are adhesion receptors that mediate dynamic adhesive cell-cell and cell-matrix interactions; because of the important roles of integrins and their ligands in biological development, immune responses, leukocyte traffic, haemostasis, and cancer, their potential as therapeutic tools is now widely recognized.[1] Our research group recently developed a library of novel agonist integrin ligands characterized by a beta-lactam scaffold[2] and demonstrated that these compounds could promote integrin trafficking and endocytosis. Therefore the research group developed some conjugates of the most active agonist candidates with fluorescent tags (Rhodamine B and Fluorescein isothiocyanate) in order to evaluate by confocal microscopy analysis their internalization together with the integrin. The preliminary results are encouraging. Because of this behavior, we have been then focusing on the development and synthesis of two new beta-lactam compounds conjugated to cytotoxic agents (Figure 1), which could act as a drug-cargo for a selective delivery of cytotoxic molecules directly into cancer cells that overexpress integrins.

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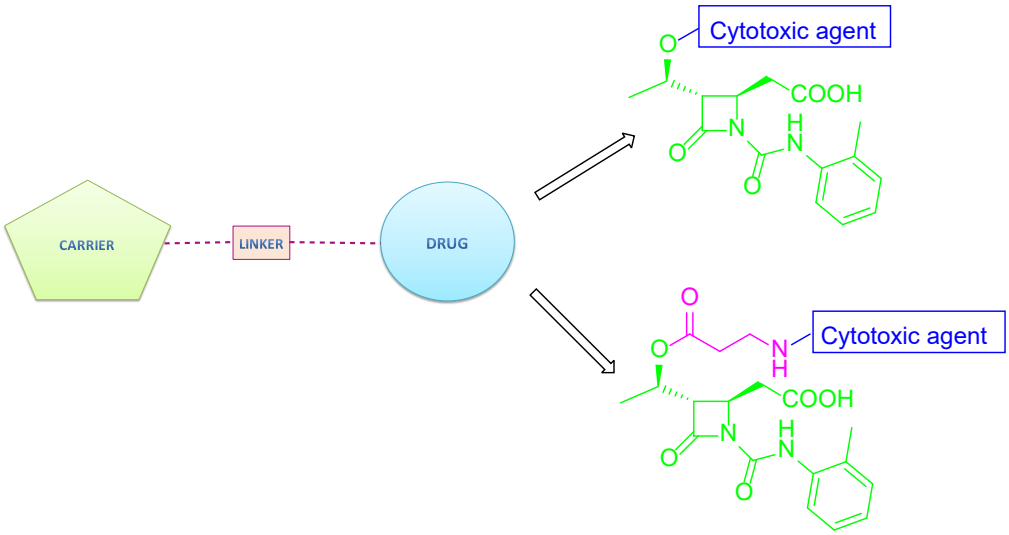

Figure 1: General scheme of targeted drug delivery system and development of two new beta-lactam-based integrin ligands conjugated to cytotoxic agents.

References:

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PC-22

Enantioselective Desymmetrization of 1,4-Dihydropyridines by Oxidative NHC-Catalysis

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According to Evans definition,1,4-dihydropyridines (1,4-DHPs) are privileged structures endowed with a plethora of different biological activities depending on substitution of the heterocyclic scaffold. 1,4-DHPs are primarily used as calcium channel blockers for the treatment of vascular disorders, but also as antitumor and antidiabetic agents, and drugs to cure many other diseases. As with other pharmaceuticals, the role of C4 stereochemistry in chiral 1,4-DHPs is fundamental to modulate the biological activity and prevent adverse effects of these molecules. Additionally, optically pure DHPs are precious precursors of different chiral N-heterocycles and may serve as NADH mimetics in asymmetric reductions.

Herein, the unprecedented desymmetrization of prochiral dialdehydes catalyzed by N-heterocyclic carbenes (NHCs) under oxidative conditions has been applied to the highly enantioselective synthesis of 1,4-DHPs starting from 3,5-dicarbaldehyde substrates. Synthetic elaboration of the resulting 5-formyl-1,4-DHP-3-carboxylates allowed to access the class of pharmaceutically relevant 1,4-DHP-3,5-dicarboxylates (Hantzsch esters). DFT calculations suggested that the enantioselectivity of the process is determined by the transition state involving the oxidation of the Breslow intermediate by the external quinone oxidant.[1]

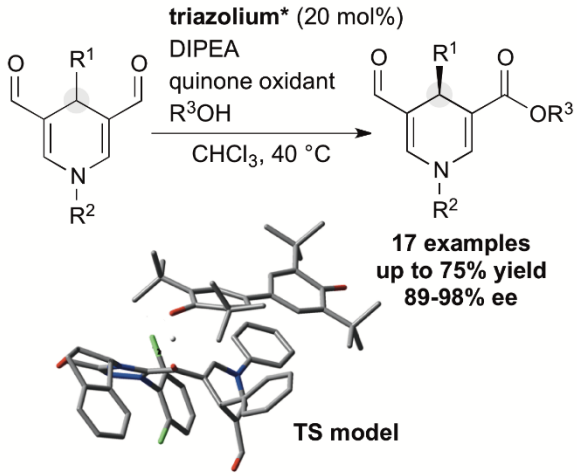

Figure 1: Desymmetrization process.

References:

[1] G. Di Carmine, D. Ragno, A. Brandolese, O. Bortolini, D. Pecorari, F. Sabuzi, A. Mazzanti, A. Massi, *Chem. Eur. J.* **2019** (https://doi.org/10.1002/chem.201901243)

PC-23

Functionalization of the BODIPY core with styryl carboranes: synthesis, characterization and photophysical properties.

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Carboranes are well-known interesting chemical species part of the boron cluster chemistry with unique physico-chemical features.[1] Many new synthetic procedures have been developed to functionalize these compounds, and the interest in studying their photoluminescent (PL) analogues in view of new applications in several fields has noticeably increased recently.[2] In fact, the carboranyl cage might influence the PL properties of the final material and gives an additional thermal stability, which is crucial in tuning the final properties of a certain material.

Owing to their unique spectroscopic properties and their easiness of functionalization, BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene) dyes have emerged as an interesting new class of fluorophores for boron clusters functionalization.[3] As part of our studies aimed at tagging a class of biological relevant compounds using fluorescent probes for live-cell imaging applications, we recently reported the synthesis of carborane-BODIPY dyads through the optimization of a Heck coupling reaction between different (aza)BODIPYs and styryl (*ortho* and *meta*) carboranes.[4] Starting from these grounds, we envisaged that the BODIPY might be functionalized with more than one styrene-containing carborane derivative and on different positions of the BODIPY core in order to tune the fluorescent properties. We herein report the synthesis of a small library of symmetric and asymmetric carborane-BODIPY triads by means of a Pd-catalyzed Heck coupling reaction (Figure 1). The characterisation, the spectroscopic and photochemical properties of these new compounds are also discussed.

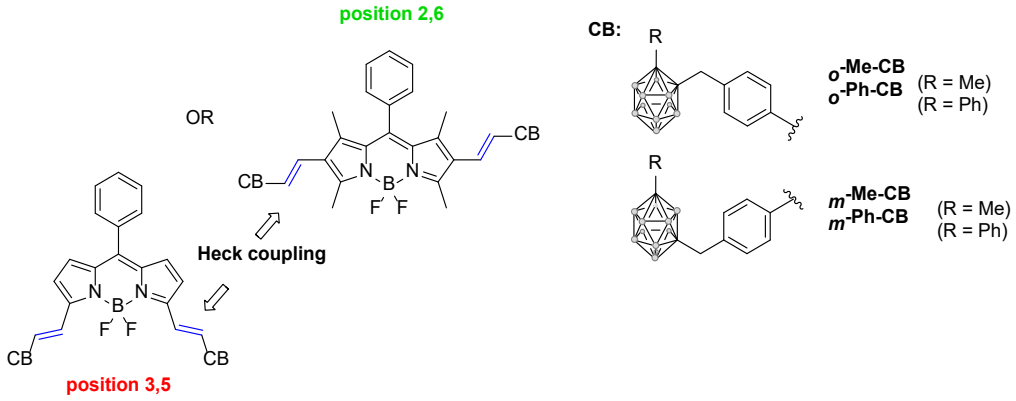

Figure 1: novel carborane-fluorophore triads by means of Heck coupling reaction.

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PC-24

Chemoselective Addition of Highly Polar Organolithium Reagents to Carboxamides in Deep Eutectic Solvents (DESs)Under Air: Novel Opportunities for the Synthesis of Ketones in Unconventional Solvents

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Discovered at the beginning of the twentieth century, organolithium reagents are nowadays ubiquitous in organic synthesis both in academic research laboratories and in agrochemical and pharmaceuticals industries. However, these reagents usually require strictly controlled experimental conditions owing to their well-known sensitivity to moisture and air.[1] Recently, it has been reported the use of these reagents in nucleophilic addition to aromatic ketones, imines, nitriles and quinolines using highly polar solvents (DESs and water) at room temperature under open air conditions.[2] Nowadays we are extending this methodology to other electrophilic functional groups using organolithium reagents in DESs as an alternative synthetic strategy for the preparation of versatile building blocks under green conditions. In this context, direct 1,2-nucleophilic addition of hard organometallic reagents onto carboxylic acid derivatives suffers from a number of limitations depending mostly on the stability of the tetrahedral intermediate, including over-additions and reduction side-reactions. We herein investigate for the first time the potential benefits of using heterogeneous bio-based solvent mixtures in the treatment of several structurally diverse tertiary carboxamides with organolithium reagents in DES under air (Figure 1). Under these conditions, the nucleophilic acyl substitution reaction proceeds in a remarkable chemoselective fashion leading to ketones in moderate-to-high yields and with almost complete suppression of the undesired competitive pathways.

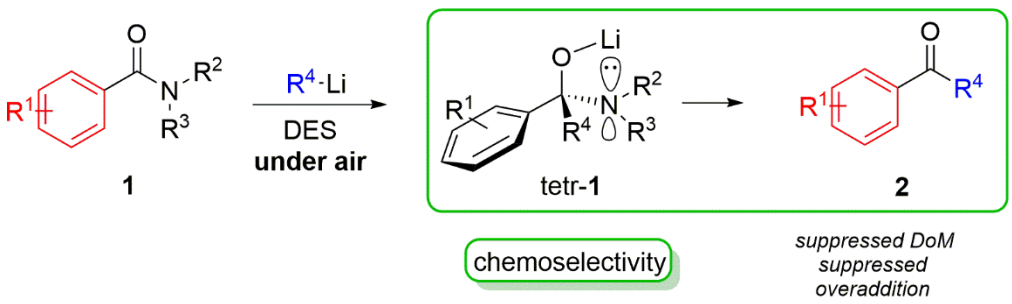

Figure 1: Chemoselective synthesis of ketones by nucleophilic addition of organolithium reagents to aromatic tertiary carboxamides

References:

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PC-25

A New Synthesis Of 2-(imidazo[1,2-a]pyridin-3-yl)acetamides By Palladium-Catalyzed Oxidative Aminocarbonylation Of (N-Prop-2-yn-1-yl)pyridin-2-amines

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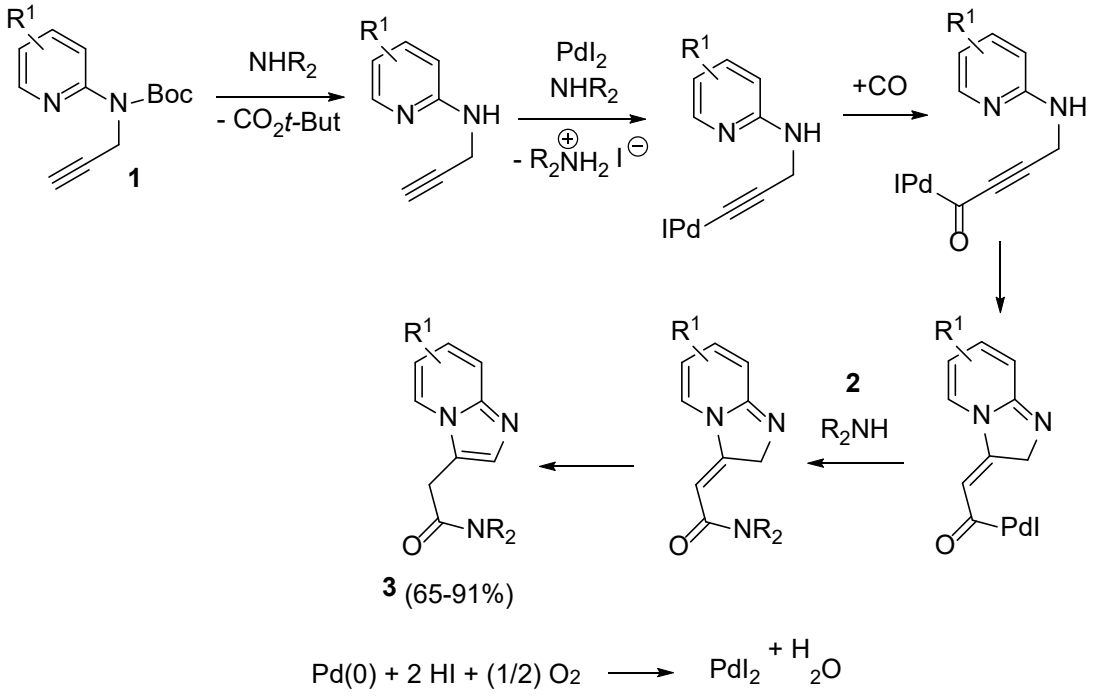
Imidazo[1,2-a]pyridines are known as hypnotic sedative drugs which maintain the hypnotic effect without the onset of side effects and phenomena of pharmacological tolerance[1]. In this communication we report a novel and simple PdI_2-catalyzed carbonylative approach to the synthesis of functionalized imidazo[1,2-a]pyridines. The method occurs in one step and consists in the deprotection of N-Boc-protected-(prop-2-yn-1-yl)pyridin-2-amines **1**, oxidative monoaminocarbonylation[2], conjugated addition and double bond isomerization. This methodology leads to 2-(imidazo[1,2-a]pyridin-3-yl)acetamides **3** to good-excellent yields (65-91%). Reactions were carried out in MeCN at 100 °C for 3 h, under 20 atm of a 4:1 mixture of carbon monoxide and air and in presence of catalytic amounts of PdI_2 (0.003 eq) in conjunction with KI (0.15 eq), using an excess of a secondary amine **2** as nucleophile. (**Scheme 1**).



Scheme 1

References:

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PC-26

An Unusually Divergent Reactivity of Basic Organolithium Compounds in Protic Unconventional Media: Novel Opportunites for the Synthetic Elaboration of Aryl Carboxyamides in Deep Eutectic Solvents

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The ability to activate a specific C-H bond and transform it into a more versatile functional group represents an important and long-standing goal in chemistry. Reactions of highly polar organometallic compounds of s-block elements are typically run in aprotic volatile organic solvents, under strictly anhydrous conditions and at low temperatures owing to their notorious air- and moisture-sensitivity[1]. Spotting a gap in potential, the direct use of Grignard and organolithium reagents to promote nucleophilic additions to aromatic ketones, imines, nitriles and quinolines has proven to be surprisingly effective also in Deep Eutectic Solvents (DESs) and water, at room temperature and under hydrous conditions[2]. Building on these achievements, we have now focused on the possible C-H bond activation of aromatic compounds by a directed *ortho*-metalation (DoM) approach using amides as direct metalation groups and organolithium reagents in DESs as alternative, environmentally friendly reaction media for the preparation of versatile building blocks. In this framework, we report an unprecedent chemoselective DoM or nucleophilic acyl substitution reaction taking place in DESs, as non-innocent reaction media, starting from the same tertiary carboxylic acid amide, according to the nature of the organolithium reagent (Figure 1).

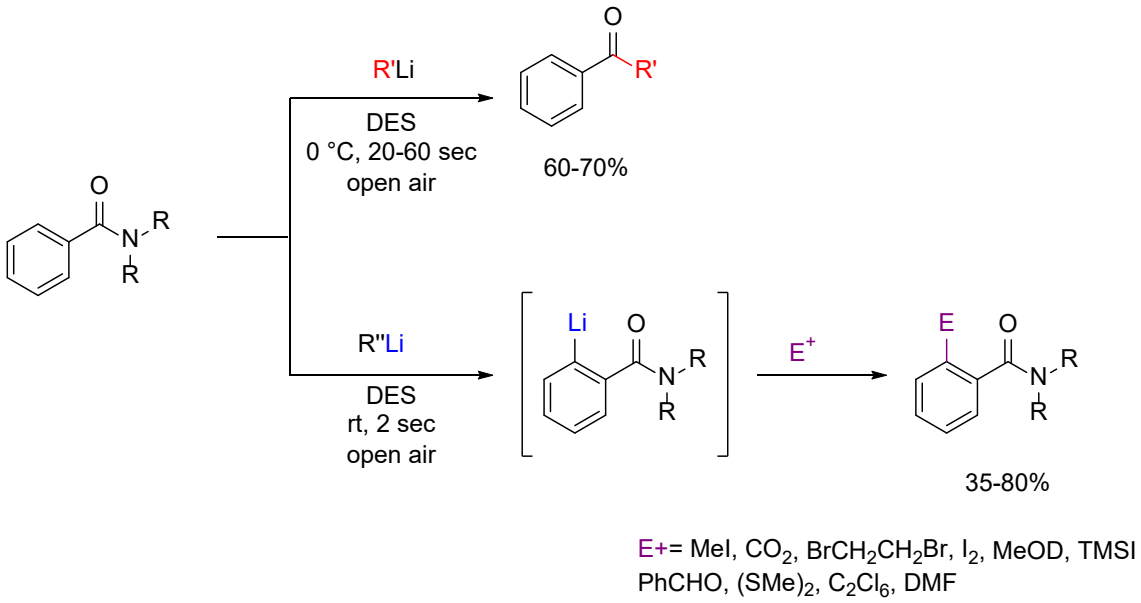

Figure 1: Chemoselectivity of organolithium reagents in deep eutectic solvents.

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PC-27

CI.O.E.: An automated workflow to simplify the early steps of Structure-Based Inverse Virtual Screening

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Structure-Based Virtual Screening (SBVS) is highly used in the early stages of the drug discovery process to identify new putative lead compounds for a given target[1]. However, it could happen that either a molecule elicits a biological effect, but its target is unknown, or the side effects observed cannot be explained by the proposed mechanism of action. In the last few years, a computational procedure, named Inverse Virtual Screening[2-5], was developed to overcome these issues. It is based on docking the selected case-study molecule against panels of target proteins to select the most promising complexes and, accordingly, the most affine targets of interaction. Protein panels contain hundreds, or thousands of proteins and they must be correctly prepared to assure the best docking performance. The target preparation, if performed manually, may be costly in terms of time and efforts and can limit the efficacy of this method. Hence, we developed an automated workflow to shorten this time-consuming step and to speed up panel development. Briefly, online databases are analyzed to retrieve structural and functional information about each protein in the panel and the related crystal structure. Then, after performing an evaluation of the molecules present in the crystal, those are not strictly necessary to the protein function (e.g. crystallization buffer, solvents, etc.) are automatically deleted. Moreover, ligand molecules are recognized, their spatial coordinates are used to map the binding site surface using the software SiteMap[6,7], and finally the necessary input files for molecular docking calculations are generated (AutoDock Vina and Glide software). This protocol was applied to a panel of viral proteins to test its performance obtaining good results (only 3.26% of errors). In addition, we applied this workflow on a small set of available compounds synthesized in our laboratory against a panel of glycosyltransferase proteins, predicting tankyrase 2 as their target and validating the binding with surface plasmon resonance (SPR) experiments. This protocol represents a novelty in the field and is a useful tool for rapid identification of the interacting target for a bioactive compound. Also, it facilitates the reevaluation of known active compounds, addressing repurposing and polypharmacology concept.

References:

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PC-28

Unravelling the interactions between an antiproliferative 1,2,5-oxadiazole derivative and STAT3

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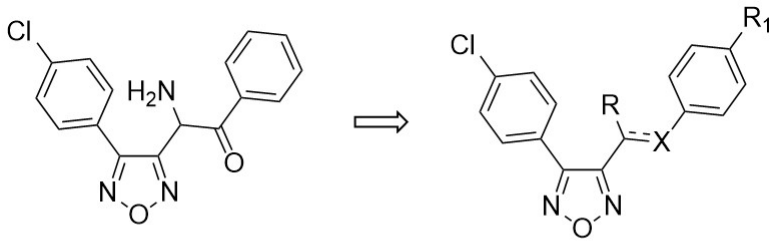
In our effort to develop novel direct STAT3 inhibitors[1], we identified the 1,2,5-oxadiazole **I** (Figure 1), which showed a promising inhibitory effect on the SH2 domain of STAT3 (inh % = 78.2 at 30 μM, IC_{50} = 8.2 μM) and a significant antiproliferative activity in the LLC murine model (tumor growth inh % = 82.6 at 75 mg/kg as i.p. daily dose)[2]. Since compound **I** is characterized by a pH-dependent enolization ratio, we decided to investigate whether the interactions with STAT3 could be related to its enolic form. Therefore, we designed several new derivatives (Figure 1) to shed light on this matter: for instance, we synthesized analogues lacking the NH_2 group or directly bearing an OH in substitution of the CO function. The results of the inhibition studies performed on these derivatives will be presented.



