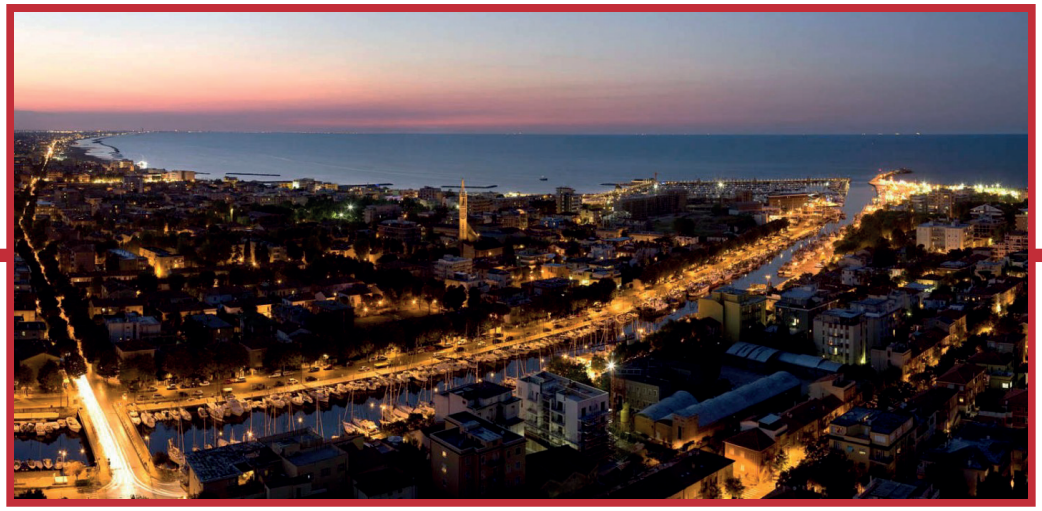
Proceedings of the Merck Young Chemists' Symposium 2019

MERCK

Young Chemists' Symposium 2019



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Società Chimica Italiana
Gruppo Giovani

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Merck Young Chemists' Symposium

XIX edition

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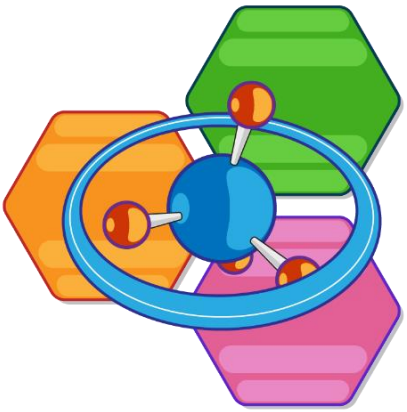

Welcome to the 19th edition of the ***Merck Young Chemists' Symposium*** (***MYCS***), formerly also known as *SAYCS* and *MEYCS*.

This event is organized by the Young Group of *Società Chimica Italiana* (***SCI Giovani***) with the financial support from *Merck* and several other sponsors, that you will meet during the conference.

The symposium covers all the disciplines of Chemistry, aiming to connect young researchers, inspire new ideas, and potentially trigger new collaborations.

MYCS is an international event, thanks to the leading role of SCI into the European framework, the support from the *European Young Chemists' Network* (EYCN), and most importantly to all of you, participants coming from 9 countries from all over the world.

This year we are honored to have the exceptional number of 240 participants. Thank you for the great trust shown towards *SCI Giovani*, *Merck* and all our supporters.

The contributions of our 4 invited plenary speakers will just be the icing on the cake of a wonderful scientific event I truly hope you will all enjoy with us.

Leonardo Triggiani
SCI Giovani Coordinator

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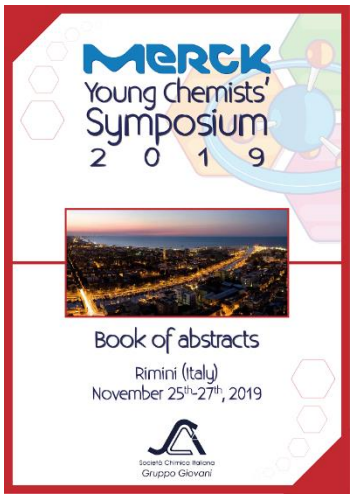

All the scientific contributions of the symposium are collected in this *international volume* with ISBN code.