I

R = H, NOH, NHOH, NH_2
R_1 = H, CF_3, OCH_3
X = CO, CHOH

Figure 1: Product **I** and its derivatives (general structure)

References:

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PC-29

One-pot synthesis of α-trifluoromethylthiolated carboxylic acid derivatives

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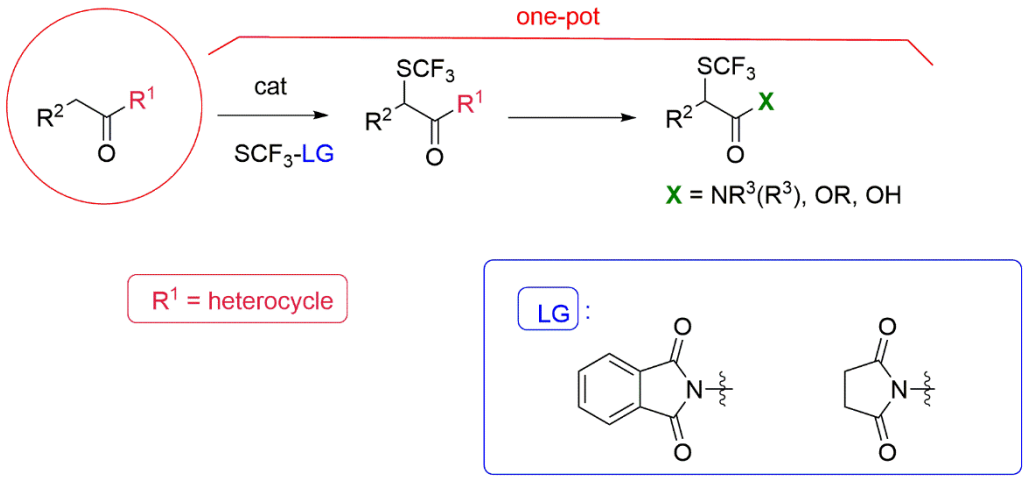
In the last decade, trifluoromethylthiolated compounds received significant interest both in academia and pharmaceutical/agrochemical industries. The strong electron-withdrawing ability and high lipophilicity of the SCF_3 group allow to modulate the properties of drug molecules.[1] Different methods for the introduction of trifluomethylthio group at α-position of ketones have been intensively investigated.[2] The purpose of this work is the development of a mild methodology for the electrophilic incorporation of the SCF_3 group at the α-position of carboxylic acid derivates such as amides or esters. Efforts are focused to employ ester surrogates as the starting reagents in a one-pot fashion (Scheme).



Scheme: One-pot approach for the α-trifluoromethylthiolation of carboxylic acid derivatives.

References:
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PC-30

Synthesis and development of linker for bioconjugation of Smo inhibitors.

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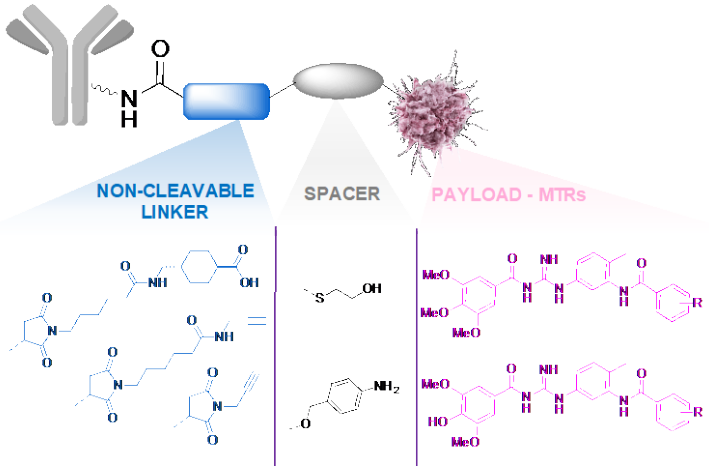
Antibody-drug conjugates (ADCs) represent a promising strategy in cancer therapy and for the treatment of different diseases. ADCs are composed by a monoclonal antibody (mAb) connected to a cytotoxic molecules trough a properly design linker. The mAb is responsible to selectively transport the drug into target cells expressing the specific antigen,[1] thus significantly reducing the off-target toxicity of the drug.

Very potent inhibitors of the Hedgehog signaling pathway (HH) have been developed in our group by a virtual screening approach.[2-4] These acylguanidine derivatives, called MRTs, show a very potent inhibitory activity on SMO receptor, being still very active in common mutant strains responsible for the tumor resistance observed in cancer therapy with HH inhibitors such as Vismodegib. MRT derivatives have interesting anticancer properties being active in the nanomolar range. However, acylguanidines lack for a poor solubility and a low half-life.[3] In order to overcome these issues, the bioconjugation of MRT derivatives has been explored to obtain a selective delivery of these inhibitors into HH sensitive tumor cells for the treatment of different types of cancers such as chronic myeloid leukemia, medulloblastoma and melanoma. Different synthetic strategies have been explored and developed to anchor differently substituted acylguanidines to lysine residues of mAb, through a traceless spacer introduced in a non-cleavable linker.



ADCs armed with MRT derivatives.

References:

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PC-31

Synthesis of substituted 1,2-dihydropyridines by cerium(III) catalyzed amine-aldehyde polycondensation

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Dihydropyridines are six-membered heterocyclic compounds having significant biological activities.[1] While the 1,4-dihydropyridine ring is present in various pharmacologically active compounds,[2] 1,2-dihydropyridine derivatives have been much less studied. One of the main reasons for this limit stems in the reduced availability of synthetic methods for their preparation.[3] For this reason, we have directed our efforts toward the development of a new and efficient synthetic procedure for the preparation of substituted 1,2-dihydropyridines (**Figure 1**). The polycondensation between primary amines and aliphatic aldehydes, in the presence of a catalytic amount of $CeCl_3 \cdot 7H_2O$, allowed us to obtain 1,2-dihydropyridines in good yield under mild reaction conditions.

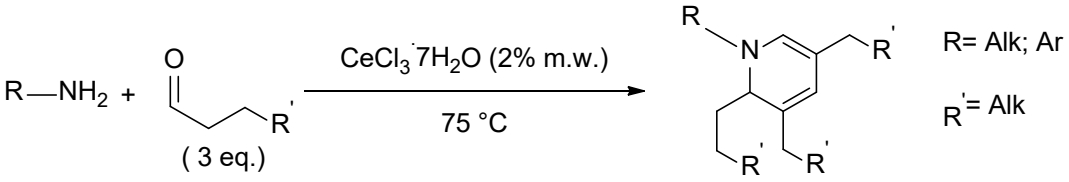

Figure 1.

Through common analytical techniques such as tandem mass spectrometry/chromatography and nuclear magnetic resonance it was possible to identify the expected products of condensation and related by-products. The target 1,2-dihydropyridine is obtained by a cascade process involving a preliminary aldehyde imination followed by a double aldol condensation and a final 6π azaelectrocyclization reaction[4] (**Figure 2**).

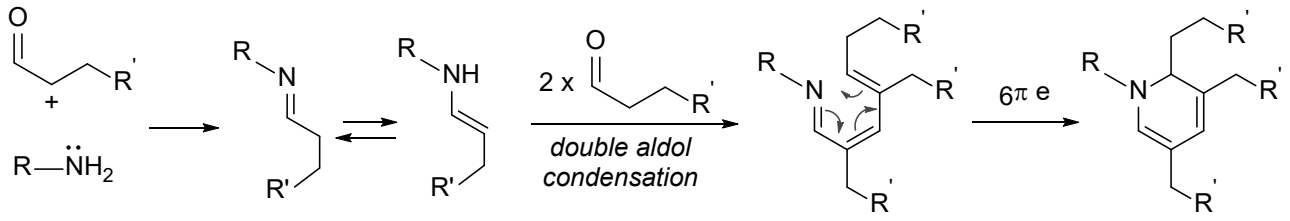

Figure 2.

References:

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PC-32

Resorc[4]arene-based site directed immobilization of antibodies for immunosensors development

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One of the main problems in the development of immunosensors is to overcome the complexity of binding antibody to the surface of the sensor. In fact, antibodies need to be immobilized with a high density and good orientation to allow the easy detection of antigens. The influence of nonspecific bindings should be minimized to improve the detection performance. Most of immobilizing methods lead to randomly oriented antibodies on the surface, which results in a low density of binding sites and alleviation of immunoaffinity of the antibodies. Therefore, oriented immobilization is required for the improvement of the performance enhancement.

Calix[4]arene derivatives have been proposed as an alternative tool for the oriented immobilization of antibodies thanks to their particular structure of lower and upper rims.[1]

To ensure the orientation control of antibodies on the sensor surface, we synthesized several resorc[4]arene derivatives able to self-assemble onto gold surface thanks to the thiol groups present on their structure.[2] Resorcarene, a type of calixarene, is a macrocycle oligomer based on the condensation of resorcinol and aldehyde. The immobilization characteristics of these artificial linkers have been evaluated by means of Surface Plasmon Resonance (SPR) technique comparing the results obtained with a random immobilization method based on EDC/NHS and an oriented immobilization with boronic acid derivatives of insulin antibody for the development insulin immunosensors. The results obtained put in evidence that the synthesized compounds show an enhancement of the insulin-insulin antibody interaction, resulting in a significative increase of the immunosensor sensitivity.

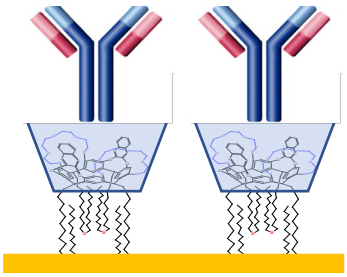

Figure 1: Immobilization on the sensor surface.

References:

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PC-33

The marine worm *Hermodice carunculata* is a promising biocatalyst for aldol reactions

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Recently, increasing efforts have been made to develop low-energy dependent and eco-sustainable enzyme-catalyzed procedures, with the aim to replace existing expensive and polluting manufacturing processes with new environmentally-friendly catalysts. The use of enzymes can frequently lead to the design of new products, otherwise unavailable by classical chemical synthesis. Generally, a relatively crude preparation is far more stable than a highly purified enzyme [1]. Crude extracts of annelids seem promising biocatalysts for various organic synthesis, but the available data only concern an earthworm species [2]. To improve the existing knowledges, in our study a crude extract of the marine worm *Hermodice carunculata* was used as biocatalyst for asymmetric aldol reactions on an assortment of aldehyde acceptors. The reactions showed moderate to good yields and stereoselectivity, and their chemical progress was affected by water concentration and temperature. The catalytic activity was present in the crude extracts obtained from different parts of the body of *H. carunculata*, even if the greatest conversion values were found with the dorsal body wall (32-45%). Our results confirm that crude annelid extract may be used as energy-efficient, safe, cheap and stable catalyst.

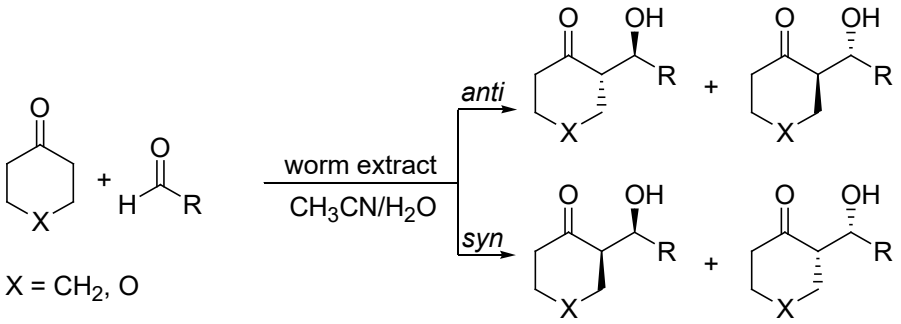

Figure 1: Aldol reactions catalysed by the crude extracts of *H. carunculata*.

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PC-34

Chemical Derivatisation of Tannins for Functional Materials

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The efficient use of all available biomass components is of utmost interest with respect to a sustainable use of renewable resources. Tannins represent one of the most versatile polyphenolic compounds of biomass.[1] Although being not as abundant as lignin, they are much more widely used already due to their unique functional features: i) unique π-stacking and complexing properties; ii) high general biocompatibility; iii) antioxidant activity; iv) ability to absorb UV light; v) anti-inflammatory activity; vi) anti-microbial activity and vii) anti-tumoral activity *via* control of reactive oxidant species (ROS).[1]

The yet unprecedented controlled functionalisation of commercially available tannins is a promising strategy that holds the potential to significantly broaden the actual scope of tannins used as natural antioxidant and antimicrobial agents -into innovative active ingredients and functional materials. Functionalised monomeric or oligomeric products serve as starting materials adding to the classical tannin features aspects necessary for targeted industrial applications in home and personal care products.

We will present the formation of a wide variety of functional tannins obtained *via* simple chemical protocols[2] that are optimised on the basis of detailed structural NMR analyses of starting materials.[3-5] Products include charged, chargeable, zwitterionic and copolymeric substances. Control of degrees of functionalisation allows for targeted tuning of macroscopic characteristics of the novel tannin-based substances.

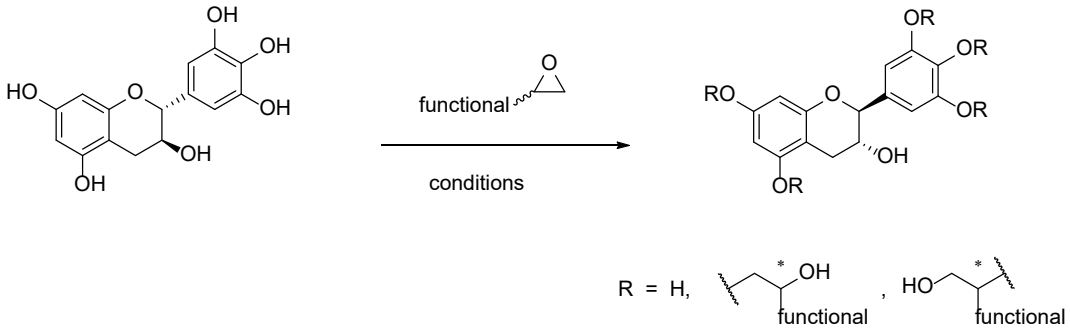

Figure 1: General functionalisation of tannins, shown using gallocatechin as one representative example.

References:

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PC-35

Stability Profiles of Lignin Microcapsules

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The efficient use of all available biomass components is of utmost interest with respect to a sustainable use of renewable resources. Almost one third of lignocellulosic biomass is comprised of polyphenolic oligomers and polymers, which are for the most part lignins.[1] The valorisation of lignin waste streams from pulp and paper and modern biorefinery processes is a crucial step for the development of circular sustainable economy. One very promising application of lignins is their use as shell material in ultrasonication-based generation of micro- and nanocapsules[2,3] for biomedical and agricultural applications.[4]

In light of various potential applications, stimuli responsive behaviour of lignin microcapsules (LMCs) has been investigated along with the detailed characterisation of their stability profiles.[5] The disassembly of LMCs was found to reflect kosmotropic and chaotropic characteristics of buffer systems and physiological solutions. A connection between the Hofmeister series and the stability profile of lignin micro-scaled materials can be delineated. LMCs showed excellent stability in water and under high temperature and pressure (autoclaving conditions). Active release is efficiently triggered by pH-changes and balancing chaotropic and kosmotropic effects via salinity tuning.

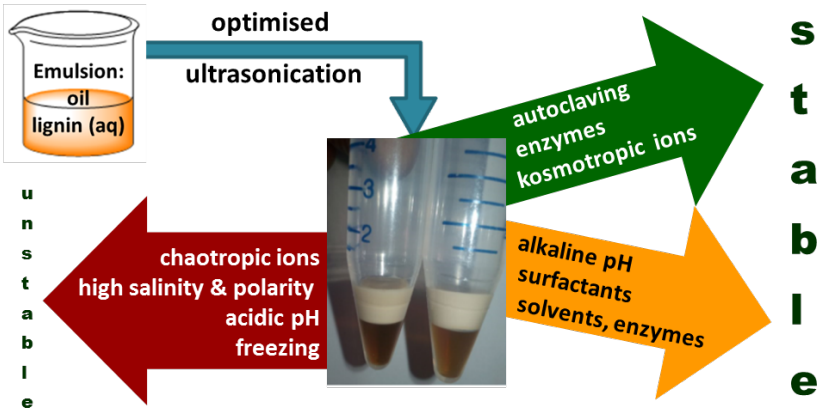

Figure 1: Lignin microcapsule stability – general overview.

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PC-36

Bio-based renewable polymeric materials from research to industrial point of view

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The current model of production and consumption relies on fossil-based resources. Climate change and environmental pollution are the main effects of this system.

National governments are developing a more sustainable economy based on biomass to overcome the negative impact of the fossil-based model. The bio-economy convert biomass into energy, feed and bio-based products, reducing the CO_2 emissions.[1]

Bio-based polymers found their application in different fields from packaging to wood coating. Aliphatic polyesters such as polylactic acid derived from renewable resources has been extensively used in packaging, medical implant and drug delivery systems.[2] PLA can be synthesized through ring-opening polymerization of lactide and polycondensation of lactic acid using different catalysts. Among them the most common used for the synthesis of high molecular weight PLA are tin-based compounds, despite the difficulties in removing the catalyst from the polymer. Moreover, the presence of tin ions in polymeric matrix has adverse effects on living organism cells.[3]

A new non-toxic and eco-sustainable catalytic system, $CeCl_3 \cdot 7H_2O$/NaI, is used for the synthesis of PLA, in order to achieve a molecular weight close to that obtained with tin compounds.

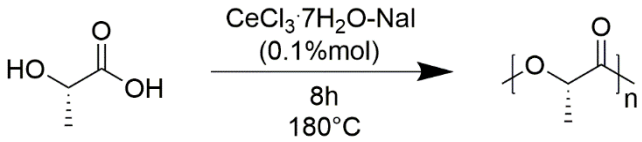

Figure 1: Synthesis PLA.

Together with lowering CO_2 emissions, a crucial role is played by reducing the release of VOCs. Development and production of acrylic and polyurethane resins for water-based paints, starting from biomass waste, lead to a reduction of VOCs emission while keeping the chemical-physical properties very close to those of synthetic resins.

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PC-37

Novel Synthetic Analogues of Climacostol as Potent Anticancer Nature-Inspired Small Molecules

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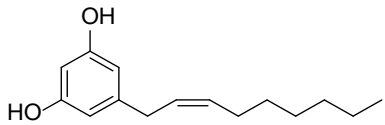
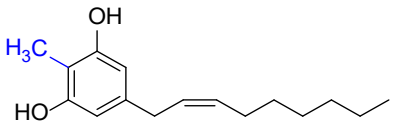
Climacostol (5-[(2Z)-non-2-en-1-yl]benzene-1,3-diol, **1**) is a natural toxin isolated from the freshwater ciliated protozoan *Climacostomum virens* and belongs to resorcinolic lipids, a group of compounds that show antiparasitic, antimicrobial and anticancer activities.[1] After developing a straightforward strategy to synthetically obtain Climacostol,[2] we recently developed the synthesis of two analogues, compounds **2** and **3** with the aim of improving the activity of the native toxin. Results showed that the analogue **2** exhibited higher toxicity against pathogen microbes, while molecule **3** is able to induce programmed cell death in protistan cells.[3]



1



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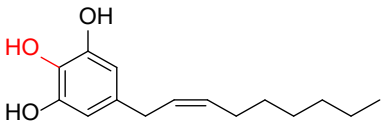
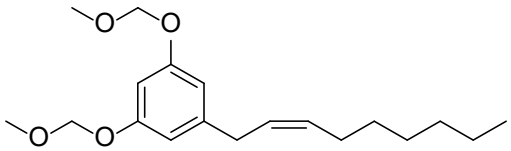


3

The choice of MOM protection of the free hydroxyl groups was a crucial step for the synthesis, since it allowed us to obtain the *Z*-isomer in a selective way through a Witting olefination, avoiding the formation of the biologically inactive *E*-diastereomer. Moreover, the mild acidic condition for its deprotection, proved compound **4** to be a promising prodrug that is efficiently activated in the mild extracellular acidosis.[4]



4

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PC-38

Synthesis of the fungal metabolites radicinin and its natural precursor deoxyradicinin: potential bioherbicides for invasive species control.

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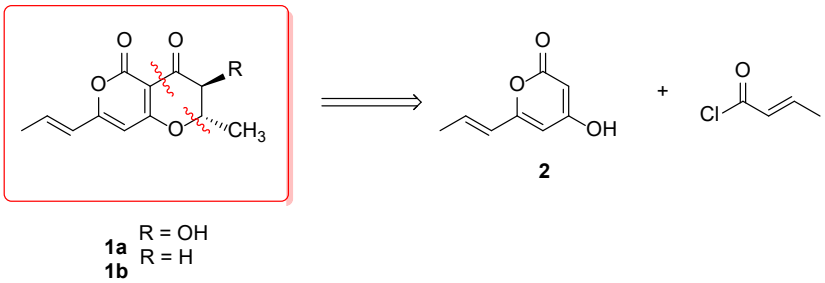
Radicinin (**1a**) is a fungal natural product first isolated in 1953 from *Stemphylium radicinum* (*Alternaria radicina*),[1] the fungus responsible for black rot disease of carrots and, since then, from a variety of other plant-associated fungi. Such secondary metabolite displays different phytotoxic and antibiotic properties.[2] Indeed, it shows phytotoxic activity against several kind of plants such as buffelgrass (*Pennisetum ciliare* or *Cenchrus ciliaris*), cress (*Lepidium sativum*) and Job's tears (*Coix lachryma-jobi*) as well as antifungal activity against *Magnaporthe grisea*, also known as rice blast fungus, and *Valsa mali*, a plant pathogen fungus. It also exhibits a strong antibacterial activity against the Gram-negative bacterial phytopathogen *Xylella fastidiosa*, that causes many devastating plant diseases. The recent growing interest for radicinin is mainly due to the possibility to use this compound as potential natural herbicides against buffelgrass, a perennial grass that has become highly invasive in the Sonoran Desert of southern Arizona. Radicinin demonstrated high target-specific toxicity on such weed, low toxicity to native plants, and no teratogenic, sub-lethal, or lethal effects on zebrafish (*Brachydanio rerio*) embryos.[3] In order to develop a target-specific bioherbicide for that invasive species, it is necessary to have quantities of radicinin much greater than those obtainable from natural sources and, for this reason, the development of an efficient total synthesis of this compound becomes mandatory. Moreover, the availability of racemic **1a** as well as of the deoxygenated derivative **1b** can also allow to carry out detailed structure-activity studies on the role of the absolute and relative stereochemistry and of the α-oxygen on the bioactivity of this compound. Accordingly, the synthetic approach to (±)-radicinin (**1a**) and its precursor (±)-deoxyradicinin (**1b**) described in Scheme 1 is reported in this communication. Such approach is based on the disconnection of their structure into pyranone **2**[4] and crotonyl chloride.



1a R = OH
1b R = H

Scheme 1: Retrosynthetic analysis.

References:

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PC-39

Enantioselective Carbolithiation-Trapping Reaction of 1-Aryl-1-Alkenyl Carbamates

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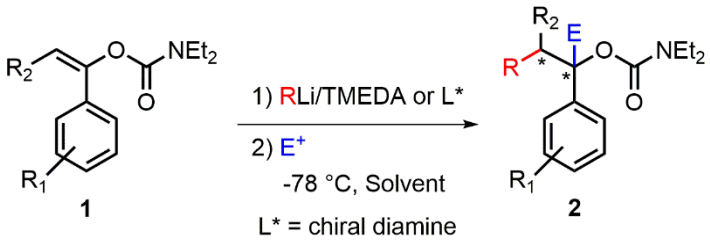
Carbolithiation reactions of styrenyl olefins represent an attractive synthetic methodology, offering pathways for the preparation of highly functionalized aromatic compounds. This transformation generates a benzyllithium species which, through a tandem carbolithiation-trapping reaction, can be reacted with carbon electrophiles, allowing the efficient regioselective formation of two new C-C bonds and of one or two new stereocenters. A potential limitation to the application of carbolithiation as a synthetic method derives from the difficulty of tempering the reactivity of the obtained organolithium intermediate towards the starting unsaturated substrate avoiding to trigger an unwanted anionic polymerization process. Therefore, despite its synthetic appeal, this class of reactions has not gained much synthetic attention. For synthetically useful carbolithiation reactions, a special stabilization of the benzyl lithium intermediate is in fact required. Such a stabilization can be obtained either by *intra*- or *inter*-molecular organolithium coordination which, at the same time, prevents polymerization and promotes the carbolithiation reaction.[1] This coordination occurs in the presence of chelating groups proximal to the reacting alkene and/or in the presence of bidentate ligands such as diamines. The aim of this study was to investigate the carbolithiation of 1-aryl-1-alkenyl *N*,*N'*-dialkylcarbamates (**1**) as a useful tool for the synthesis of multi-functional compounds, also in optically active forms.[1] The organolithium intermediate obtained after the carbolithiation step was then reacted with several electrophiles, obtaining trisubstituted benzyl carbamates (**2**) as direct precursors of tertiary benzylic alcohols. The tandem carbolithiation-trapping with electrophiles was also carried out in an enantioselective manner, in the presence of chiral diamines as chelating agents,[2] obtaining enantioenriched tertiary benzyl carbamates (Scheme 1).



Scheme 1: Carbolithiation-trapping reaction.

References:

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PC-40

Intriguing role of iodine on the reactivity and stability of dihalomethyllithium carbenoids

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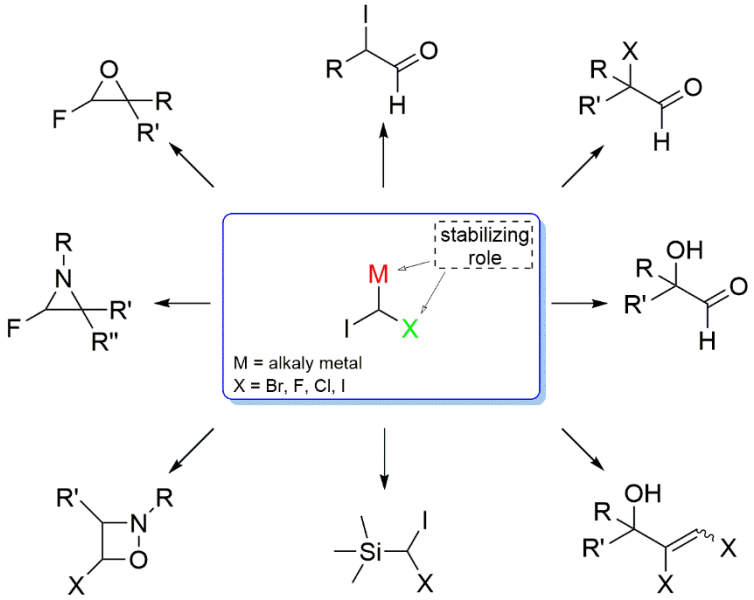
Halo and dihalomethyllithium carbenoids represent actractive tools in organic synthesis due to their dicothomic reactivity as nucleophiles and electrophiles. Generally, genesis (Li-halogen exchange or deprotonation) and *in-situ* trapping require cryogenic conditions (usually below -78°C),[1,2,3,4,5] although microfluidic reactors are able to control the thermal (and chemical) instability allowing external quenching even at higher temperatures.[6] Recent works demonstrate that iodinated lithium carbenoids could react with electrophiles after 20 minutes at -78°C in batch conditions.[7]

Motivated by these promising results and by the shortage of detailed studies, we analyzed the reactivity and stability of dihalomethyllithium carbenoids, highlighting the role of iodine atom on the carbenoid properties. Herein, the reactivity of dihalomethyllithiums (LiCHIBr, LiCHIF, LiCHICl, $LiCHI_2$) is investigated, disclosing interesting synthetic pathways depending on the nature of the electrophile.



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PC-41

Diastereoselective synthesis of axially chiral styrenes

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Recently, we have reported a new synthesis of 3-vinylindoles based on a clean and direct dehydrative coupling reaction between acetophenones and indoles in the presence of catalytic amounts of aryl-(3-indolyl)methylium tetrafluoroborates as Lewis acid catalysts.[1] 3-Vinylindoles feature the 1,1-diarylethene scaffold often present in molecules showing strong biological activities; furthermore, 3-vinylindole and derivatives have been used as complex building blocks in the asymmetric synthesis of substituted indoles.[2]

Owing to the wide interest in these compounds, we decided to extend the reaction to alkyl aryl ketones other than acetophenones and, subsequently, to other aromatic and heteroaromatic nucleophiles. The reaction requires an acidic catalyst and we tested both the above Lewis acid carbocations and simple Brønsted acids. The expected dehydrative coupling products were, in this case, α-aryl-β-alkyl (or aryl) α-indol-3-ylethenes containing two stereogenic elements; they are axially chiral styrene derivatives, achievable as a mixture of *E* or *Z* diastereomers, as already reported in literature when prepared by similar synthetic methods.[3] In preliminary results, in our conditions, we obtained predominantly *Z*-diastereomers, as confirmed by spectroscopic and X-ray diffraction measures. The computational study reproduced and explained the observed diastereoselectivity.

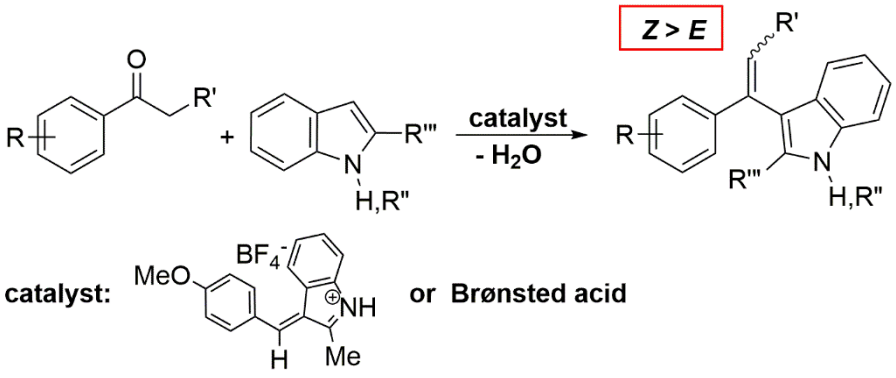

Figure 1: Dehydrative coupling reaction for the synthesis of axially chiral styrenes.

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PC-42

GLYCOG Lab 4.0, the sweet nanofiller: a tangible case of transfer of technology (TOT)

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In the last ten years, companies have been often faced with stringent environmental regulations imposed by the European Legislation related to the use of hazardous chemicals in final products. Most of these chemicals are used as preservatives, thus, they are crucial additives ensuring the durability of end products. Therefore, environmental issues are forcing the industry to steadily updated and, in particular, manufactures are dealing with the need of high-quality products not only in terms of technical performance but also in terms of controlled impact on health and environment. Moreover, the development of innovative and eco-friendly solutions, providing a lower impact to human health and environment, is one of the top priorities for industry.

Carbon based nanocomposites are an emerging technology that have generated great expectations as demonstrated by the significant number of companies involved in the commercialization of these materials,[1] by the huge amount of private and EU funding opportunities (*e.g.* Graphene flagship)[2] and by the substantial body of publications from academia. However, despite many impressive achievements in the preparation of carbon-based nanocomposite with tailor-made properties,[3-4] the main industrial applications rely on the use of raw materials.[5] Indeed, the main issues related to the transfer of technology (TOT), in the field of functionalized nano-materials, concern the scale up and the final physiochemical properties of the products.

GLYCOG Lab 4.0, a close partnership between industry and academia, arises from the necessity to answer these issues, guaranteeing the highest level of innovation and research. In particular, we report here on the development of a novel smart and multifunctional carbon-based nanocomposite containing a new eco-friendly biopolymer as a case study of transfer of technology. Indeed, the strong point of the proposed nanomaterial is the possibility to be applied by a wide range of companies (*e.g.* textile, naval and construction paint industries) that deal with the issue of long-term UV-shielding and bio-deterioration combined with the optical, mechanical and electronic properties of the functionalized glyco-nanomaterial. The nanoadditive was designed employing glycopolymers as biocompatible component and water as main solvent, in accordance with the green chemistry guidelines. Moreover, the scale-up of the process on the gram scale dealing with the problem of the technological transfer from basic research to applied science has been taken into account by GLYCOG Lab 4.0.

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PC-43

Accelerating water exchange in Gd^{III}-DO3A-acetophenone derivatives by favouring the dissociative mechanism through hydrogen bonding

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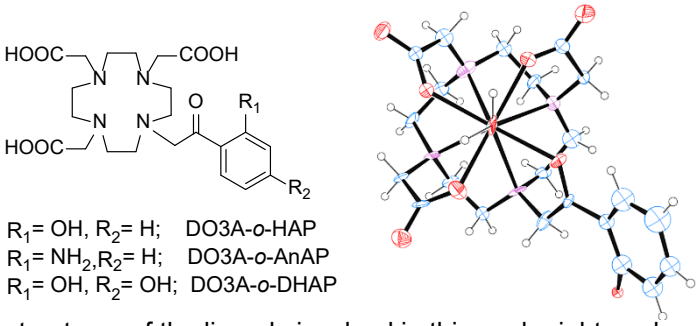
MRI contrast agents (CAs), usually Gd^{III} or Mn^{II} complexes, are often used to increase the diagnostic information of the image by enhancing the signal intensity and the contrast between normal and diseased tissues.[1] A reduction of the doses used in clinical practice could be beneficial and this can be obtained through the development of more efficient CAs with fast exchange rates (k_{ex}) of the coordinated water molecule(s), which lead to high relaxivity values. We have recently shown that Gd(DO3A-o-HAP), a DO3A-like ligand with a fourth pendant arm consisting of a 2'-hydroxyphenacyl group, has a hydrogen-bond acceptor in the periphery of the coordinated water molecule that accelerates dramatically the water exchange rate, as measured by ^{1}H and ^{17}O NMR relaxometry.[2] Furthermore, a Density Functional Theory (DFT) study confirmed that intramolecular hydrogen-bonding interactions with the peripheral phenolate group favour the exchange of the coordinated water molecule, thereby accelerating k_{ex}. A single crystal of GdDO3A-oHAP was also obtained and the X-ray diffraction analysis showed that complex presents a square antiprismatic coordination around the metal centre with a cis/trans disordered 2-hydroxyacetophenone moiety at 20/80 ratio. The phenolic OH forms an intermolecular H-bond in *trans* conformation while an intramolecular water assisted H-bond is observed in the *cis* conformation.

Then, in order to evaluate the effect of different hydrogen-bond acceptors in this family of phenacyl-based complexes, we also synthesized and characterized via ^{1}H and ^{17}O NMR relaxometry two novel macrocyclic ligands, bearing a 2'-aminophenacyl (DO3A-An-AP) and a 2',4'-dihydroxyphenacyl (DO3A-DHAP) group as the fourth pendant arm (**Figure 1**).



R_1= OH, R_2= H; DO3A-*o*-HAP
R_1= NH_2, R_2= H; DO3A-*o*-AnAP
R_1= OH, R_2= OH; DO3A-*o*-DHAP

Figure 1: left: chemical structures of the ligands involved in this work; right: molecular structure of the major *trans* conformation of GdDO3A-*o*-HAP viewed along Gd-water bond

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PC-44

Mixed phenolate/carboxylate AAZTA-like ligands for MRI applications

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Magnetic resonance imaging (MRI) is a leading technique in modern clinical diagnostics. Contrast-enhanced MRI requires the use of suitable paramagnetic metals (*e.g.* Gd^{3+}) that increase the water-protons relaxation rate (R_1). We have designed new ligands based on the AAZTA platform (*Figure*),[1] since it has proved to chelate lanthanide and *p*-block ions with excellent thermodynamic stability and kinetic inertness, which is crucial to ensure *in vivo* safety. GdAAZTA possesses optimal parameters to attain a high MRI performance, particularly two water molecules coordinated to the metal center (q = 2), affording a R_1-enhancement per millimolar Gd-concentration (*relaxivity,* r_{1p}) of 7.1 mM^{-1} s^{-1} at 20 MHz and 25 °C. Our novel ligands (*Figure*) contain one (**L1** and **L2**) or two (**L3**) phenolic moieties in addition to traditional acetate arms. Phenolate anions can be strong donor groups, and macrocyclic and acyclic chelates functionalized with hydroxyphenyl units are widely reported in the literature as ligands for transition-metal ions. However, their applications as lanthanide chelators are very uncommon, particularly for use in aqueous environments: only a few cases are reported for Gd^{III}.[2] The synthesis of **L1**-**L3** (*Figure*) involves a nitro-Mannich cyclization with a suitable disubstituted ethylenediamine to obtain a 6-nitroperhydro-1,4-diazepine, followed by reduction of the nitro-group and mono- or dialkylation of the resulting primary amine with *t*-butyl bromoacetate. The phenolic moieties are introduced by reacting the primary or secondary amine(s) with 2-(bromomethyl)phenyl acetate or salicylaldehyde. The ligands are obtained upon deprotection of the acetate and hydroxybenzyl arms. Gd^{3+}-complexations and a preliminary relaxometric characterization (20 MHz, 25 °C) allowed to determine r_{1p} values of 7.2, 5.7 and 4.9 mM^{-1} s^{-1} for Gd**L1**, Gd**L2** and Gd**L3** respectively, with the first confirming a q = 2 as for GdAAZTA. Further and more advanced investigations (^{17}O-measurements, interaction with HSA and endogenous anions *etc*.) have been carried out on these promising chelators and their potential MRI applications.

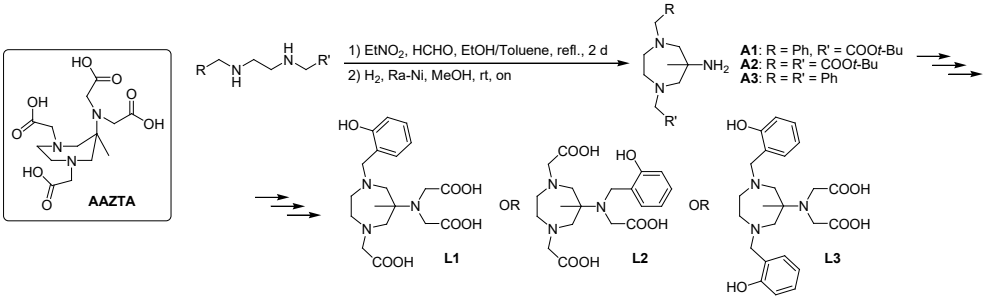

Figure: AAZTA-ligand and synthetic pathway for ligands **L1**-**L3**.

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PC-45

Targeting mPGES-1 by a combinatorial approach: identification of 2-aminobenzothiazoles as scaffold for new PGE_2 modulator in human cancer cells

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Microsomal prostaglandin E_2 synthase-1 enzyme (mPGES-1) has emerged as an attractive target for the discovery and development of new efficient anti-inflammatory and anticancer drugs[1]. This enzyme is responsible for the production of inducible prostaglandin PGE_2, and its inhibition is an alternative option to control PGE_2-related pathologies with respect to the strategies targeting the upstream cyclooxygenases[2]. For these reasons, inhibition of mPGES-1 represents an attractive strategy for developing new anti-inflammatory and anti-cancer drugs with reduced side effects. Design of these inhibitors was done following a computational protocol; the synthones 2-amino-6-bromobenzothiazole and 2-amino-5-bromobenzothiazole were combined with 318 acid-chlorides at position 2 and 570 boronates at position 6 or 5, respectively, obtaining 181,260 molecules for each library, using *CombiGlide* software[3]. Docking calculations were performed using *Glide* software. In particular, different levels of Glide sampling and scoring precision algorithms were accounted (HTVS, SP, and XP modes). The best-selected compounds (**3**-**20**) were synthesized, using Pd-catalyzed Suzuki-Miyaura cross-coupling between 3-(hydroxymethyl)phenylboronic acid and 2-amino-6-bromobenzothiazole or 2-amino-5-bromobenzothiazole followed by acylation. mPGES-1 inhibitory activity of synthesized compounds was evaluated *in vitro* performing cell-free and cell-based assays[4]. The effects of synthesized molecules against mPGES-1 activity were studied by monitoring the enzymatic conversion of the substrate PGH_2 to PGE_2 in a cell-free assay using microsomes of IL-1β-stimulated A549 cells as a source of mPGES-1, disclosing **3**, **5**, **8**, **12**, **20** as active compounds able to inhibit the target at low micromolar concentrations (IC_{50} < 3.0 μM). Afterwards, the evaluation of melanoma cancer cell vitality disclosed **3**, **5**, **12** as the most promising hits with IC_{50} < 20.0 μM.

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PC-46

Unprecedented use of a deep eutectic solvent as hydrogen source for Ru(II)-catalyzed transfer hydrogenation of carbonyl compounds under mild conditions

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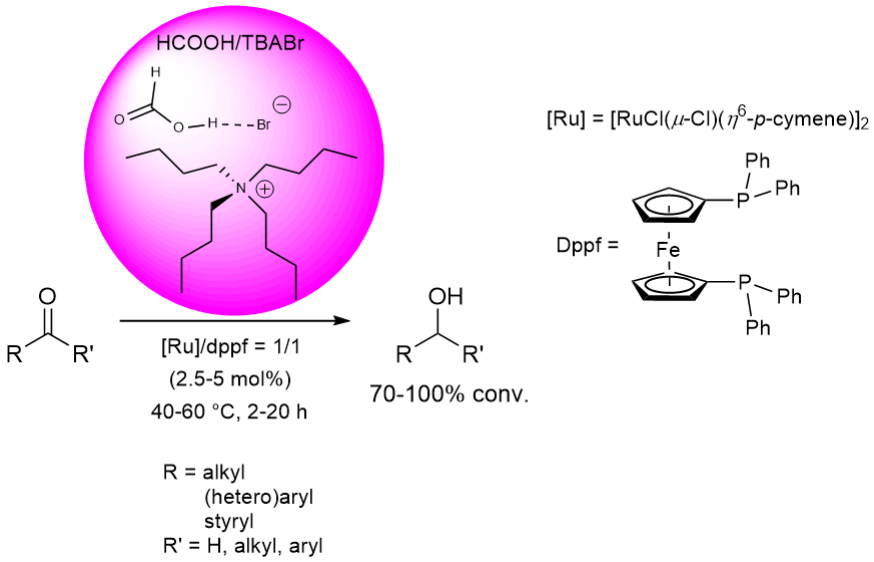
Deep eutectic solvents (DESs)[1] are systems formed from a eutectic mixture of Lewis or Brønsted acids and bases which can contain a variety of anionic and/or cationic species. They have emerged in the last two decades as a promising alternative to volatile organic compounds (VOCs).[2] They have recently been used as unconventional solvents in several and diverse synthetic transformations,[2a] such as transition metal catalyzed hydrogenation,[2b] often showing novel reactivity, selectivity and efficiency compared to traditional VOCs. In addition, DESs are not volatile, non-toxic, non-flammable, completely biodegradable and easy to handle and synthesize. Given their peculiar properties, in our pursuit of simple and efficient catalysts for the Ru(II)-mediated reduction of carbonyl compounds,[3] we envisaged the possibility to employ DESs both as reaction media and hydrogen sources, combining readily accessible Ru-precursors with different diphosphane and diamine ligands.

Herein we report the unprecedented use of the eutectic mixture HCOOH/TBABr as hydrogen source in the transfer hydrogenation of commercial-grade carbonyl substrates to their corresponding alcohols, catalyzed by the in situ generated system [RuCl(*μ*-Cl)(*η*^{6}-p-cymene)]$_2$ / dppf under mild conditions.



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PC-47

Quinoline cyclic tripeptoids as novel DNA bis-intercalating agents

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Bis-intercalators are a class of secondary metabolites produced by several bacteria species.[1] The main interest in these compounds is due to their remarkable anti-tumor activity, as well as the unique DNA binding mode, which usually is enhanced by GC-rich DNA sequences. Non-covalent DNA binders exert their function via intercalation of a polyaromatic unit between two bases; this interaction can be enhanced by a positively charged nitrogen atom on the intercalator scaffold (which usually is a cyclic peptide or depsipeptide) and the oxygen atom of the phosphodiester group of DNA.[2] The chromophores face out from the scaffold and are constituted either by a quinoline or a quinoxaline unit; the intercalation causes severe alteration in the replication or transcription of the DNA, which results in the cytotoxic effect.[3]

Cyclic peptoidic systems, oligomers of *N*-alkyl glycines,[4] have already proven to be remarkably promising as small molecules mimicking the activities of natural cyclodepsipeptidic counterparts.[5] Our approach to a synthetic class of bis-intercalators consists in the functionalization of a cyclic trimeric peptoid core with two or three quinoline appendages, in order to evaluate the effect of a free amino group, potentially able to interact with the DNA's phosphodiester group. In this communication we will report both the synthesis and the activities of our compounds as cytotoxic agents against human cancer cell lines.

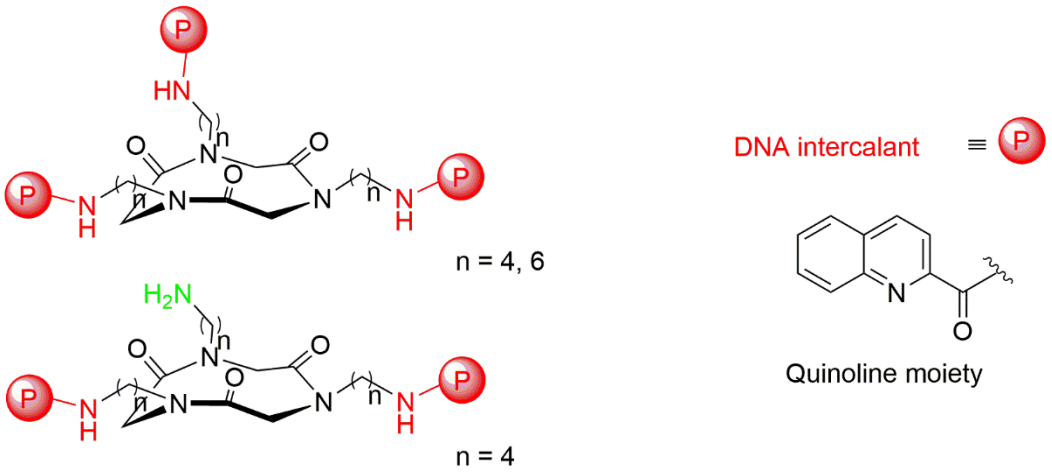

Figure 1. Cyclic tripeptoids examinated in this communication.