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PL04	Fabrizio CAVANI

Sympathy for the methyl: A library-on-library approach to identify small-molecule ligands of methyl-lysine reader proteins

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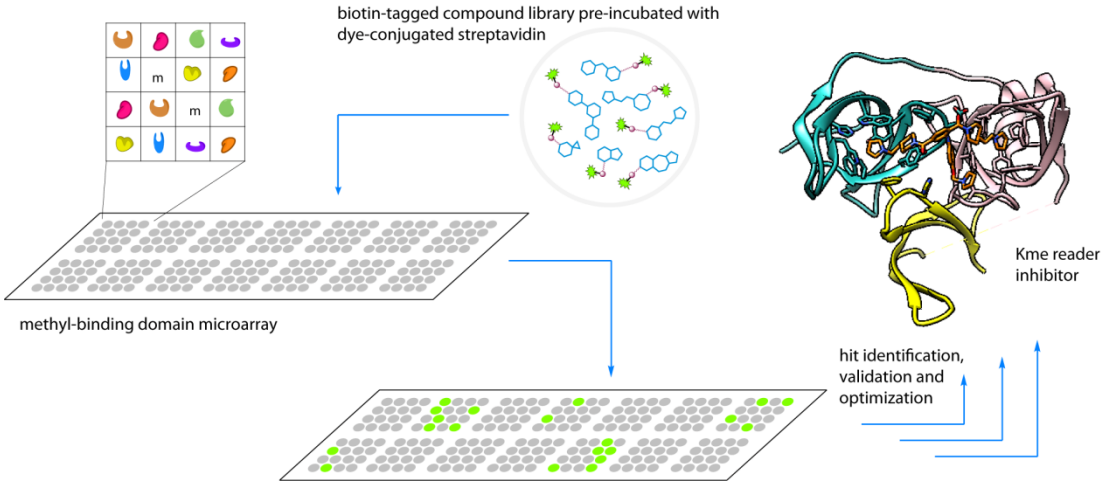
The discovery of inhibitors of methyl- and acetyl-binding domains has provided evidence for the "druggability" of epigenetic effector molecules. Using a library of biotin-tagged analogs we screened a protein domain microarray of methyl-lysine effector molecules to rapidly detect compounds with novel binding profiles - either improved or loosened specificity [1]. Using this approach, we identified compounds that acquired novel interactions with Tudor domain-and MBT domain-containing proteins.



[1] N. Bae, M. Viviano, X. Su, J. Lv, D. Cheng, C. Sagum, S. Castellano, X. Bai, C. Johnson, M.I. Khalil, J. Shen, K. Chen, H. Li, G. Sbardella, and M.T. Bedford, *Nat. Chem. Biol.* **13** (2017) 750-756.

Application of nanotechnology to medicine: novel approaches and barriers to cross

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Nanoscale systems for drug delivery hold the potential to overcome the limits of conventional drug therapies thus, providing a solution to unmet medical needs. Still, despite the promising results, nanocarriers in which drugs are physically encapsulated face important obstacles including the poor drug loading and the rapid release of the drug simply adsorbed at their surface. In this context, the prodrug approach represents an interesting alternative strategy.

In the last years, I mainly focused on lipid prodrugs based on terpenoids. They demonstrated capacity to modify the drug pharmacokinetics leading to an enhanced efficacy compared to the free drug in several preclinical tumor models. And, we demonstrated [1] that the specific delivery of drugs to target cells occurs indirectly, simply exploiting the endogenous lipoproteins as carriers. (Fig 1a)

Together with the elaboration of novel nanomedicines, it is essential to dispose of relevant models to accurately assess their efficacy. Hence, we are constructing heterotype 3D tumor models [2] (Fig 1b), as screening tools to achieve insights on the accumulation of variously engineered nanomedicine and to identify the parameters which will prompt their penetration thus allowing to achieve the highest therapeutic benefit.