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COMUNICAZIONI POSTER
Sessione 2

PC-48

Modulation of biological target selectivity through an appropriate scaffold decoration

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Small-molecules are powerful tools both as therapeutics and as probes for investigating key cellular processes governed by biological macromolecules.[1] With the aim of disclosing new molecular entities able to selectively modulate strategic therapeutic targets involved in both cancer and inflammatory pathologies, here we describe a valuable combined approach for generating new chemical hits. In particular, starting from a versatile synthetic strategy we had access to a wide variety of highly functionalized heterocyclic scaffolds representing the initial seed for investigating protein-ligand interactions involved in key biological processes. A computational approach by molecular docking calculations drove the strategic synthesis of selective molecules able to interact with a specific target.[2,3] Our purpose was the optimization of synthetic strategy leading to a fused heterocyclic ring as building block *via* suitably functionalized starting materials. These advanced intermediates could further derivatized, by nucleophilic aromatic substitution as well as by Palladium catalyzed Suzuki-Miyaura reactions, in order to obtain the whole series of designed compounds.[4] Following these strategies, the easy and fast preparation of a wide number of new potential bioactive compounds is allowed. The synthesized molecules were screened to confirm their biological profile.

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PC-49

A multistep computational protocol towards the identification of 2-amino-1,3,4-thiadiazole-based molecules as novel mPGES-1 inhibitors

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In light of the well-known involvement of microsomal Prostaglandin E_2 Synthase-1 (mPGES-1) in the development of inflammatory and tumor diseases, the mentioned protein target is recently getting one of the most investigated towards the individuation of novel drugs for the treatment of both the pathologies.[1] The synthase, in fact, catalyzes the conversion of the unstable peroxide prostaglandin H_2 (PGH_2) in prostaglandin E_2 (PGE_2), and it is over-expressed in inflammation and cancer.[1] Thus, a structure-based multistep computational protocol coupled to a previously selected synthetic approach was applied, with the main purpose of identifying novel promising hits.

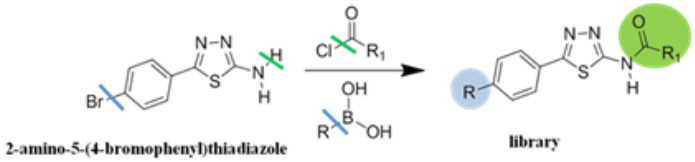

Figure 1: Generation of the library.

In detail, commercially available acyl chlorides were introduced on the amino group at position 2 of 2-amino-5-(4-bromophenyl)thiadiazole (Figure 1), as a substitution reaction is the first step of the chemical route (Figure 2), while commercially available boronic acids, involved in the Suzuki coupling reaction, were used for the replacement of the bromine. A new library of 181,260 *N*-(5-(4-arylphenyl)-1,3,4-thiadiazol-2-yl)arylcarboxamides was generated *in silico*, and a *Virtual Screening Workflow* for the docking studies (*Glide software*)[2] onto the crystal structure of mPGES-1 was performed, affording a final selection of 9 promising compounds for the synthetic step. All the compounds were synthesized applying the reported synthetic strategy. Performed cell-free and cell-lines assays confirmed the inhibitory activity on the enzyme of 3 among the synthesized compounds, presenting an IC_{50} < 3 μM in the cell free assay.

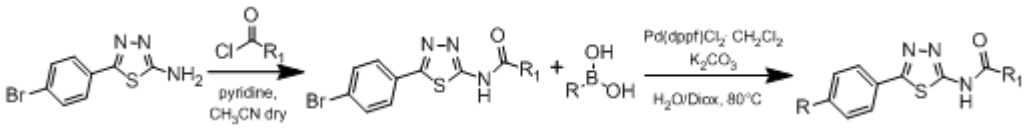

Figure 2: Selected and applied synthetic strategy.

References:

[1] J. G. Luz, S. Antonysamy, S. L. Kuklish, B. Condon, M. R. Lee, D. Allison, X.-P. Yu, S. Chandrasekhar, R. Backer, A. Zhang, M. Russel, S. S. Chang, A. Harvey; A. V. Sloan; M. J. Fisher, *J. Med. Chem.* **2015**, *58*, 4727.

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PC-50

Synthesis of bifunctional inhibitors to address type 2 diabetes by dual enzyme targeting

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The diffusion of type 2 diabetes (T2D) throughout the world represents one of the most important health problems of this century and the development of new anti-diabetic drugs remains an urgent challenge. Indeed, none of the currently marketed drugs is capable of reproducing the physiological action of insulin and often they have several side effects. Multi-target drugs could offer new therapeutic opportunities for the treatment of T2D. [1] α-Glucosidases and Protein Tyrosine Phosphatase 1B (PTP1B) are considered important targets for the treatment of T2D: the first enzymes digest oligo- and disaccharides in the gut, while the latter regulates the insulin-signaling pathway. With the aim of generating new drugs able to inhibit both enzymes, we synthesized a series of bifunctional compounds bearing both a nitro aromatic group and an iminosugar moiety (Figure 1). [2] The synthesis relies on the connection of an iminosugar key intermediate to the nitroaromatic moiety through the CuAAC approach or via an amide bond.

The results of tests carried out both *in vitro* and in a cell-based model, show that these bifunctional compounds maintain activity on both target enzymes and, more importantly, two of them showed a good insulin-mimetic activity in *ex-vivo* assays, increasing phosphorylation levels of Akt in the absence of insulin stimulation. These compounds could be used to develop a new generation of anti-hyperglycemic drugs useful for the treatment of patients affected by T2D.

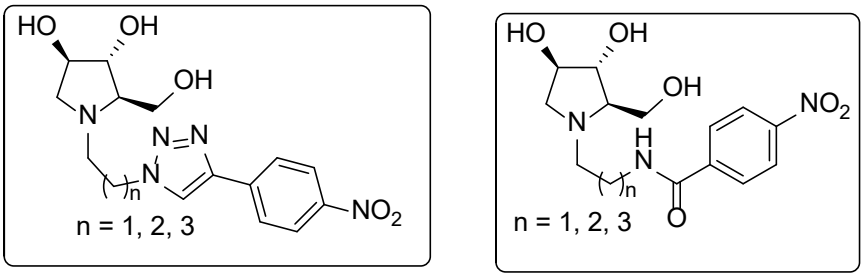

Figure 1: The bifunctional compounds designed to inhibit both α-Glucosidases and Protein Tyrosine Phosphatase 1B (PTP1B) enzymes

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PC-51

Micellar Assisted Synthesis of Chalcones as Intermediates for Bipyridines

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Chalcones are well known molecules, having several applications as intermediates and drugs.[1] They are often easily obtained by performing aldol reaction in solvents, with good yields. They are essential intermediates for the Kröhnke reaction, which give access to pyridines, bipyridines and terpyridines.[2] The bipyridine structural motif is often exploited as a ligand to form metal complexes which showed electrochemical CO_2 reduction activity.[3] In order to produce chalcones for the preparation of bipyridine ligands, we tried a green chemistry approach. While the solvents used for this reaction are in general mild (often alcohols are used), the use of water by surfactant assistance is an attractive alternative, which is not new but in the last few years it reached important results from the preparative point of view.[4] The aldol reaction was studied and applied to the synthesis of a few chalcones, useful for the preparation of bipyridine ligands. Several surfactants were used and among them, PTS, Nok and TPGS-750-M are truly green surfactants.[4] The use of surfactants shortened the reaction time and increased the yield. Whether the chalcone is sufficiently soluble in the micellar medium, the reaction can proceed with a Michael addition on the chalcone. The chalcone was easily isolated by filtration when it was slightly soluble in the micellar solution. Reactions performed in presence of a cosolvent (10% ethanol), showed an increased yield and gave pure solids by simple filtration (yields: 76-91%). The scope of the reaction was studied, and also the less deactivated substrates reacted easily. The chalcones were used to prepare some bipyridine derivatives, with Kröhnke reaction, under both standard conditions (acetic acid and ammonium acetate at 80°C) and an original and green way, performed in water.

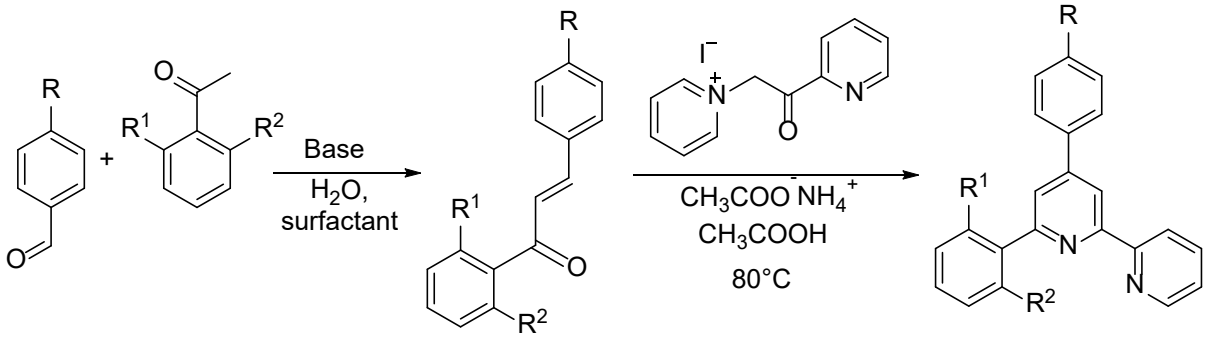

Figure 1: Synthetic Pathway to chalcones in surfactant medium and to bipyridines by Krohnke reaction.

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PC-52

Synthesis and characterization of polymers as HTMs for perovskite solar cells

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Among alternative energy sources, Perovskite Solar Cells (PSC), raising in efficiency from 3.2% to 22-23% in only few years,[1] are the new frontier of the photovoltaic research. The polymeric Hole Transport Materials (HTM) extract holes and protect perovskite from moisture degradation due to their superior sealant ability.[2] We prepared several P3HT and PTAA conductive polymers. P3HT structure was modulated in molecular weight (20 to 300 kDa) and regioregularity (78-100%), to search for correlations between structure and solar cell efficiency.[3] The P3HT were prepared by different synthetic methods (oxidative,[4] C-H activation[5] and Grignard Methatesis[6]).

The PTAA were prepared by polymerization of dibromo-substituted linkers with different anilines, with a Pd catalyst bearing a NHC ligand,[7] obtaining polymers with short to medium molecular weight. Upon characterization, the polymers showed a very good stability and the estimation of energy levels was compatible with the most common perovskites used in perovskite solar cells. Those HTMs were used in crystal engineering perovskite[8] solar cells, reaching a photoconversion efficiency of 17% and 13.4% respectively, confirming their good potential as HTMs for PSCs.

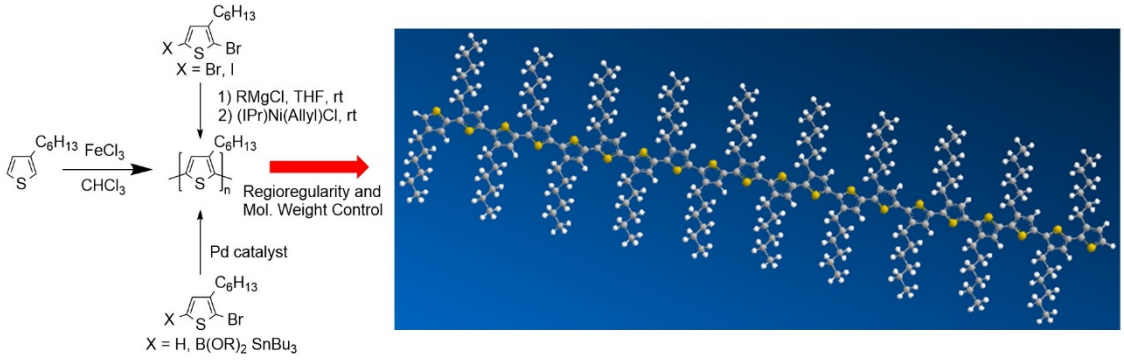

Figure 1: Different synthetic methods for P3HT.

Acknowledgements

This work was supported by the Italian Ministry of Economic Development in the framework of the Operating Agreement with ENEA for Research on the Electric System.

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PC-53

Synthesis of a donor-acceptor polymer for perovskite solar cells

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The increasing world energy demanding makes compulsory the search of energy sources alternative to fossil fuels. Among alternative energy source, the solar energy is green, renewable and not exhaustible. Perovskite Solar Cells (PSC), which rose in efficiency from the 3.2% (2012) to 22-23% in only 5-6 years,[1] are the new frontier of the photovoltaic research. Unfortunately, perovskites show instability towards moisture, which rapidly deteriorates the device performances. The use of polymeric Hole Transporting Material (HTMs) layers on the perovskite surface seems to overcome those problems, granting a good stability increase, since the optimal filming properties of hydrophobic polymers.

Most HTMs need to be doped to show good conductivity levels, useful for PSC cells, but doping agents are detrimental for cell stability since they are hygroscopic and, through them, water can reach the perovskite layer. Recently, we prepared P3HT and PTAA as HTM, but we are also interested into polymeric HTMs showing an inherent high conductivity, which recently became the new HTM research hot topic, the "dopant-free" conductive polymers.[2] To prepare a promising dopant-free polymer, a donor-acceptor monomer (**1**) was prepared by Suzuki coupling on a dibromoaldehyde derivative, followed by Knoevenagel condensation with malononitrile under microwaves. The final polymerization using $FeCl_3$ gave a red colored polymer (**2**). The polymer was characterized by NMR, GPC, UV, Fluorescence, CV, thermal analysis (TGA and DSC). A high molecular weight polymer was obtained, showing very good thermal stability. The HOMO and LUMO levels, obtained by electrochemistry and spectroscopy, showed that the polymer can be considered an interesting HTM for perovskite solar cells.

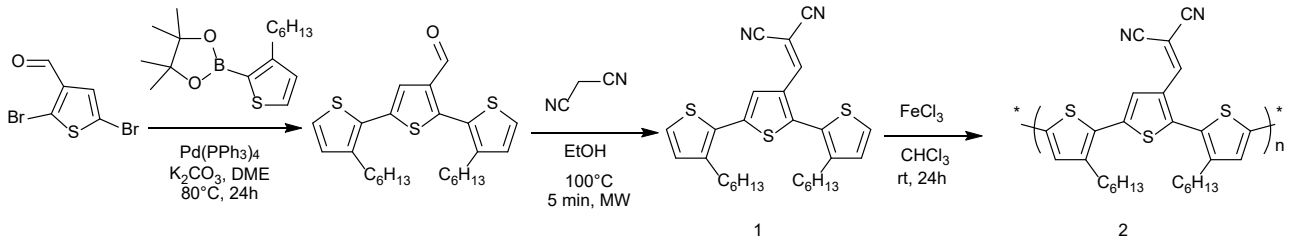

Figure 1: Scheme for the synthesis of the monomer (**1**) and the polymer (**2**).

Acknowledgements:
This work was funded by ASI, through the project PEROSKY.

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PC-54

Azodyes based polymers for 3D printing

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Three-Dimensional Printing (3DP) is one of the most promising innovative technologies, used not only in prototyping, but also in the production processes. The main advantages of this new technique are the high versatility, the progressive printers' price knock off and the considerable saving of raw materials. The exploitation of new functional materials, for example temperature-, light- and pH-responsive polymers, is one of the most interesting survey field[1]. Azo-based scaffolds have been reported to provide well-defined either photohardening or photosoftening 3D devices[2].

a) b)

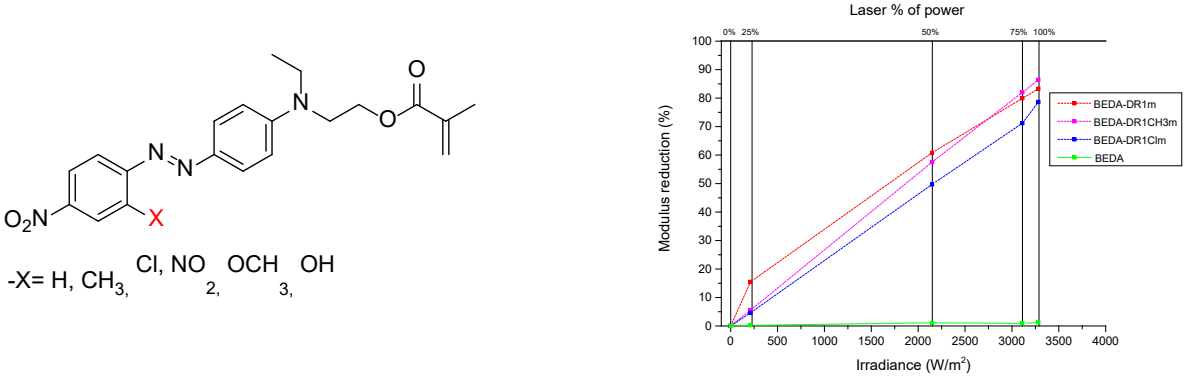

Figure a) Molecular scaffold of the azo monomers; b) Elastic modulus reduction as a function of laser irradiance

In the present work, we designed, synthetized and characterized dye-functionalized polymethacrylates for Digital Light Processing (DLP). Our attention was focused on the azo-benzene methacrylate monomers, because they give mechanical responses, upon irradiation, probably due to the *trans-cis* isomerization. Various substituents (Figure 1a) have been introduced, in *ortho* position to the azo moiety, to tune the monomer/polymer properties, both by steric and electronic effects. We have noticed that the polymers glass-transition temperature (T_g) and the elastic modulus have shown remarkable variations, as a function of the laser power at 532 nm (Figure 1b).

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PC-55

Squaraine dyes: interaction with bovine serum albumin to investigate supramolecular adducts with aggregation-induced emission (AIE) properties

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In the last decades great attention was dedicated to the development of new dyes as markers in biological applications. Squaraines are a class of highly fluorescent near-IR dyes with potential applications as sensors. Even though squaraines have favourable properties relevant in several fields (Dye-Sensitized Solar Cells, organic solar cells, organic light emitting diodes and biomedicine),[1] their poor solubility in aqueous media and the formation of non-emissive aggregates heavily hampered their utilization under biological conditions.[2] However, squaraines exhibited fluorescence enhancement after non-covalently binding with bovine serum albumin (BSA).

In the present study, BSA–squaraine supramolecular adducts with aggregation-induced emission (AIE) properties were prepared and investigated by spectroscopic methods. AIE is a photophysical phenomenon exhibited when non-emissive luminogens are induced to emit by the aggregate formation.[3] While squaraine dyes showed very low fluorescence quantum yield in water, a great enhancement in the fluorescence of the aggregated BSA adducts was achieved due to the abnormal aggregation-induced emission properties of squaraines.[4] The adducts formation was studied from a kinetic point of view and we observed that the dye backbone structure as well the length of the alkyl chain play a crucial role in the kinetics of the interaction (Figure 1).

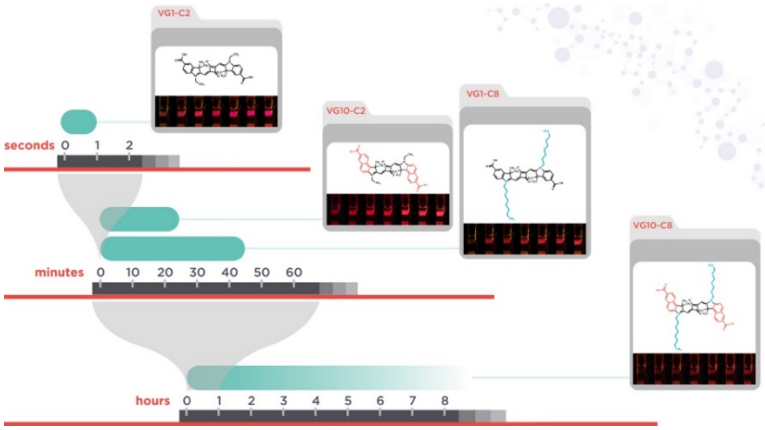

Figure 1: kinetic behaviour of the four BSA-squaraine complex formation

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PC-56

Sigma-1 Receptors: Computational Model to Predict the Agonist/Antagonist Effect

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Originally mistaken for a subtype of opioid receptors, sigma receptors (σ_R) are now considered as an enigmatic and distinct receptor class. Widely distributed as two subtypes (σ_1 and σ_2), in the central nervous system, and also found in peripheral tissues including liver, kidney, heart, eye, and endocrine, immune and reproductive tissue;[1] furthermore, σ_1 and σ_2 receptors were over-expressed in several tumour cell lines.[2]

Despite its increasing importance in human physiology and disease, the molecular architecture of the σ_1 receptor and mechanisms of action remain, in some aspects, unanswered.

At present, the classification of σ_1 ligands as agonists and antagonists is based on modulation of typical pharmacological responses, defining agonists as ligands that induce specific effects through binding to σ_1, while antagonists are σ_1 ligands that inhibit or decrease these responses.

It has been shown that the different oligomeric states of σ_1 receptors are significantly influenced by the different interaction with agonists and antagonists. The agonists decrease the oligomer state, while the antagonists increase the stability of the oligomer state.[3]

Through computational methods, our research group has recently identified new potent and selective sigma receptor ligands.[4] In an attempt to study the conformational changes of σ_1 receptors with MD simulation methods provided by antagonists and agonists, we have developed a computational protocol capable of predicting the physiological activity of different ligands. This computational approach could facilitate the task of pharmaceutical chemists for the rational synthesis of new drugs with σ_1 activity.

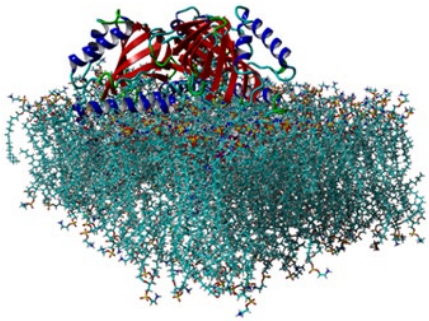

Figure 1: Viewed to the transmembrane domain of the human σ_1 receptor.

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PC-57

Flow technology for the preparation of Active Pharmaceutical Ingredients

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The continuous flow synthesis has attracted interest in chemical and pharmaceutical industries as it guarantees lower production costs, better safety and a greater sustainability. In many cases, it has been demonstrated that some economic savings can be achieved in the production chain if some processes or the entire production could be transferred in continuous flow microreactors.[1-3]

A continuous-flow reduction of (*R*)-2-hydroxy-*N*-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide, a direct percursor of Mirabegron, has been developed, demonstrating the possibility to safely handle BH_3 within microfluidic reactors using 2-MeTHF as greener alternative to traditional solvents.[4]

A fast, sustainable and environmental friendly synthesis of the □-blocker Propranolol, has been developed by using a continuous flow process. The synthetic routes tested show that, within microreactors, it is possible to realize a more sustainable synthesis of pharmaceutical targets, with higher yields, purity and productivity if compared to batch processing.

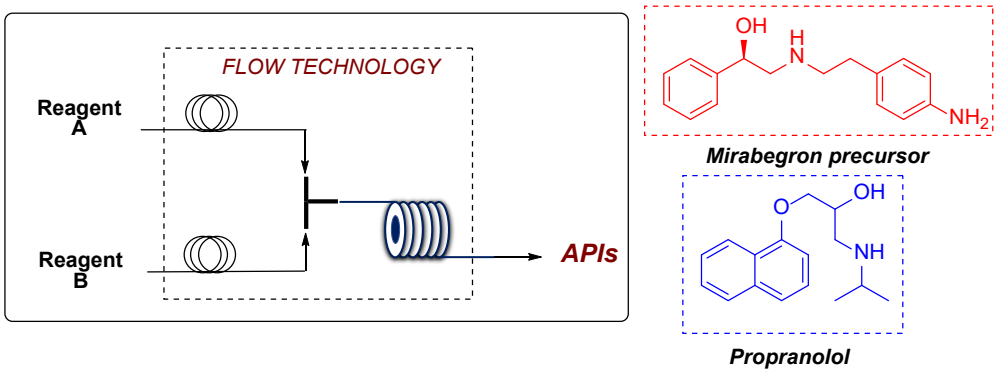

Figure 1: Flow technology for the synthesis of APIs.

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PC-58

Zwitterionic Natural Deep Eutectic Solvents as green alternative for the CO_2 capture

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The increase in emission of greenhouse gases is largely responsible for global warming, with carbon dioxide, CO_2, being the main contributor, as a consequence of human activities such as the burning of oil, coal and gas, as well as deforestation. The capture of CO_2 is a valid option to reduce emission and many technologies based on the use of solid and liquid sorbents or membranes[1] have been proposed. Among these technologies, the chemical absorption using aqueous amine solutions seemed to be the most effective, due to their high affinity for CO_2.[2] However, the amine-based method has some negative aspects such as corrosion and high energy consumption. For this reason, the development of alternative technologies for CO_2 capture and storage is the most relevant goal to be achieved and is receiving significant attention by researchers. Recently, classical[3] and amine-based[4] deep eutectic solvents (DESs) have been investigated as sorbents for CO_2 capture. DESs are obtained by combining solid compounds, generally a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), capable to self-associate, and form liquid mixtures having a melting point that lies below those of the individual starting materials. DESs are often related to ionic liquids (ILs), with which they share many physicochemical characteristics such as thermal stability, low vapor pressure, non-flammability and a great solvating ability. These properties can be tuned simply by changing the nature or the ratio of the constituents, to obtain the most appropriate HBD-HBA combination for a target application. The major advantage of DESs over ILs is that their synthesis is very simple, safe and environmentally benign. Some DESs have been synthesized by natural metabolites such as organic acids, amino acids and sugars. These Natural Deep Eutectic Solvents (NADESs), have gained much attention especially in the green chemistry area due to their biodegradable properties and their safe components.

In the present work, we have investigated the CO_2-capture ability of some zwitterionic NADES based on N,N,N-trimethylglycine (TMG) and carboxylic acids as the HBA and HBD component, respectively. The solubility of CO_2 in the DES was measured gravimetrically at different temperatures in the range 298.15 - 333.15 K, and different pressures in the range 0.1 - 4 MPa. It can be observed that the solubility of CO_2 in the DES increases as the pressure increases while it decreases as the temperature increases. The highest uptake has been observed for phenylacetic acid/TMG DES at 313.15 K and 4 MPa (45.5 g CO_2/g DES). The same DES has been reused in two successive cycles with a consequent decrease in CO_2 capture efficiency (up to 27% less).

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PC-59

Bioactive metabolites produced by the fungal pathogens *Diplodia fraxini* and *Hymenoscyphus fraxineus* isolated from infected *Fraxinus* spp. trees

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During the last two decades widespread ash population decline has happened in Europe. This epidemic disease, commonly known as ash dieback, is the result of biological invasions by the two ascomycetes fungi *Diplodia fraxini* and *Hymenoscyphus fraxineus*. On *Fraxinus* spp. both fungi are able to cause the same symptoms, corresponding to the typical ones due to the infections of *Diplodia* species on woody hosts characterized by V-shaped necrotic sector visible in cross section.[1]

D. fraxini is a fungus belonging to the Botryosphaeriaceae family. It was found to be a pathogen associated to symptomatic *Fraxinus angustifolia* trees in South Europe and isolated also from branch and twigs of *Fraxinus excelsior* in initial and advanced stages of dieback in Poland.

A new phytotoxic isochromanone, named fraxitoxin (**1**, Fig. 1), was isolated together with (–)-mellein and tyrosol, already known toxic fungal metabolites, from the organic extract of the *D. fraxini* culture filtrates.[1] The structure of fraxitoxin was characterized using spectroscopic methods (essentially NMR and HR-EI-MS) while its absolute configuration was assigned by electronic circular dichroism (ECD) measurements and calculations.

H. fraxineus is a fungus belonging to the Helotiaceae family. It was identified as the pathogen causing the *F. excelsior* dieback in Europe. *H. fraxineus* was introduced in Europe from Asia and has gradually spread from East to West continental Europe including the British Isles.[2] Viridiol (**2**, Fig. 1) was isolated as the most abundant and phytotoxic metabolite, from the organic extract of the *H. fraxineus* culture filtrates.[3] The purification and chemical and biological characterization of these two metabolites as well as those of other related compounds will be illustrated in this communication.

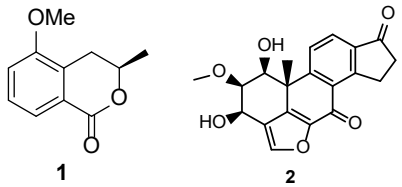

Figure 1: The structures of fraxitoxin and viridiol (**1** and **2**).

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PC-60

Natural products as stimulants and inhibitors of parasitic seed germination and radical growth

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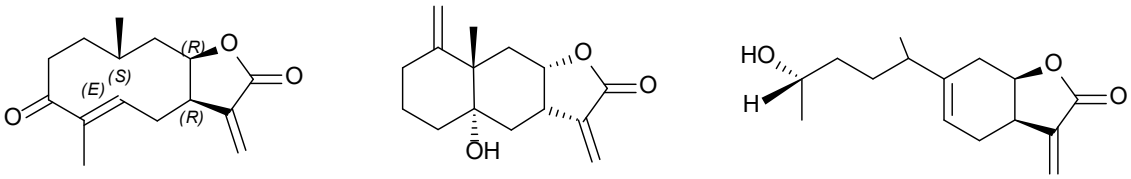
A number of parasitic plants have adapted to agricultural environments becoming weedy and posing a serious threat to important crops. Available control measures rely heavily on use of synthetic herbicides. The side effects on environmental pollution and food health of chemical control prompted studies to find alternative strategies based on the use of natural products.

Some sesquiterpene lactones named inuloxins A-D, belonging to different subgroup as germacrane, eudesmane and seco-eudesmane, were isolated from the aerial parts of *Dittrichia viscosa* (family Asteraceae) and showed to stimulate seed germination leading to suicidal germination, or inhibit germination or disrupting germling growth and haustorium development.[1,2]

The absolute configuration (AC) of inuloxin A was determined by chiroptical and computational methods.[3] The same methods were successively used to assign the AC to inuloxin C,[4] while studies are in progress to assign that of inuloxin D. Recently, considering the potential herbicidal activity of inuloxin A, it was formulated in β-cyclodextrins to overcome its low water solubility and preserving its ability to inhibit *Phelipanche ramosa* seed germination.[5]

In this communication, the purification of other germination stimulants and/or inhibitors of parasitic seed germination, isolated from the same plant, will be illustrated as well as the results of structure-activity relationship studies comparing the biological activity of the natural sesquiterpenoids to that of some their hemisynthetic derivatives.



Inuloxin A Inuloxin C Inuloxin D

Figure 1: Structures of inuloxins A, C and D.

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PC-61

New degradation products of Irbesartan: Analysis and identification from a simulated chlorinated disinfection treatment[1]

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A wide range of pharmaceutical compounds is used for the treatment of various diseases in both humans and domestic animals. These compounds and their metabolites are excreted through urine and faeces into domestic wastewater and make their way to wastewater treatment plants (WWTPs). Some of them are not totally removed in the WWTPs and remain in the effluents entering surface waters[2] and even groundwater.[3] The potential for a drug to reach the aquatic environment depends on three factors: the sales amount, the pharmacokinetic behaviour (half-life, urinary and faecal excretion, metabolism, etc.) and the rate of its degradation in the sewage system and WWTPs. In the meantime, a high amount of drugs and related metabolites have been detected in the aquatic environment and the list is continuously increasing.[4] One non-extensively investigated drug is Irbesartan, used alone or together with other medicines to treat high blood pressure, on the market for about 19 years and with an annual production of about 20,000 kg. Irbesartan is an orally active substance that is rapidly and effectively absorbed, reaching peak plasma after approximately 2 hours. After its biological effect, Irbesartan, following hepatic metabolism, is mainly eliminated through the faeces, even if a share of about 20% is found in the urine. Here the degradation pathway of Irbesartan has been investigated by simulating the chlorination process normally used in a WWTPs to reduce similar emerging pollutants.[5] The structures of the isolated degradation by-products have been determined from the crossing of MS and 1D-2D NMR data and justified by a proposal mechanism of formation. The new by-products, together with Irbesartan, have been assayed on different living organisms (*C. elegans* and *Daphnia magna*), to test their acute and chronic toxicity.

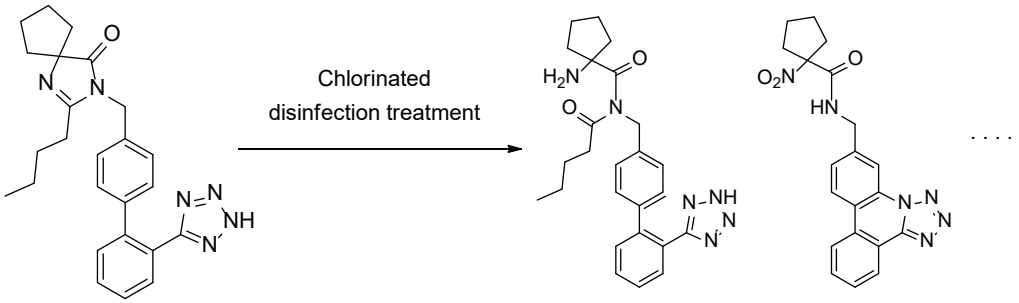

Figure 1: Structures of Irbesartan and some its degradation by-products

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PC-62

Sulfur, Selenium, and some silicon: A new access to disulfides and mixed chalcogenides with GPx-like activity

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Omo-disulfides (RSSR) and diselenides (RSeSeR) are of paramount importance for their applications in material sciences and for their involvement in biological chemistry.[1,2] At the same time, mixed-dichalcogenides (RSSeR) represent a synthetic challenge while maintaining their relevance at biological level.[3]

Recently, bringing together our expertise in sulfur and selenium chemistry,[4] we have developed new procedures for the synthesis of disulfides (RSSR)[5] and selenylsulfides (RSSeR).[6] Using N-thiophthalimide derivatives as electrophilic sulfur transfer reagents and a selenosilane, or selenols, as nucleophiles, we could easily access both classes of compounds with a huge variability and tolerance of the substituents (Figure 1).

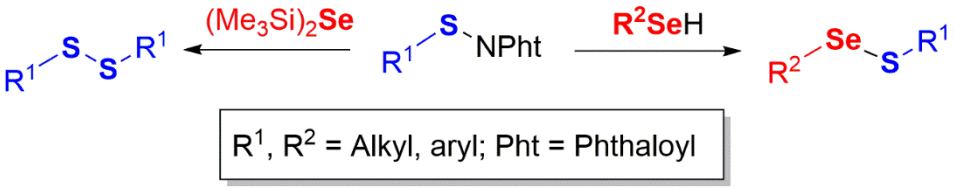

Figure 1: Synthesis of disulfides and selenenylsulfides

The scope and limitation of these new procedures as well as the stability and the properties of the obtained disulfides and selenylsulfides will be discussed in the communication.

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PC-63

New Phosphate-Linked Tyrosol Dimers: Synthesis, antioxidant activity, metal chelating capacity and effect on Aβ aggregation[1]

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Phenylpropanoids are secondary metabolites widely distributed in plants. They are believed to protect human cells against oxidative stress and in turn, to prevent various diseases associated with it, such as cancer, cardiovascular, and neurodegenerative disorders as well.[2,3] Recently, many natural phenylpropanoids have emerged as a particularly promising class of small molecules able to inhibit β-amyloid aggregation and disrupt preformed amyloid fibrils that represent important targets in the development of pharmacological treatments of Alzheimer's disease (AD).[4] Unfortunately, natural phenylpropanoids often have poor pharmacokinetic properties and low bioavailability. In this frame an interesting approach in the design of new bioactive compounds could be the combination of two or more polyphenolic "fragments". This "natural-fragment-based drug-discovery" approach would allow the assembly, also in a combinatorial manner, of libraries based on complex polyphenols in a few steps. This strategy provides us with the possibility of easily modifying both scaffold and decorations and modulating pharmacodynamic and pharmacokinetic properties.[5] Therefore, we planned to join two "tyrosol-fragments" by a phosphodiester bridge to obtain a new class of phosphate-linked compounds,[6] which are potentially more bioactive than the corresponding precursors.

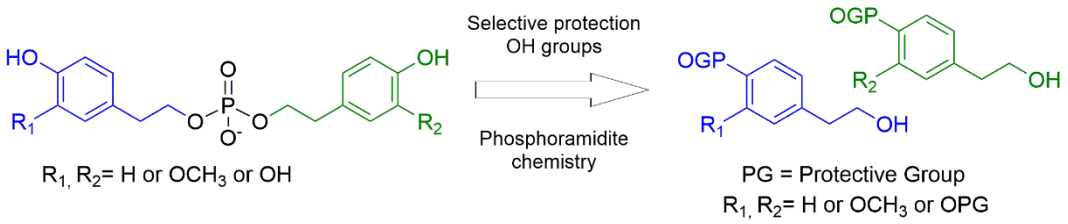

Figure. Retrosynthetic scheme of phosphate-linked tyrosol dimers.

We report here the general synthetic strategy to obtain new phosphate-linked tyrosol dimers in good yield and their full characterization. Since oxidative stress, as well as metal ion dyshomeostasis, are known to play important roles in AD pathogenesis, preliminary studies are focused on the evaluation of their antioxidant activity, metal chelating ability and their ability to inhibit β-amyloid aggregation.

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PC-64

A general synthetic strategy and preliminary investigations of *pro*-drug Silibinin conjugates[1]

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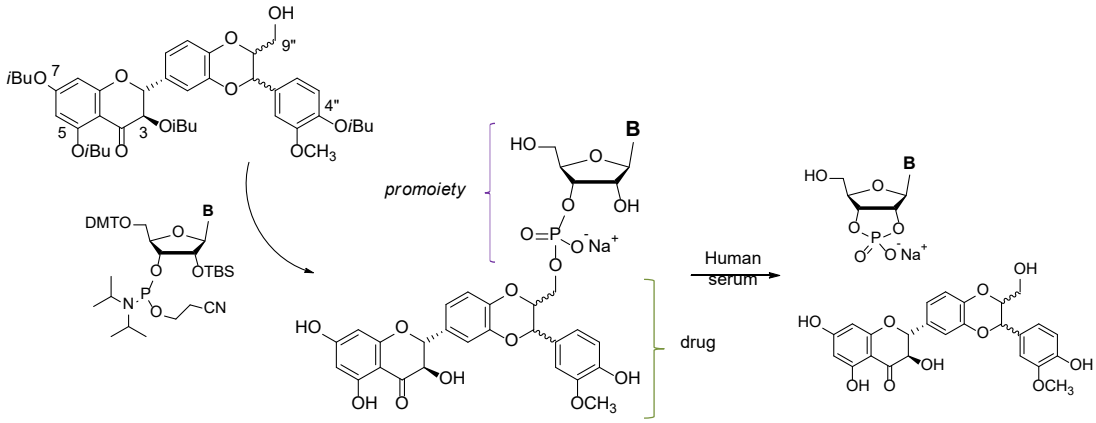
Silibinin is the major component of an extract, known as Silymarin, obtained from the seeds of the milk thistle (*Silybum marianum*). Structurally, Silibinin is diastereoisomeric equimolar mixture of two flavonolignans (Silybin A and Silybin B). As extensively reported in literature, Silibinin displays multiple biological activities, most of them related to its radical scavenging activity. In the past two decades, in addition to hepatoprotective effects, Silibinin has demonstrated remarkable anti-cancer as well as cancer chemopreventive efficacy in pre-clinical cell culture and animal models of several epithelial cancers, including skin, bladder, colon, prostate, and lung.[2] Oral administration of chemotherapeutic agents is the mainstay for the treatment of disease. Sustained release formulations have been crucial for the safe and effective dosing of orally administered drugs.[3] In this frame, the synthesis of phosphodiester derivatives can improve the oral bioavailability of poorly water-soluble metabolites maintaining their pharmacologic activity.[4,5] Here, we reported the synthesis of new Silibinin conjugates with 3'-ribonucleotide units. The phosphodiester junction is typically used in *pro*-drug strategies, in which the phosphate group is susceptible to hydrolysis by endogenous phosphatases, allowing the release of the active compound.



Scheme: Synthesis of ribonucleotide-Silibinin conjugates and their cleavage by serum nucleases.

The new conjugates were prepared in few steps and in good yields, starting from the suitable Silibinin or Silybin building blocks and nucleotide phosphoramidites. All compounds were full characterized by NMR and Maldi-TOF and their serum stability was evaluated by HPLC analyses.

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PC-65

Structural modification of pyridine-containing ligands: customize optical and electrochemical properties of Cu complexes

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Organometallic Cu(I) complexes with diimine ligands have tuneable optical and electrochemical properties suitable for applications in the field of Dye-Sensitized Solar Cells (DSSCs) as both redox shuttle and photoactive media.[1] The balance between the electron withdrawing/donating character and the structural properties of the heteroaromatic ligand rule over the redox potentials of the Cu(I/II) couple and the visible light absorption of the Cu(I) complexes.[2]

In his work, we report different strategies for the modification of the canonical 2,2′-bipyridine and 1,10-phenanthroline ligands to insert substituents with relevant electronic and steric effects. The diversification of the ligands structures (Figure 1) allowed us to prepare two small libraries of Cu(I) complexes (homoleptic and heteroleptic) which exhibit a broad spectrum of optical and electrochemical properties.

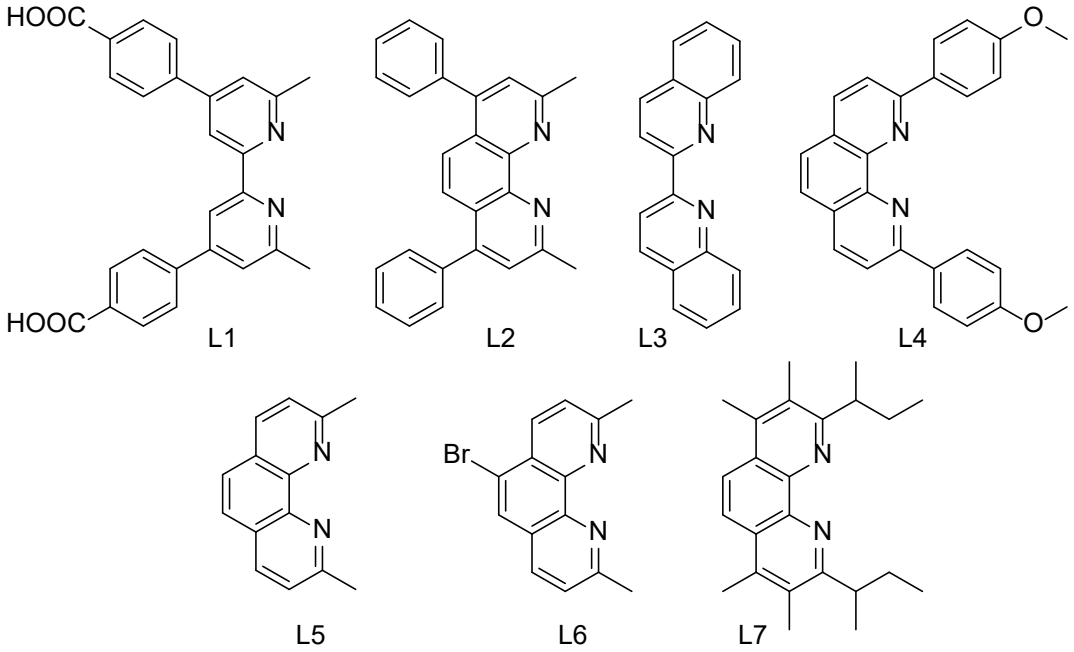

Figure 1: Synthesized ligands bearing substituents with relevant electronic and steric effects.

The comparison of the two libraries, in terms of the complexes properties, showed a good correlation but diverse patterns were found for the absorption maxima and the half-wave potential. This highlights the individual dependence of each property by some of the ligands features and sets the bases for the prediction of the properties of heteroleptic complexes.