During this talk, the most significant results obtained in this two research fields will be presented.

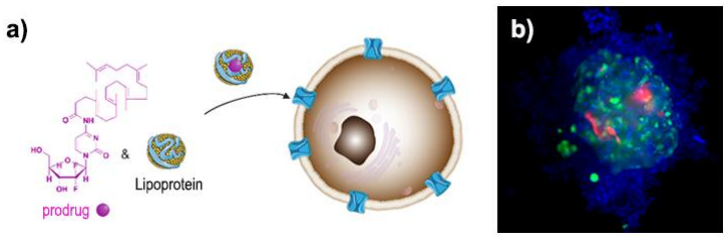

Figure 1. (a) Schematic representation of the lipoprotein-mediated targeting of cancer cells; (b) 3D heterotype spheroids.

[1] D. Sobot, S. Mura, S. Yesylevskyy, L. Dalbin, F. Cayre, G. Bort, J. Mougin, D. Desmaële, S. Lepetre-Mouelhi, G. Pieters, B. Andreiuk, A.S. Klymchenko, J.L. Paul, C. Ramseyer, and P. Couvreur, *Nature Comm*. **8** (2017) art. no 15678.
[2] G. Lazzari, V. Nicolas, M. Matsusaki, M. Akashi, P. Couvreur, and S. Mura, *Acta Biomat*. **78** (2018) 296-307.

Sustainable low temperature wet-chemistry routes for inorganic nanomaterials: state of the art and perspectives

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Control on shape, morphology, size and crystallinity of inorganic nanomaterials are major requirements in many applicative fields such as catalysis, energy production and storage, microelectronics, optics, magnetic devices. In this context, the paradigms of green and sustainable chemistry are currently raising a sharply growing interest in all fields of inorganic materials chemistry [1]. Resorting to sustainable, green and easy scalable wet-chemistry, typically aqueous-based, synthesis routes is a convenient approach to produce nanostructures for different application ranging from catalysis, to optics, to electronic applications. In particular, inorganic chemistry represents an exciting playground for the design and optimisation of green chemistry-inspired routes which can also be implemented on a larger scale, which is a relevant aspect for industrial applications of catalysts. The controlled exploration of experimental parameters discloses exciting perspectives in orienting, *inter alia*, the morphogenesis and the final structure and shape of the crystalline materials. In this framework, we have explored and optimised a versatile and effective synthetic toolbox encompassing different low temperature (T< 150°C) and sustainable wet chemistry and colloidal routes [1] (Fig. 1) The toolbox encompasses (i) hydrothermal routes [2], (ii) very low (0°C) temperature precipitation, (iii) continuous flow synthesis, (iv) seeded-growth) and combinations thereof, to prepare different inorganic functional nanomaterials ranging from metal and metal alloys nanoparticles for gas exhaust after-treatment, metal oxides for possible oxidation catalysis reactions, zinc sulphide and metal titanates for photocatalytic applications. These syntheses have been recently extended to the preparation of further sulphides and mixed oxides. Common factors of all these approaches are the low temperature of processing, the easy procedure, the reproducibility, the possibility to up-scale the optimised route, the achievement of highly crystalline size-controlled nanostructures.

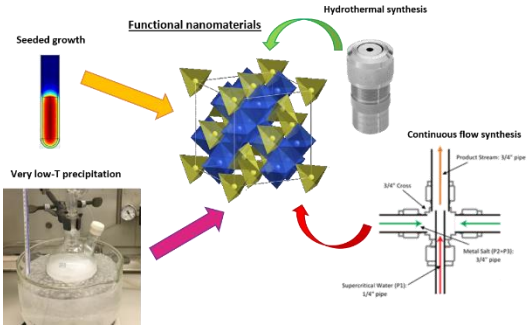

Figure 1: Synthetic toolbox for low temperature synthesis of inorganic nanostructures