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PC-66

Luminescent rhenium(I)-peptide nucleic acids conjugates for microRNA targeting

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Peptide Nucleic Acids (PNA) are a quite unique example of mimics of native nucleic acid structures able to target natural DNA or RNA with high sequence specificity and affinity and are therefore potential excellent candidates in diagnostics and antisense and antigene therapy. In place of the ribose phosphodiester backbone of DNA and RNA, PNA contain a pseudopeptide backbone, composed of *N*-(2-aminoethyl)glycine units, on which the four nucleobases are inserted (Figure).[1] Unmodified PNAs display low cellular uptake,[2] and this feature constitutes a drawback towards its effective use in therapy. One of the strategy to overcome this problem is the conjugation of PNA to metal complexes that can modify their intrinsic chemico-physical and spectroscopic properties.[3,4]

Within our research on PNA, we have prepared some bioorganometallic PNA-dirhenium complexes (Figure), which have been used to target a specific microRNA, that is miRNA-21 in the DU145 prostate cancer cell line. Thanks to the presence of the dirhenium fragment, these bioconjugates are luminescent and act as fluorescent probes to track the cell uptake of PNA that is easily taken up by the above mentioned cells, thus showing that the Re(I) complexes are indeed useful tools for the intracellular delivery of PNA.

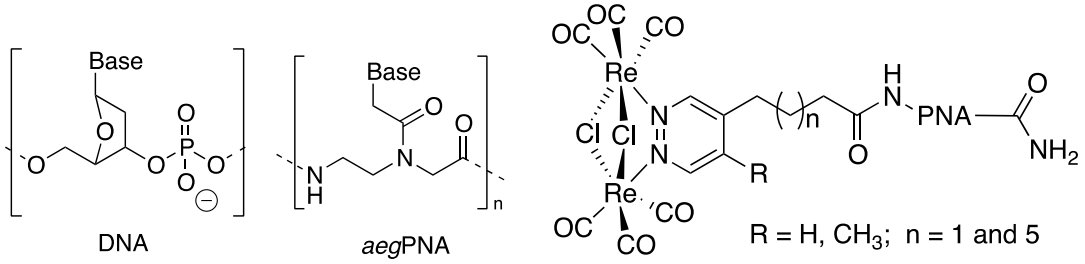

Figure.

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PC-67

Synthesis and characterization of chiral bis-benzo[1,2-*b*:4,3-*b*']dithiophenes

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Thiophene-containing fused aromatic compounds are a versatile class of π-conjugated systems with applications in functional organic materials.[1] Among them, benzo[1,2-*b*:4,3-*b*']dithiophene (**BDT**) and its derivatives are widely studied, for instance as units in mono and polydisperse oligomers in materials science,[2] and as π-spacers in push-pull organic chromophores for photovoltaic applications.[3] Moreover, **BDT** is a key intermediate for the synthesis of inherently chiral helical systems such as tetrathia[7]helicenes.[4] In our ongoing studies on the synthesis and functionalization of **BDT**s,[5] we have developed a strategy to prepare new chiral atropoisomeric heterobiaryl derivatives **2-4** starting from bromides **1** (Figure).

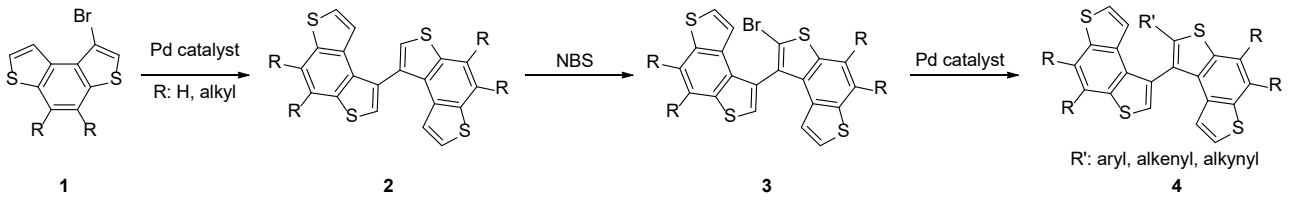

Figure: general synthesis of chiral bis-benzo[1,2-*b*:4,3-*b*']dithiophenes.

The configurational stability of these systems have been fully elucidated by experimental and theoretical studies, and thanks to their chiroptical properties, some of these atropoisomers will be exploited as useful intermediates for the enantioselective synthesis of the corresponding tetrathia[7]helicene derivatives.

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PC-68

Lipase catalyzed oxidation in sugar-derived Natural Deep Eutectic Solvents

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Chemoenzymatic oxidations offer a valid alternative to the oxidative processes normally used in industries that show problems in terms of safety and waste disposal. Lipases are very versatile enzymes that thanks to their high selectivity, good stability and mild reaction conditions, can represent a valid and sustainable alternative to classic chemical catalysts. In the field of oxidations, lipases act as perhydrolases to produce peracids in situ, which subsequently act as catalysts for oxidation reactions.[1]

In the present work we show results obtained using Candida antarctica lipase B (CAL B) for the epoxidations of alkenes and for the conversion of ketones to esters or of aldehydes to acids (Baeyer-Villiger). These reactions have been carried out in DES (Deep Eutectic Solvents), taking advantage of the fact that these sustainable solvents can increase the stability of the supported enzymes.[2]

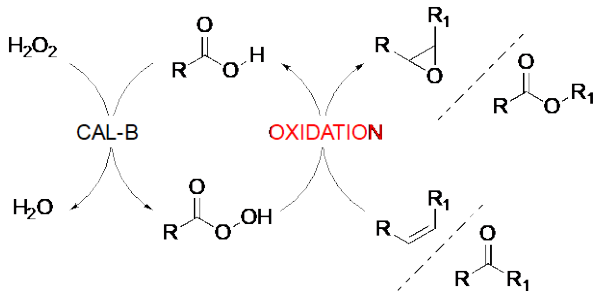

Figure 1: Chemoenzymatic oxidations investigated.

Some of the crucial parameters for obtaining high substrate conversions have been found to be the nature and the amount of the peracid precursor and the nature of DES. The best results were obtained with medium-long chain carboxylic acids such as octanoic acid or dodecanoic acid. The best yields in all types of reactions tested were obtained using a NaDES (Natural DES) consisting of sugar mixtures capable of increasing the stability of the CAL B with respect to other tested NaDES and with respect to organic solvents or aqueous reaction media. Moreover, some of the DES studied (especially those containing Choline Chloride, with and without the addition of a superbase) have also been shown to be systems that catalyze the incorporation of CO_2 into epoxides for the synthesis of cyclic carbonates.[3]

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PC-69

Synthesis of heterohelicenes through the Povarov reaction

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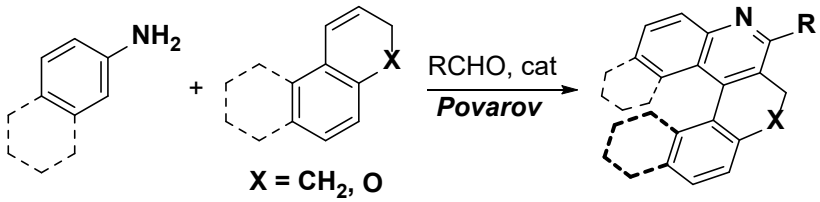
Helicenes and heterohelicenes are challenging chiral structures that continuously stimulate new interest and find new applications. From just a chemical curiosity due to their inherent chirality, these compounds are now commonly used in asymmetric synthesis, materials science and medicinal chemistry.[1] On the other hand, among imino cycloadditions, the Povarov reaction, *i.e*. the reaction of electron-rich olefins with *N*-aryl imines, provides a straightforward and modular entry to tetrahydroquinolines and, after oxidation, quinolines, in turn very useful heterocyclic systems.[2]



In this communication, we report how, with the proper choice of electron-rich olefins and N-aryl imines, under lanthanide salts catalysis, the Povarov reaction can be exploited for the synthesis of aza- and azaoxaheterohelicenes.[3] Scope and limitation of the procedure as well as a study on the resolution of helical shaped quinolines obtained will be presenetd.

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PC-70

Sustainable and Water-Soluble Non-Fullerene Acceptors for Bulk Heterojunction Solar Cells

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Bulk Heterojunction solar cells (BHJ), are very promising amongst emerging technologies for solar energy conversion for their unique properties, such as flexibility, low cost and possibility to be printed on plastic substrates. They are composed of an intrinsic mixture, organized at the nanoscale, of an Acceptor and Donor organic material in the photoactive, photon absorbing active layer[1]. Traditionally, fullerene derivatives, possessing good electron transporting capability, have been used. Recently, a new class of non fullerene Acceptors (NFAs) they have boosted BHJ cells efficiencies in terms of solar energy conversion to over 17%.[2] The most efficient molecular scaffold, the ITIC family, has optimal properties with respect to range of absorption, and morphology in the active layer. Materials for BHJ have several problems linked to their non-sustainable synthesis: a) they often require Stille cross couplings, which produce toxic by-products in stoichiometric quantities; b) they require toxic solvents for processing into thin films over the substrate. We present our results on the synthesis of novel NFAs for which innovation will be brought on two levels: a) synthesis of sustainable NFAs using cascade or one-pot methodologies such as multicomponent reaction or Domino Direct Arylation-Cross Aldolization[3] and b) functionalization of NFAs with hydrophilic side chains (poly(ethylene glycols (PEG), hyperbranched glycerols (HBP), or alkylsulfonates), in order to increase their solubility in green solvents for processing.

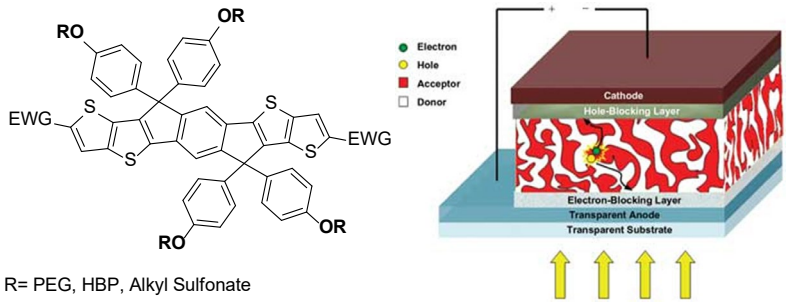

Figure 1

References:

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PC-71

Influence of flat and helical peptide spacers on the redox properties of two covalently bound, ferrocenyl moieties

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The conjugation of ferrocene (Fc) with biomolecules has been exploited to create new systems endowed with both organometallic and bio-properties[1] or to investigate electron transfer processes through peptide backbones.[2] In this contribution we report the synthesis and preliminary electrochemical studies of new Fc-peptide systems. Thanks to the appropriate placement of Fc redox probes along a peptide chain, we aim at modulating the electronic properties as a function of the applied potential.

For the synthesis of our peptide spacers we relied on two amino acid building blocks, namely 2,3-diaminopropionic acid (Dap) and 2-amino-2-methylpropionic acid (Aib), and on two Fc derivatives characterized by a carboxylic (Fc-COOH) or an amino (Fc-NH_2) function (Figure 1).

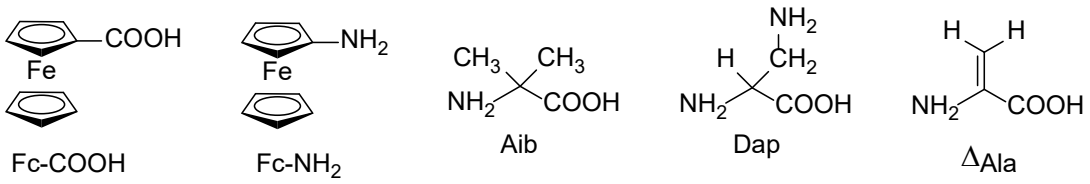

Figure 1: Molecular structures of Fc-COOH, Fc-NH2, Aib, Dap and ΔAla.

The use of Dap offers two opportunities: (i) incorporation along the peptide chain of a Fc probe by exploiting the amino group on the side chain; (ii) synthesis of dehydroalanine (ΔAla)[3], through a Hofmann elimination of the amino function of Dap, thus obtaining a flat, all sp^2 molecule.

The structures of the hybrid systems designed for goals (i) and (ii) are, respectively:

Z-Aib-Dap(**Fc**)-(Aib)n-Dap(**Fc**)-Aib-NH*i*Pr (**1**) (Z = benzyloxycarbonyl; n = 1-3)
Fc-CO-[Dap(Boc)]$_n$-NH-**Fc** (**2**) **Fc**-CO-(ΔAla)$_n$-NH-**Fc** (**3**) (Boc = *t*butyloxycarbonyl; n = 1-4)

The peptide of series **1**, helical thanks to Aib, allows to locate the two Fc on the same or on opposite faces. Thus, we will be able to determine the influence of distance, mutual orientation and peptide macrodipole on the Fc···Fc interactions. On the other side, the flexible peptides **2** and the flat peptides **3** have no dipole moments, but the latter possess a conjugated π system that could promote a very efficient electron transfer.

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PC-72

Squaraine-Based Porous Organic Polymers Containing Trigonal Linkers

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Porous organic polymers (POPs) are a type of organic polymers with large surface area, tunable skeleton and high thermal and chemical stability[1]. They are attractive for applications in the fields of gas storage and separations, catalysis, optoelectronic and energy storage[2,3]. There are various methodologies reported for the preparation of porous polymers. Among them, Schiff base reaction is one of the most adjustable ways owing to facile, one-pot, catalyst-free, quantitative synthesis[4]. Squaraines are appealing dyes with a zwitterionic resonance structure and have extensive applications in areas such as imaging, nonlinear optics, photovoltaics, photodynamic therapy, and ion sensing[5]. For example, squaraine-toluidine motif, through the condensation of squaric acid with *p*-toluidine, exhibits planar zigzagged zwitterionic resonance structure[6] (Figure a). There have been no studies about squaraine-bridged POPs containing different tritopic linkers. Our goal focuses on the syntheses of these squaraine-bridged POPs using tritopic linkers such as: TAPT, TAPB, TAPA and TAPM (Figure b). We have synthesized these polymers through Schiff base reaction by refluxing a tritopic linker with the squaric acid. These 2D-materials containing trigonal building blocks can have different chemical and electrochemical properties suitable for important developments.

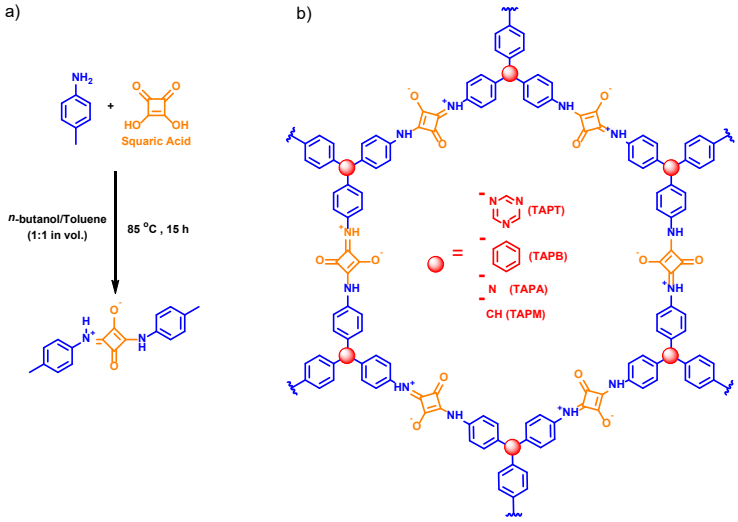

Figure: a) Model compound of SQ-Toluidine, b) SQ-POP based on different tritopic linkers.

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PC-73

Coinage-metal catalyzed functionalizations of propargylic amine derivatives

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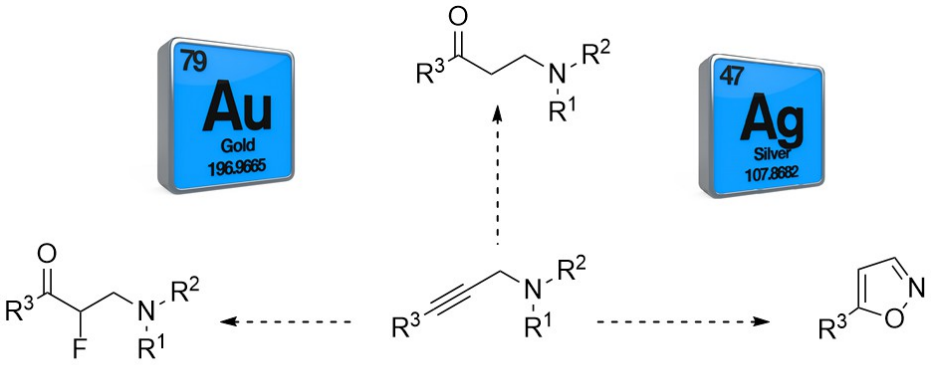
Coinage-metals, especially those belonging to the group 11 of the modern Periodic Table, have always been used by mankind in the production of jewellery and currency; in contrast, the past decades have seen an increase in the use of these metals as efficient catalysts for organic transformations. In particular, Au and Ag have been widely employed in the activation of unsaturated C-C bonds towards several types of transformations, such as nucleophilic additions and cycloisomerization reactions, thanks to their strong π-Lewis acidity.[1]

As C-C unsaturated bonds, alkynes bearing proximal nitrogen atoms, such as propargylamines, are very interesting building blocks in synthetic organic chemistry because of the presence of both electrophilic and nucleophilic moieties that enable the generation of complex structural architectures and some transformations have already been described in literature.[2]

Considering our interest in innovative metal-catalyzed transformations and the collaboration between our two research groups,[3] we would like to report the results of our study on the use of these substrates to access valuable chemical compounds by means of coinage-metal catalysis (Figure 1).



1

Figure 1: Metal-catalyzed reactions of functionalized propargylic derivatives **1**.

References:

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PC-74

Spectroscopic elucidation and antimicrobial screening of myrtogalloyl glicosides from *Myrtus communis*

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After the "golden era", when almost all groups of important antibiotics were discovered, the history repeats itself nowadays and these antimicrobial agents are in danger of losing their efficacy because of the occurence of microbial resistance[1]. In this scenario, natural products are of great interest since a large part of antibiotics derive from natural sources.

Myrtus communis has already attracted attention for its peculiar molecules, myrtucommulone acylphloroglucinol and analogues compounds with several pharmacological properties, including antimicrobial activities[2].

In this communication, we explored the antimicrobial potential of *Myrtus communis* leaves collected from Sardinia, with the ultimate goal to find new antimicrobial metabolites. NMR-based metabolomic approach[3] can be an excellent tool in order to identify the metabolic composition of bioactive extract. In fact, metabolomics seeks to identify and quantify the complete set of metabolites, which can be measured by NMR, requiring shorter times and rapid sample preparation. Therefore, the antimicrobial potential of myrtle crude extract has been asses against a panel of gram-positive and gram-negative bacteria, while NMR-based metabolomic screening of the myrtle crude extract, thanks to 1D and 2D NMR experiments, reveals from the a complex metabolic profile. It is already possible to highlight the presence of two glycosylated myricetins and some non-prenylated acylphloroglucinols.

Based on the encouraging antimicrobial results, especially against gram-positive bacteria, a detailed bio-guided fractionation led to the isolation of four new myrtogalloyl glicosides elucidated based on NMR experiments (HSQC, CIGAR-HMBC, DQ-COSY, and NOESY) and spectrometric techniques (ESI-Q-TOF). These insights pave the way to future experiments that will focus on asses the antibacterial properties of this purified compounds with the ultimate goal of identifying new antimicrobial agents.

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PC-75

Collagen capped halloysite nanotubes as multifunctional drug carriers

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In the past decade, the investigation of nanoparticles usage in medicine has revolutionized the universal viewpoint of drug delivery. Such submicron materials characterize with potential for crossing biological barriers, reducing toxicity and site effects of incorporated drugs as well as providing protection for such immobilized therapeutics from fast hydrolytic and enzymatic degradation in the body[1].

From a multitude of nanoparticles under current investigation, halloysite nanotubes (HNTs) stand out as biofriendly, inorganic nanoparticles with drug-loading capabilities and drug release characteristics. The complexity of HNT's morphology results in variation of inner and outer surfaces' properties, endowing their site-specific modification, towards various methodologies for therapeutics incorporation[2].

Herein we report two strategies for immobilization of model drugs, aspirin and epirubicin within HNT's inner lumen. In the forward step we present encapsulation of drug loaded HNTs in natural polymer, collagen. Such collagen capping has a multifunctional effect: it allows to entrap immobilized drug until nanoconstructs reach the suffering organ; allows to control the duration and speed of drug release as well as allows to trigger therapeutics release in response to decreased pH and enzymes activity. The proposed collagen coating has another exceptional feature: it is bioresorbable and moreover it is potentially capable of selective wounds, fibrotic tissues and tumour cells targeting, since collagen is recognized by several receptors of pathological cells[3]. We have focused on qualitative as well as quantitative characterization of formed nanoconstructs, to finally complete our studies with biological tests.

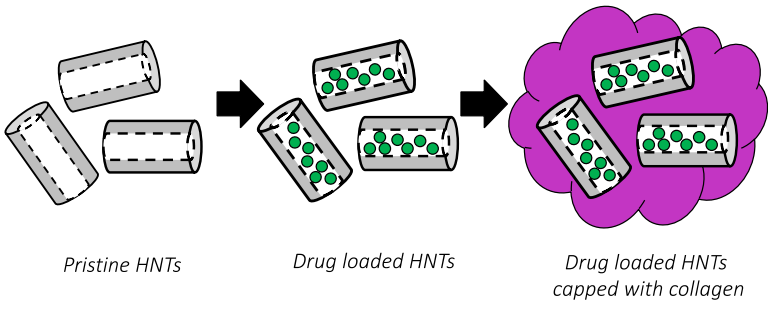

Figure 1: Illustration of halloysite nanotubes loading with a drug and forward nanoconstructs' encapsulation in collagen shell.

References:

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PC-76

Visible-Light Promoted Dearomatizing Spirocyclizations of Ynone-Tethered Indoles

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Dearomatizing spirocyclizations are an effective means to generate three-dimensional scaffolds starting from simple aromatic precursors. Spiroindolines and spiroindoles are an important class of spirocyclic compounds present in a wide range of pharmaceuticals and natural alkaloids.[1]

We have recently reported a one-pot protocol for the dearomatizing spirocyclization/cross-coupling of alkyne-tethered indoles/pyrroles, where palladium complexes generated in situ act as both π-acid and cross-coupling catalysts (Figure 1a).[2]

The dearomatization strategy described herein is based on a thiyl radical cascade process mediated by visible light which enables the simultaneous metal-free preparation of synthetically challenging spirocyclic carbons and tetrasubstituted alkenes, converting indole derivatives **1** into spirocycles **2** under operationally simple reaction conditions (Figure 1b).[3]

This highly efficient radical cyclisation process is compatible with a wide range of ynone-tethered indoles and thiols.

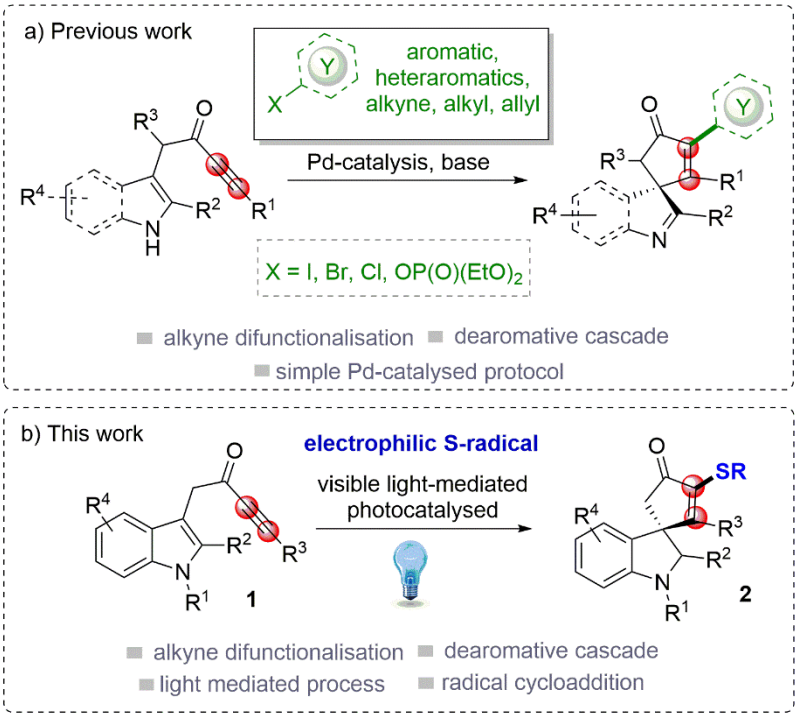

Figure 1: a) merged π-acid spirocyclization/Pd-catalyzed cross coupling; b) light promoted radical cascade spirocyclization.

References:

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PC-77

Plasticizers from Natural Resources

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A plasticizer, according to the IUPAC council, is defined as "a substance or a material incorporated into a plastic to increase its flexibility, workability or distensibility."[1] The most widely plasticized polymer is poly(vinyl chloride) (PVC) because of its excellent plasticizer compatibility characteristics and it is applied in packaging, toys, wires, cables, clothes and healthcare devices. The largest class of plasticizer for the PVC are phthalic acid esters that found applications for the first time in 1920. Nevertheless, concerns and controversy have been raised regarding their use. They exhibit a migration phenomenon and are suspected to produce bioaccumulation in the environment, justifying restrictive regulations in several countries about the use of phthalates as plasticizer.[2] With the growing interest for plasticizers with low migration levels and low toxicity, researchers are paying more attention to bio-based plasticizers. Many plasticizers can be prepared from different agricultural resources: cereals, oleaginous plants, trees, fruits, and vegetables or their wastes. In particular, vegetable oils coming from soybean, linseed, palm, castor bean, permit to elaborate several plasticizers after chemical modifications. They have various compositions of fatty acids depending on the plant and the growing conditions, can intersperse and intercalate between polymer chains, increase intermolecular spacing and bring mobility, and they have the ester groups can interact with polymer chains (van der Waals interactions for instance) and bring compatibility.[3] In this communication we want to evaluate the synthesis of new bio-plasticizers for PVC derived from vegetable resources for a possible industrial use.

Figure 1: Plastics derived from natural resources.

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PC-78

Synthesis of Pre-cannabinoid Terpenyl esters, an Unexplored Class of Native Phytocannabinoids

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Phytocannabinoids occur ion Cannabis mainly in carboxylated form (pre-cannabinoids), that undergo decarboxylation upon prolonged storage or heating and generate the neutral phytocannabinoids.[1] The bioactivity profile of pre-cannabinoids is significantly different from the one of their corresponding neutral analogues, although their further development is hampered by decarboxylation-related overlapping of their biological profile with the one of their neutral analogues. On the other hand, Cannabis contain also esters of pre-cannabinoids with terpenyl alcohols (mono- and sesquiterpenes) that are stable toward decarboxylation, but whose biological profile is unexplored because of the difficulties of their isolation. Thus, these compounds are trace constituents of Cannabis, occurring in concentration <<0.1% of the plant material, and occur as very complex mixtures from which single compounds are difficult to obtain.[1] For these reasons, we have investigated the esterification of pre-cannabinoids with a selection of primary-, secondary- and tertiary terpenyl alcohols to capture the chemical diversity of these compounds, largely elusive by isolation.

The presence of the *ortho-para* dioxygenation makes the chemistry of the carboxylate group idiosyncrasic, as manifested by the facility of decarboxylation, a feature absent in *ortho*- and *para*-hydroxybenzoic acids, rationalizing the failure of all the most common esterification procedures based on either alcohol or acyl activation. After considerable experimentation, a protocol involving the use of carbodiimides in the presence of Broensted acids was found to give satisfactory results. Although precedented in the literature,[2] this esterification method has very rarely been used, and is mechanistically distinct from the Keck esterification that involves the combined used of DMAP and acids. Its application was validated by the preparation of a library of pre-cannabinoid terpenyl esters, and its other difficult cases of esterification of phenolic acids were also explored.

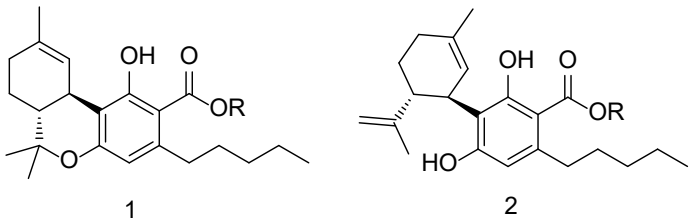

Figure 1: General formula of pre-THC (**1**) and pre-CBD (**2**) terpenyl esters (R = mono or sequiterpene residue)

References:

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PC-79

Molecular Editing of Cannabichromene (CBC)

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Phytocannabinoids can modulate the endocannabinoid system directly, by interaction with the cannabinoid receptors (CB1 and CB2), or indirectly by potentiation of the endocannabinoid tone, an activity mediated by the interaction with the enzymes responsible for the production and degradation of the endocannabinoids anandamide (AEA) and 2-arachydonoylglycerol (2AG). The most potent indirect phytocannabinoid is cannabichromene (CBC), a compound available by total synthesis via the condensation of citral and olivetol (Figure 1), that can selectively inhibit the degradation of 2AG by the enzyme monoacylglycerol lipase (MAGL). The therapeutic potential of non-narcotic boosters of the endocannabinoid tone provided a rationale to investigate the generality of this tandem Knoevenagel-electrocyclic reaction to edit the CBC chemotype.

The modification investigated were the oligomerization of the isoprenyl aldehydes (from C-5 to C-20), the substitution and the isosteric hetorocyclic replacement of the resorcinyl core, and the nature of the promotion (acidic, basic, nucleophilic, electrophilic, microwave, NHC). The reaction turned out to be synthetically useful only for disubstituted resorcinols, and a different course was observed with heterocyclic substrates. Surprisingly, the C-15 isopreny aldehyde (farnesal) failed to generate its corresponding chromene.

A second set CBC analogues was prepared by modification of the chromene core by alkylation, oxidation and reduction, identifying more potent inhibitors of MAGL worth additional pre-clinical evaluation.

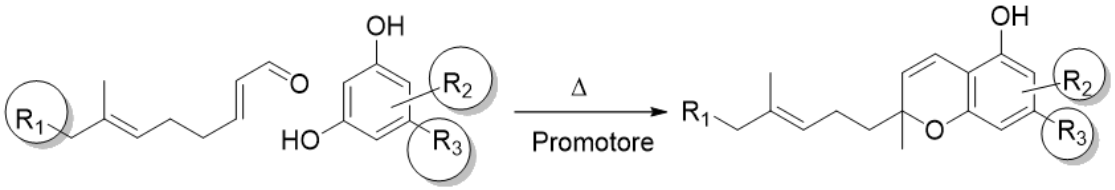

Figure 1: synthesis of CBC analogues (CBC: R_1= R_2 =H, R_3 = nC_5H_{11})

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PC-80

Synthesis of Nucleobase-Containing 1,2,3-Triazoles with Potential Biological Activity through Metal Catalyzed Azide-Alkyne 1,3-Dipolar Cycloaddition

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1,2,3-triazoles are five-member *N*-heterocyclic compounds bearing three nitrogen atoms in the ring. They are an important nucleus for the development of drugs because they are resistant to oxidation, reduction, and hydrolysis in both acidic and basic conditions for their aromatic nature.[1] Thanks to their active participation in hydrogen bond formation, dipole–dipole, and π-stacking interactions they can mimic peptide bonds, enhancing their binding ability with different biological targets. Therefore, triazoles represent a significant class of nitrogen compounds with important biological properties, such as antibacterial, anticancer, antivirus, antimalarial, anti-inflammatory, and antituberculosis. In particular, 1,2,3-triazoles have found a broad spectrum of biological applications such as β-lactum antibiotic tazobactum, cefatrizine, and anticancer compound carboxyamidotriazole (CAI), which are some drugs available on the market.[2] In addition, the presence of nucleobase portion bonded on triazole core increase the biological activity because these compounds mimic the natural nucleosides exercising enzyme inhibition, viral toxicity and cytotoxicity.[3]

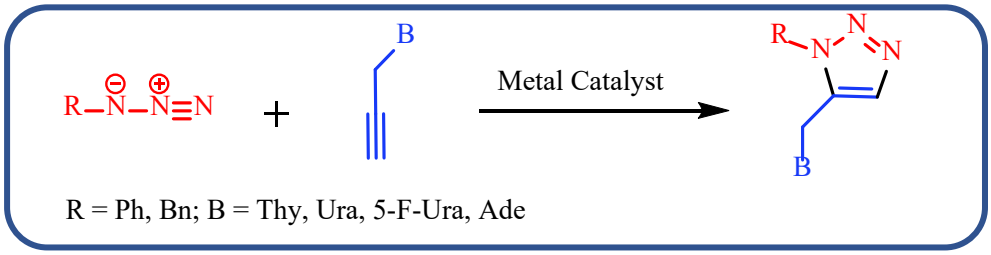

Figure 1: 1,3-dipolar cycloaddition reaction for nucleobase-containing 1,2,3-triazoles

In this work, our research group has designed and synthesized a new class of nucleobase-containing 1,2,3-triazoles (**Figure 1**) through 1,3-dipolar cycloaddition reaction using azides as 1,3-dipoles and propargyl nucleobases as dipolarophiles. The reaction is catalyzed with metal Lewis acid and the products are obtained with high yields and excellent regioselectivity because only 1,5 disubstituted 1,2,3-triazoles are obtained.

References:

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PC-81

Preparation and characterization of graphene oxide foils for applications in the biomedical field

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Graphene oxide (GO) is the oxidized derivative of graphene. It retains some of the exceptional features of graphene and the capacity to be well dispersed in water.[1] The good *in vitro* biocompatibility of GO has paved the way for investigating it in numerous biomedical applications.[2]

In the present study we report the synthesis of GO foils, characterized by cross-linked GO sheets that impart to the foil an extraordinary stiffness and strength,[3] with the aim of exploiting their capacity to induce differentiation of Dental Pulp Stem Cells (DPSCs) towards the osteogenic/odontogenic lineage.[4] The obtained foils have been investigated in terms of structure via Scanning Electron Microscopy (SEM) measurements, surface topography and nanomechanical characterization via Atomic Force Microscopy (AFM) measurements and stability in aqueous fluids. After proper sterilization, DPSCs were cultivated on GO foils for 28 days and conventional cell viability assays were performed to follow the growth process. DPSCs differentiation towards the osteoblastic lineage was investigated by measuring alkaline phosphatase (ALP) activity.

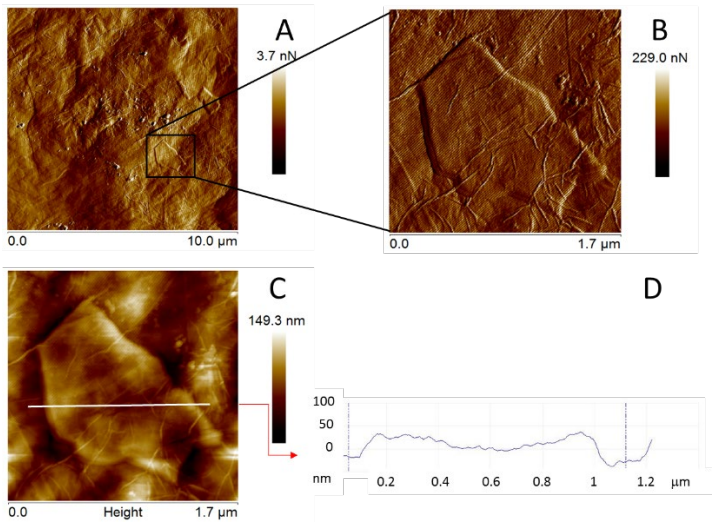

Figure 1: AFM images of GO foil obtained with Peak Force QNM reporting: A) peak force error (10 μm × 10 μm), B) inset of image A; C) and D) high of the inset B in planar and trace profile, respectively.

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PC-82

Developing new ways to introduce the boron atom in organic molecules by ring-opening reactions

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Introducing boron atom in organic molecules in a regio- and stereoselective fashion is a fascinating challenge for the organic chemist. In fact, boronic acids and esters are important intermediates in synthetic organic chemistry and have a wide range of applications in medicinal chemistry.[1] After seminal contributions about the ring opening of vinyl epoxides and vinyl aziridines with nucleophilic diboron reagents,[2] some other advances in the field of borylative ring opening of epoxides and aryl aziridines using diboron reagents have been quite recently made.[3] However, a general approach for the borylative ring opening of alkyl aziridines is still lacking.

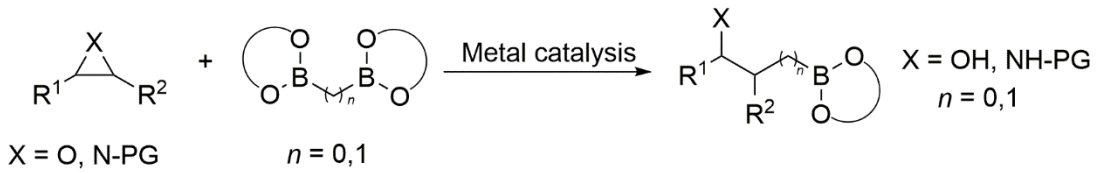

Figure 1: Ring-opening reactions with boron-containing reagents.

We herein report our study about the individuation of reaction conditions able to open a variety of alkyl aziridines using diboron reagents (*n* = 0, Figure 1) and diborylmethane derived reagents (*n* = 1).

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PC-83

Synthesis of fluorinated curcumin-based molecules for detecting amyloid plaques by ^{19}F-MRI

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The detection of Aβ plaques is one strategy for Alzheimer's Disease (AD) diagnosis. Amyloid imaging can be successfully pursued by ^{19}F-MRI using fluorinated curcumin-based compounds.[1] The developed probes contained a limited number of ^{19}F atoms/molecule, and, furthermore, they were directly conjugated to the aromatic portion of the molecule, thus potentially reducing the detection sensitivity due to the broadening of the ^{19}F signal. This work aims at synthesizing a series of novel F-containing curcumins with a high number of ^{19}F nuclei, suitably spaced from the aromatic part of the molecule. The preparation of F-containing curcumins (Fig. 1) started from the synthesis of mono and bi-carboxylic acid derivatives of curcumin followed by an amide coupling with two different perfluorinated amines, one of them incorporated a carboxylic functional group to improve solubility. All the compounds obtained were dissolved at 10 mg/mL in DMSO or in a mixture of normal saline and Cremophor® and characterized by ^{1}H and ^{19}F NMR. The deposition of the compounds on brain slices explanted from APP-PS1 mice (transgenic AD model) showed a reduced affinity of the derivatives with respect to the parent curcumin. However, a qualitative assessment of the fluorescent signal allowed to rank the affinity of the compounds towards the plaques in the order: mono-F9 > mono-carboxy-F9 > bi-F18 > bi-carboxy-F18. Most likely, the higher affinity showed by the mono-derivatives is due to the preservation of one phenolic group in the aromatic portion of the structure involved in the binding to the plaque. On this basis, compound mono-F8 appears to be the more promising to be tested in vivo on preclinical AD models for amyloid imaging by ^{19}F-MRI.

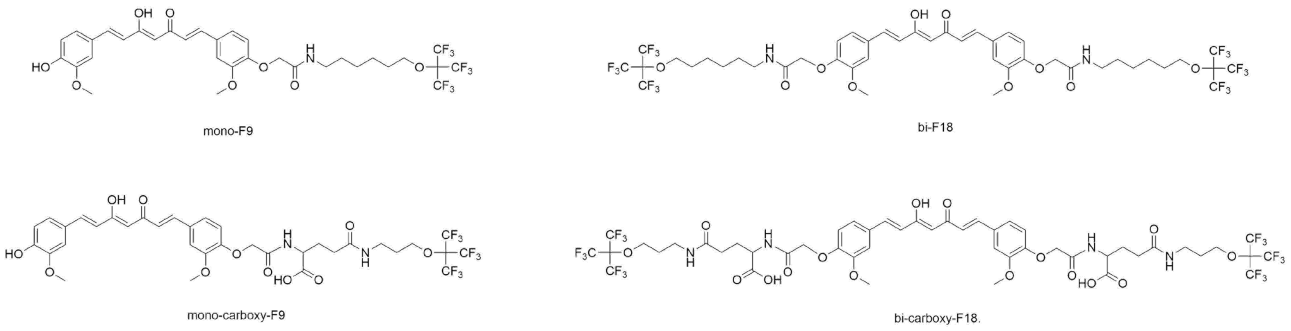

Figure 1: Chemical structures of Curcumin derivatives.

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PC-84

Ruthenium-catalyzed ring transformation of 4,4-disubstituted isoxazolin-5-ones to different heterocyclic systems

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Isoxazol-5-ones have been identified as a versatile building block for the preparation of a variety of functionalized molecules, exploiting their high reactivity and the relative ease of ring opening.[1] The isoxazolone derivatives were object of studies by our research group for a long time, regarding their reactivity and the ring transformation in different heterocycles.[2] We report here the reactions of the isoxazol-5-ones bearing an unsaturated system in position 4 under ruthenium catalysis. The results are depending on the different substituents present on the ring and different reaction conditions. The novel reactivity by using ruthenium-complexes provides a step-economic strategy towards benzo[*f*]indole-4,9-diones, and 2,3,4,5-tetrasubstituted pyrroles, through a decarboxylative ring-opening and ring closure.

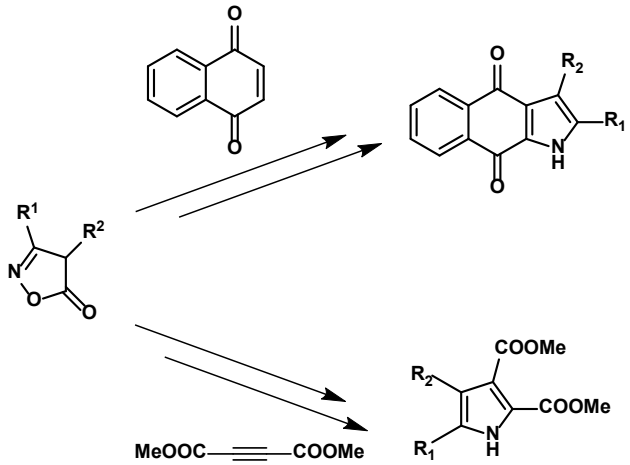

Figure. Isoxazol-5-ones ring trasformation

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PC-85

N,N-bis-Triazol-Sulfenamides: A New Family of Halogen Free Flame Retardants

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In response to the urgent need to develop new high-performance and halogen-free fire resistant materials with low environmental impact,[1] different alternative flame retardant (FR) systems have been introduced. In many applications, traditional inorganic, non-halogenated flame retardants such as ammonium polyphosphate (APP) and aluminum or magnesium hydroxides (ATH, MDH) are widely used, but there is still a need to find more effective solutions. The proposed alternatives are mainly based on the employment of different reactive or additive organophosphorus or nitrogen containing additives that can act in gas phase and/or in condensed phase. In addition, various families of radical generators have been prepared and their viability in a series of polymer applications has been recently demonstrated.[2]

We have developed a new class of sulfenamides linked to the triazole systems. This specific group of compounds is characterized by the presence of a bond between a divalent sulfur atom and a trivalent nitrogen atom, which by homolytic cleavage generates aminyl and thiyl radicals, and by the presence of the triazole unit able to generate nitrogen and ammonia by splitting, thus providing excellent flame retarding properties to polymer substrates.

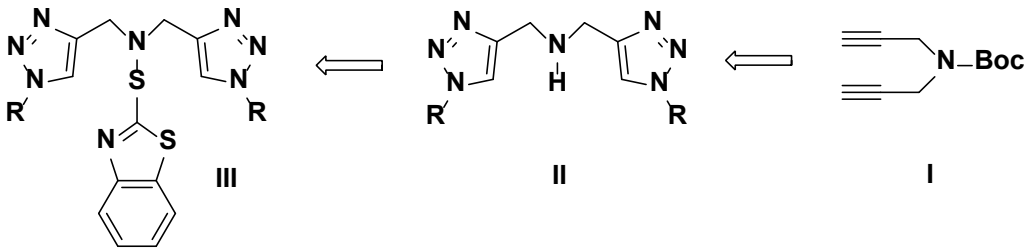

Figure 1: Retrosynthetic approach for the synthesis of *N,N*-bis-Triazol-Sulfenamide derivatives.

The general synthetic procedure have been developed through two key substrates as shown in the retrosynthetic scheme (Figure 1): the protected dipropargylamine **I** and the bis-triazolyl derivative **II** which is subsequently converted into the final product **III**.

The obtained products were investigated by thermogravimetric analysis (TGA) to evaluate their thermal stability and the best compounds were incorporated in polypropylene (PP). Flame stability of the composite thus obtained was evaluated.

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PC-86

Decoration of carbon nanotubes for the combined therapy of cancer

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A drug delivery system (DDS) for combined therapy, based on a short oxidized multiwalled carbon nanotube, is reported. It was prepared exploiting a synthetic approach which allowed loading of two drugs, doxorubicin and metformin, the targeting agent biotin and a radiolabeling tag, to enable labeling with Ga-68 or Cu-64 in order to perform an extensive biodistribution study by PET/CT. The DDS biodistribution profile changes with different administration methods. Once administered at therapeutic doses, the DDS showed a marginal beneficial effect on 4T1 tumor bearing mice, a syngeneic and orthotopic model of triple negative breast cancer, with survival extended by 1 week and 2 days in 20% of the mice. This is encouraging given the aggressiveness of the 4T1 tumor. Furthermore our DDS was well tolerated, ruling out concerns regarding the toxicity of carbon nanotubes.