[1] S. Diodati, P. Dolcet, M. Casarin, and S. Gross, *Chem. Rev*. **115** (2015) 11449-11502
[2] P. Dolcet, S. Diodati, F. Zorzi, P. Voepel, C. Seitz, B.M. Smarsly, S. Mascotto, F. Nestola, and S. Gross, *Green Chem.* **20** (2018) 2257-2268

The heritage of an East side story: bio-olefins for a more sustainable chemical industry

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The so-called *biorefinery* is the emblem of a chemical industry striving to become more sustainable, by replacing conventional fossil-based sources with renewable ones. In the context of the *bioeconomy*, the attempt to use the *platform molecules* to produce chemicals is also one of the most efficient ways to contrast the greenhouse effect by "recirculating" CO_2 emissions, an objective which perfectly fits the *Circular Economy* strategy.

In this lecture, I will report some recent results on the synthesis of alkenes from bio-alcohols, with special focus on the transformation of bioethanol into butadiene, a monomer for the production of elastomers. The reaction was invented in Russia by the scientist S. Lebedev at the beginning of the 20th century and used for the synthesis of rubber for tires in military trucks during the 2nd WW. Recently, interest for this forgotten technology has been reborn, because tires manufacturers are wiling to satisfy the increasing market demand for bio-based products. We investigated the reaction mechanism and the chemical characteristics of the catalyst necessary to perform the complex transformation.[1-3] We studied the "Lebedev" reaction, and the similar "Guerbet" reaction, by means of reactivity experiments, in-situ spectroscopic investigation and DFT calculations, which allowed us to understand the role of each element in the multifunctional catalysts showing the best performance.

[1] A. Chieregato, J. Velasquez Ochoa, C. Bandinelli, G. Fornasari, F. Cavani, and M. Mella, *ChemSusChem* **8** (2015) 377-388.
[2] J. Velasquez Ochoa, C. Bandinelli, O. Vozniuk, A. Chieregato, A. Malmusi, C. Recchi, and F. Cavani, *Green Chem.* **18** (2016) 1653-1663.
[3] J. Velasquez Ochoa, A. Malmusi, C. Recchi, and F. Cavani, *ChemCatChem* **9** (2017) 2128-2135.

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OR89	Linda LEONE
OR90	Eleonora MONTI

Peroxisome Proliferator-Activated Receptor (PPAR) agonists as Fatty Acid Amide Hydrolase (FAAH) inhibitors: screening and preliminary structure-activity relationships

Leonardo Brunetti, Antonio Laghezza, Luca Piemontese, Paolo Tortorella, and Fulvio Loiodice

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Peroxisome-proliferator activated receptors (PPARs) have been known for some years as part of the cannabinoid signaling system. Indeed, their various receptor subtypes (PPARα, PPARγ and PPARδ) are activated by phytocannabinoids and endocannabinoids alike. This endocannabinoid-mediated activation has multiple downstream effects that could be beneficial in pathological conditions such as Neurodegenerative Disorders and even certain types of cancer [1,2].

In order to harness this connection, we have explored the feasibility of coupling PPAR agonism with the enhancement of the endocannabinoid tone. Such an enhancement can be achieved by inhibiting one of the most important enzymes which quickly inactivate endocannabinoids *in vivo*, namely Fatty Acid Amide Hydrolase (FAAH)[1-3].

With this goal in mind, we have conducted a screening for FAAH inhibitory activity. First, we tested known PPAR agonists that had previously been synthesized in our laboratories; then, we also tested a panel of natural substances and other small phenolic molecules to better investigate the structural requirements for FAAH inhibition.

Thus, we tentatively identified a scaffold for the design of dual-acting compounds, whose fascinating potential will be explored in the future.

[1] L. Brunetti, F. Loiodice, L. Piemontese, P. Tortorella, and A. Laghezza, *J. Med. Chem.* DOI: 10.1021/acs.jmedchem.9b00885.
[2] L. Brunetti, A. Laghezza, F. Loiodice, P. Tortorella, and L. Piemontese, *Neural Regen. Res.* **15** (2020) 67-68.
[3] L.V. Panlilio, Z. Justinova, and S.R. Goldberg, *Pharmacol. Ther.* **138** (2013) 84–102.

Compound collection management: dynamic fully automated platform and operative workflow for high throughput screening

Letizia Lazzaro, Costanza Iaccarino, Vincenzo Summa, Adele Pirolli, and Steven Harper*

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The high-throughput screening of large compound collections to identify hits or even lead structures is very frequently the starting point for small-molecule drug discovery programs. Therefore the Compound Management is an essential tool to handle compounds and data associated in an ultra-secure and reliable procedure. Originally, this process was somewhat haphazard, currently it is a full occupation of a screening scientist into a highly controlled and scientific disciplined environment, incorporating logistics and automation management [1]. Using technologies as robotics, data processing/control software, liquid handling devices, and sensitive detectors, high-throughput screening allows a researcher to quickly conduct millions of chemical, genetic, or pharmacological tests. This means that the design and the implementation of an accurate and high-quality compound collection to be screened is a key part of the initial phase of a new medicinal chemistry program and often dictates the final fate of a drug discovery campaign.

Considering that the chemical space to be explored in research programs is practically infinite and sparsely populated, significant efforts and resources need to be invested in the generation and maintenance of high quality libraries. Here we describe the whole workflow for the building and the management of the IRBM internal collection, from the criteria used for the selection of new libraries with drug like properties, to compounds handling for HTS purposes [2].

[1] M. Zaragoza-Sundqvist, H. Eriksson, M. Rohman, and P.J. Greasley, *J. Biomol. Screen.* **14** (2009) 509-514.
[2] A. Karawajczyk, F. Giordanetto, J. Benningshof, D. Hamza, T. Kalliokoski, K. Pouwer, R. Morgentin, A. Nelson, G. Müller, A. Piechot, and D. Tzalis, *Drug Discov. Today* **20** (2015) 1310-1316.

* This abstract is dedicated to the memory of our wonderful colleague, Dr. Steven Harper, who recently passed away.

Label-free metabolic monitoring of living cells by mid-infrared optoacoustic microscopy

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We achieved metabolic imaging in living cells based on label-free observation of carbohydrates, lipids, and proteins by introducing bond-selective mid-infrared optoacoustic microscopy (MiROM). MiROM achieves low-micromolar concentration sensitivity with negligible cell photodamage using up to three orders of magnitude less laser power than other vibrational-spectroscopy imaging modalities, such as Raman imaging. We showcase the unique label-free biomolecular contrast capabilities of MiROM in living cells by monitoring the spatiotemporal distribution of carbohydrates, lipids, and proteins in 3T3-L1 cells during lipogenesis as well as monitoring the lipid-protein dynamics in brown and white adipocytes during lipolysis. For the first time, we visualize carbohydrate patterns in early-stage adipocytes revealing, over time, an initial spread throughout the adipocyte body, followed by a co-localization with lipid droplets upon adipocyte maturation. MiROM yields unique label-free metabolic imaging abilities for a broader range of bioanalytical studies in living cells, showing additionally its potential application for analytical histology in fresh/unprocessed tissues. [1]

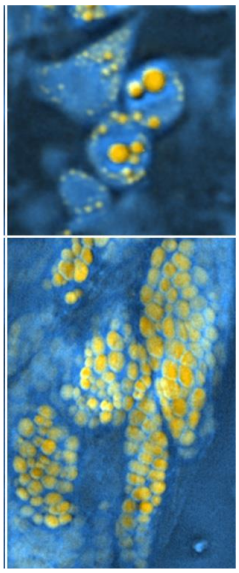

Figure 1: Merged lipid and protein maps of: (top) differentiated 3T3-L1 cells and (bottom) freshly excised unstained pancreatic mouse tissue.