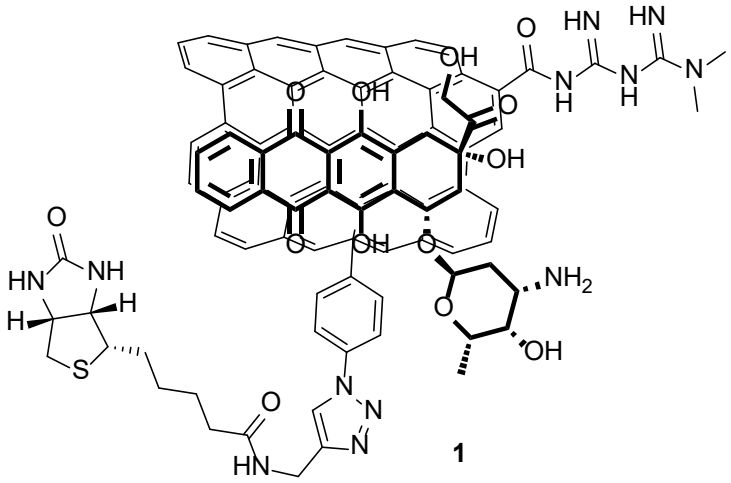

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Figure 1: Structure of the drug delivery system loaded with doxorubicin and metformin.

References:

[1] G. Biagiotti, S. Fedeli, G. Tuci, L. Luconi, G. Giambastiani, A. Brandi, F. Pisaneschi, S. Cicchi, P. Paoli, *J. Mater. Chem. B* **2018**, *6*, 2022-2035.

PC-87

Synthesis of new amphiphilic Zn-Salophen complexes derivatized by bile acids

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The amphiphilic Zn-salophen complexes have lately been receiving attention due to their aggregation behaviour, dependent upon some experimental parameters, such as concentration and polarity of solvents.[1] The possibility to control their aggregation morphologies, and their well known capability to accept one axially coordinated donor species make them suitable candidates for the development of new materials with applications in sensing.[2] The search of new amphiphilic derivatives of Zn-salophenes is thus an active research field. Our group have recently been working on the functionalization of bile acids which are an important class of natural surfactants showing amphiphilic properties strictly related to their rigid backbones. We prepared new derivatives linking natural bile acids to other natural compounds, such as sugars and aminoacids. The aggregation properties of the resulting derivatives were studied, and interesting aggregates and nanostructures were observed, making these compounds ideal building blocks for the bottom up synthesis of new materials for applications in the field of materials chemistry, in pharmacology and in the field of nanotechnologies, also thanks to the morphological variability.[3] Thus here we describe the functionalization of metal-salophen complexes with substituted bile acids to obtain complex derivatives, in principle able to aggregate both thanks to the metal salophenic core, and bile acid subunit.

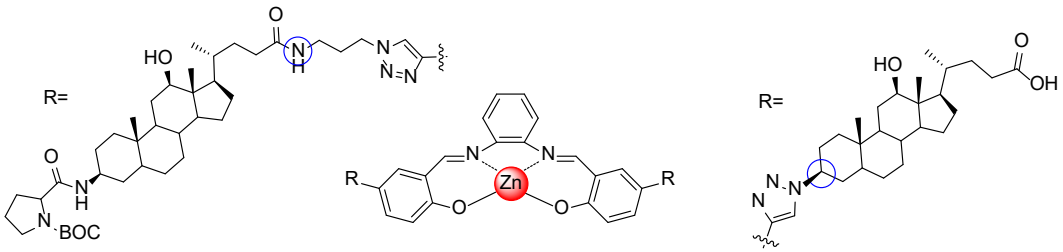

Figure 1: new amphiphilic Zn-Salophen compounds.

The strategies to functionalize bile acid backbone at C-3 or at its side chain to afford are discussed (**Figure 1**).

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PC-88

Naphtochromenones as Cross-Border Light Photoredox Catalysts

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During the last decade photochemistry has experienced an exponential growth. This, pushed by the development and utilisation of an increasing number of photocatalysts (PCs) in synthetic and material chemistry. Despite their cost and scarce sustainability, Ru- and Ir-based PCs have played a dominant role. This can be mainly ascribed to their easy use under common light sources irradiation (LEDs or CFL bulbs) that guarantees reagents and products stability. On the other hand, UV-light absorbing PCs generate wider redox windows which potentially result in broader applications.[1] Unfortunately, the use of highly energetic photons hampers their utilisation in diverse photoreactions. The identification of a general PC that combines the advantages of visible-light absorption with a redox window as wider as possible, efficiently catalysing the highest number of transformations is crucial to the future development of the field.

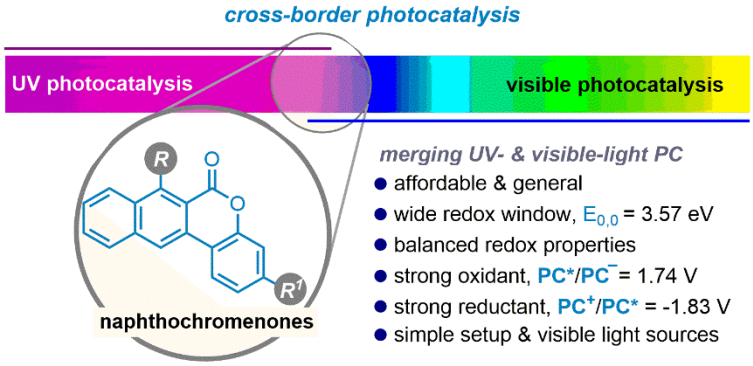

Figure 1: Naphtochromenone photocatalysts as a new class of fully organic PCs.

I herein present a novel class of purely organic PCs, with a distinctive absorption across UV- and visible-light regions. Thanks to a robust microfluidic light-driven synthetic protocol their synthesis can be easily accomplished starting from readily available benzophenones and coumarins.[2] Remarkably, naphthochromenone PCs combine the benefits of an extremely wide redox window, $E_{0,0}$ = up to 3.57 eV, typical of UV-absorbing PCs, to the advantages of the use of simple setup and product stability of visible-light photocatalysis. Their well-balanced excited state redox potentials, $PC^*/PC^{\bullet-}$ = up to +1.74 V and $PC^{\bullet+}/PC^*$ up to -1.83 V vs SCE, ensure the ability of performing diverse challenging photoredox transformations through both reductive and oxidative quenching cycles.[3]

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[3] *Submitted manuscript.*

Microfluidic Dearomatisation of Indoles by a Light-Driven [2+2] Paternò-Büchi Process

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Excited state molecules can react in unconventional ways, offering synthetic opportunities that cannot be realized under classical thermal activation.[1] For this reason, the field of light-mediated synthetic chemistry has recently witnessed a tremendous growth.[2] The advancements of different technologies including new light sources, such as: high-power LEDs or compact fluorescent light bulbs, have been key for boosting the development of novel photochemical transformations.[3] However, the use of a microfluidic photoreactor setup (MFP) offers decisive advantages with respect to photochemical batch protocols – improving the efficiency and selectivity of diverse light-driven processes.[4]

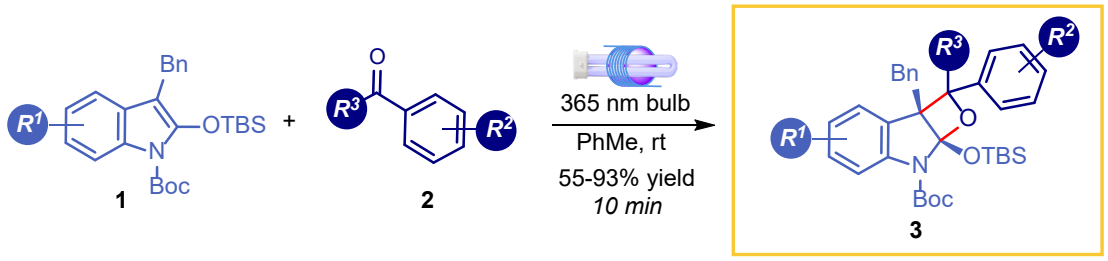

Figure 1: Dearomatisation of indoles by a Paternò-Büchi reaction.

I herein present our progress towards novel microfluidic dearomatisation of indoles triggered by a light-driven hetero-[2+2]-cycloaddition (Paternò-Büchi) reaction. This procedure allows the one-step access to differently substituted tetrahydrooxeto-indoles **3** (Figure 1). Interestingly, these motifs are present in a large number of alkaloids and natural products.[5] Adopting the MFP setup we demonstrate the generality of the light-driven method by evaluating a variety of indole silyl enol ethers **1** and carbonyl compounds **2**. Remarkably, the present method allows the construction of valuable all-carbon quaternary stereocenters with high regio- and stereocontrol.

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PC-90

Higher order cycloadditions: from a stereoselecrive rediscovery to a computational fascination.

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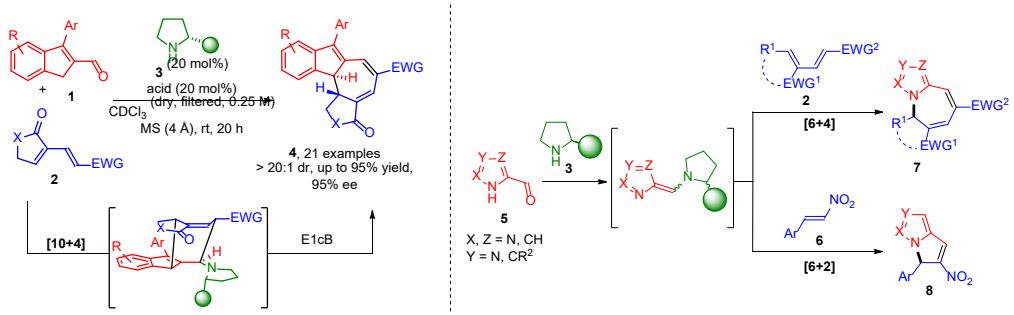
Higher order cycloadditions (HOCs), i.e. cycloaddition reactions involving more than six π-electrons, became a popular research topic in organic chemistry, following the computational and experimental reports of Woodward, Hoffmann and Houk.[1] Organocatalysis was shown to be a competent strategy to induce enantioselectivity in HOCs, as demonstrated by a recent report by Jørgensen.[2] Following this principle, we developed a strategy to disclose the first catalytic stereoselective [10+4] cycloaddition. Amino isobenzofulvenes, generated *in situ* from aldehydes **1** and catalyst **3**, were reacted with dienes **2**, affording intriguing tetracyclic scaffolds **4**.[3] Experimental and computational evidence suggest that the observed stereoselectivities arise from kinetically controlled amino isobenzofulvene formation. Moreover, we have developed a novel concept for the activation of heteroaromatic compounds, such as pyrrole-, imidazole- and pyrazole-carbaldehydes **5** by organocatalysis, generating electron-rich hetero-6π-intermediates acting as nucleophiles.[4] These react in a highly chemo-, regio- and stereoselective manner with various types of electron-deficient dienes **2** and olefins **6**, in [6+4] and [6+2] cycloaddition reactions, respectively. The methodology provided bio-attractive pyrrolo-azepine scaffolds **7** and pyrrolizidines alkaloid scaffolds **8**. As suggested by computational studies, stereocontrol occurs at the second C–C bond forming step, rather than the N–C bond forming transition state. Based on these two examples, this presentation will demonstrate that HOCs, besides being a powerful tool to construct complex and biologically relevant scaffolds, are extremely fascinating on the computational point of view, revealing peculiar features in reactivity and stereoselectivity.



Scheme 1. Organocatalytic enantioselective [10+4], [6+4] and [6+2] cycloadditions.

References:

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PC-91

Stereocontrolled synthesis of pyrrolidine iminosugars' lipophilic derivatives

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Iminosugars, carbohydrate analogues with a nitrogen atom in place of the endocyclic oxygen[1], turned out to be of great interest in their ability to inhibit important enzymes, such as glycosidase and glycosyltransferase[2]. Thanks to this property, these alkaloids are considered a great target in treating a wide range of diseases like cancer, viral and bacterial infections, sphingolipid storage disorders[3].The working group we refer to has already provided a synthetic strategy to obtain pyrrolidine iminosugars in a stereocontrolled way. According to several studies, the selectivity and power of these inhibitors significantly increase when lipophilic chains are introduced[4,5,6,7,8], allowing them to enter the cells' lipophilic double layer, reaching the central nervous system. From this perspective, we are focusing on functionalization of primary and secondary hydroxyl groups, introducing the alkyl chains in various steps of the synthetic pathway mentioned before.

A future aim will include the immobilization of synthesized compounds on magnetic nanoparticles and silver nanoclusters in drug delivery applications.

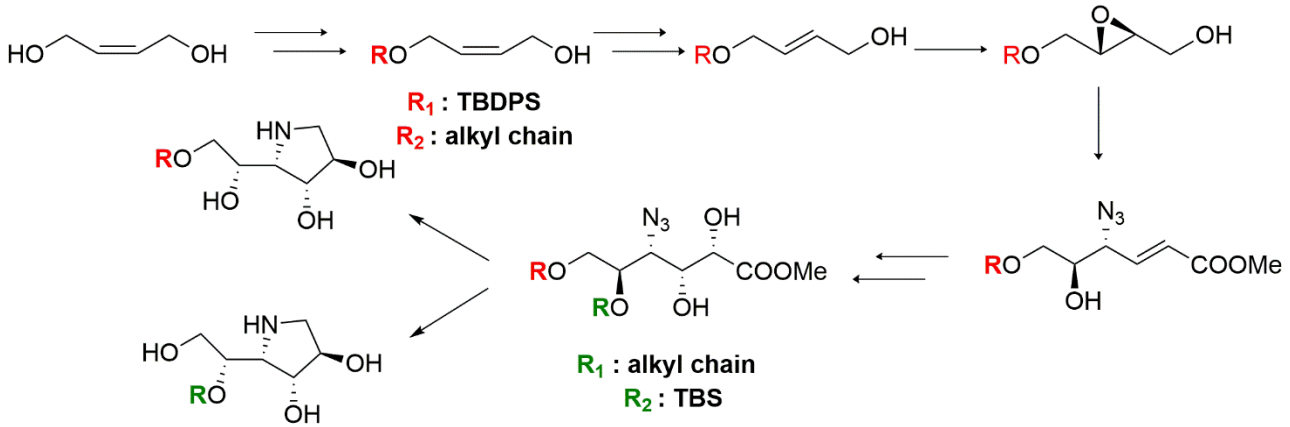

Figure 1: synthetic strategy of lipophilic derivatives

References:

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PC-92

Synthesis of new 1,2-diaminic ligand for the asymmetric Henry reaction

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Over the years, asymmetric catalysis has taken on increasingly central in enantioselective synthesis. Using chiral catalysts, both synthetic and of natural origin, optical active molecules can be obtained starting from prochiral molecules, with high yields and enantiomeric excesses.[1]

Recently, we have developed a new ligand with an amino alcoholic structure, ligand **1** (Figure 1), which has proved to be an excellent chiral catalyst in the dialkylzinc addition reaction to aldehydes.[2]

Having found in literature significant advantages in the use of 1,2-diaminic ligands[3] in asymmetric synthesis and in light of the good results obtained with **1**, the work we present concerns the synthesis and of a new chiral ligand with diaminic catalytic site, taking as model ligand **1**.

Once any attempt to transform the ligand **1** into the desired structure failed, it was decided to construct the new ligand by passing through the formation of an aziridine ring and the subsequent regioselective opening of the same (Figure 2). Currently, the synthetic strategy chosen to optimize ligand structure involves its application in the Henry reaction.[4]

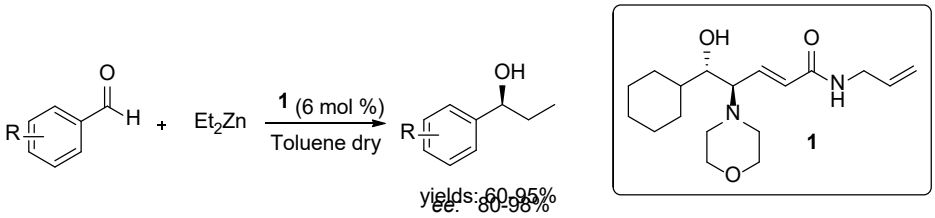

Figure 1 Catalytic efficiency of **1** in the asymmetric addition of diethylzinc to aldehydes **1.**

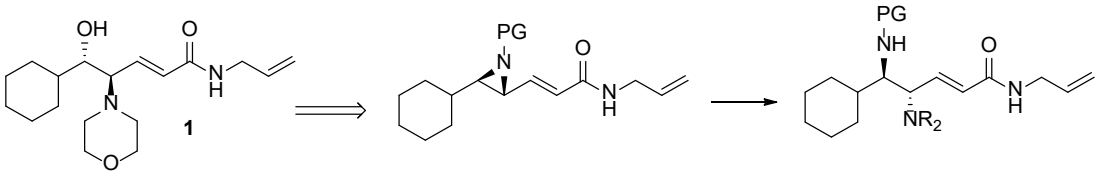

Figure 2 Developed synthetic strategy to obtain a chiral 1,2-diaminic ligand

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PC-93

Catalytic Asymmetric Oxidative γ-Coupling of α,β-unsaturated Aldehydes with Air as the Terminal Oxidant

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Readily available chiral amines have been extensively used as catalysts for the activation of carbonyl compounds in the field of polar reactivity, which by reaction of electrophile and nucleophiles, provide products in a highly stereoselective manner.[1] In contrast, the involvement of short-lived open-shell species in asymmetric catalysis has remained relatively unexplored until recently, due to the inherent challenge of efficiently controlling the stereoselectivity of the product formation from high-energy intermediates.[2] The use of radicals in open-shell strategies can give access to different reactivity, for instance the coupling of two nucleophiles, which would not be feasible with polar reactivity.[3] This communication presents the catalytic enantioselective coupling of two nucleophiles generated from α,β-unsaturated aldehydes *via* dienamine catalysis and a sub-stoichiometric amount of a single electron transfer-oxidant (SET-oxidant), that is reoxidized by air (Scheme 1). Merging organocatalysis with a transition metal featuring the appropriate redox properties provides the synergy necessary for the oxidation and subsequent radical coupling of the activated dienamine **I**. Air is used as the terminal oxidant of the process (Scheme 1).[4]

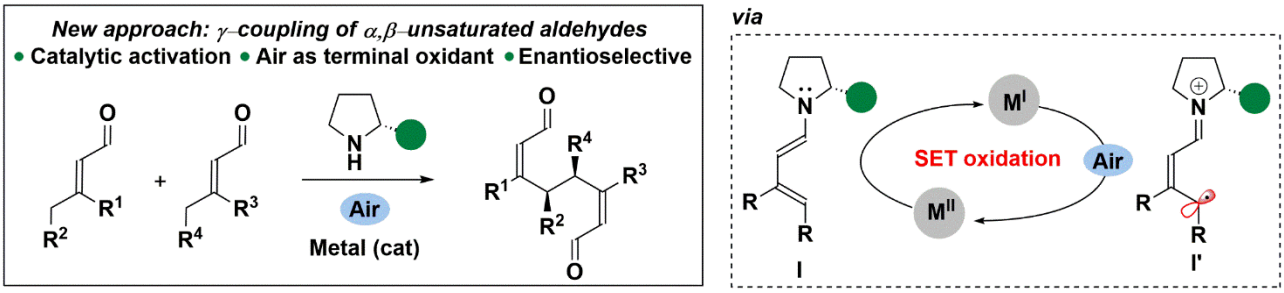

Figure 1

References:

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PC-94

Synthesis of α-Amido Silyl Enol Ethers via Silylative Ketene 3-Component Reactions: Synthetic Applications in Organic and Natural Products Synthesis

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Silyl enol ether chemistry is nowadays well-grounded and established, as they proved to be invaluable intermediates in organic synthesis. However, despite the quantity of synthetic protocols that have been established over the years to achieve these useful molecules, the synthesis of silyl enol ethers from secondary α-ketoamides remained a challenge because of the presence of an acidic hydrogen on the amide group. Exploiting the experience of our group in photoinduced multicomponent reactions[1] and diazoketones reactivity,[2-3] we designed a simple and straightforward reaction to access this virtually unexplored class of molecules.[4]

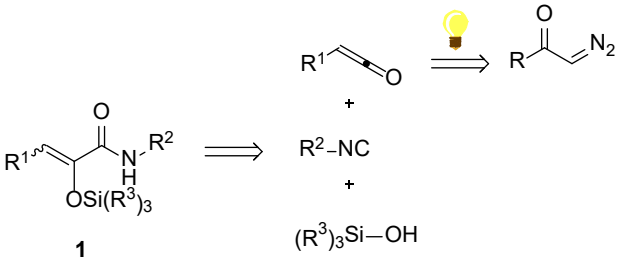

Figure 1: retrosynthetic approach for α-silyloxyarylamides of general structure 1

Silyl enol ethers of general structure **1** were achieved in high yield and in a stereoselective fashion, affording high percentages of Z isomer (generally > 95%) after an adequate screening and tuning of reaction conditions. We reported several synthetic applications for these molecules and paved the way for a straightforward synthesis of natural product analogues (Figure 2).

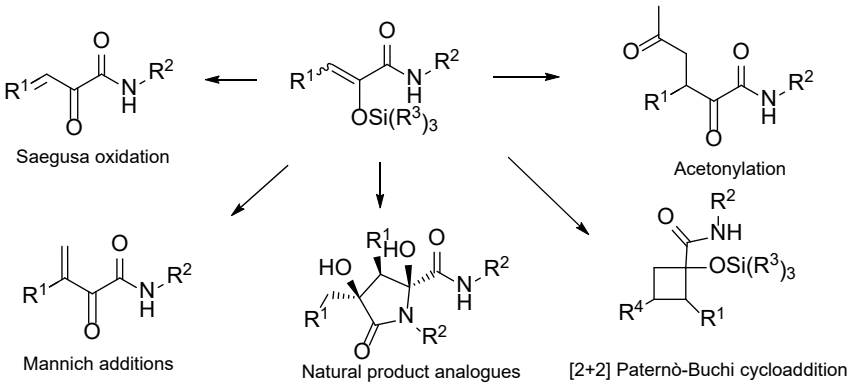

Figure 2: some synthetic applications of α-amido silyl enol ethers

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