[1] Miguel A. Pleitez, Asrar Ali Khan, Josefine Reber, Andriy Chmyrov, Markus R. Seeger, Stephan Herzig, Marcel Scheideler, Vasilis Ntziachristos, *BioRxiv* (2018) 270082

New stilbene-ammonium based nicotinic ligands: insights into alpha9-10 and alpha7 nAChRs responses

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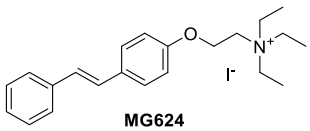
α9-α10 and α7 nicotinic acetylcholine receptors (nAChRs) are overexpressed in extra-neuronal tumours, like adenocarcinomas and glioblastomas. Whereas nicotine induces hyperproliferation of tumoral cells expressing the α9-α10 and α7 subtypes, specific antagonists revert it [1].

MG624 is a nicotinic ligand, able to block agonist-evoked currents at the α9-α10 and α7 subtypes. We demonstrated that the elongation of its ethylene linker provides ligands with higher potency in blocking the agonist-evoked currents and with a high anti-adenocarnicoma and anti-glioblastoma activity, which increases with the length of the linker [2,3].



MG624

Aiming at identifying the key structural features that modulate α9-α10 and α7 affinities and activities, MG624 was modified at the ammonium head, at the oxyethylene linker and at the stilbene scaffold.

The analogues were tested in binding assays at the α7 subtype and in electrophysiological assays at the α9-α10 and at the α7 nAChRs. Selectivity against other nicotinic subtypes, such as α4β2 and α3β4, was considered.

Overall, this SAR study provided ligands with interesting electrophysiological profiles, among which a new lead compound with subnanomolar binding affinity and very high selectivity.

[1] V. Mucchietto, F. Fasoli, S. Pucci, M. Moretti, R. Benfante, A. Maroli, S. Di Lascio, C. Bolchi, M. Pallavicini, C. Dowell, M. McIntosh, F. Clementi, and C. Gotti, *Br. J. Pharmacol*. **175** (2018) 1957-1972.
[2] C. Gotti, B. Balestra, M. Moretti, G.E. Rovati, L. Maggi, G. Rossoni, F. Berti, L. Villa, M. Pallavicini, and F. Clementi, *Br. J. Pharmacol*. **124** (1998) 1197-1206.
[3] F. Bavo, S. Pucci, F. Fasoli, C. Lammi, M. Moretti, V. Mucchietto, D. Lattuada, P. Viani, C. De Palma, R. Budriesi, I. Corradini, C. Dowell, J.M. McIntosh, F. Clementi, C. Bolchi, C. Gotti, and M. Pallavicini, *J. Med. Chem.* **61** (2018) 10531-10544.

How to productively interact with FtsZ to block bacterial replication: a computational and SAR investigation for developing potent antimicrobials

Valentina Straniero,[a] Victor Sebastián-Pérez,[b] Martina Hrast,[c] Carlo Zanotto,[d] Andrea Casiraghi,[a] Lorenzo Suigo,[a] Irena Zdovc,[c] Antonia Radaelli,[d] and Ermanno Valoti[a]

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FtsZ is a crucial prokaryotic protein involved in bacterial cell replication [1]. It recently arose as a druggable target, searching for antimicrobial agents able to fight antibacterial resistance [2].

Here are presented our recent updates in the developing of FtsZ 2,6-difluoro-benzamide inhibitors linked by a methylenoxy or ethylenoxy or propylenoxy bridge to 7- substituted 1,4-benzodioxane or to 1,4-naphtodioxane [3]. Computational studies helped us in elucidating the mandatory structural features of new promising derivatives (Figure 1).

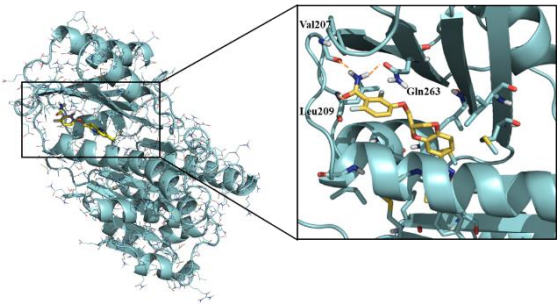

Figure 1: FtsZ binding mode of the most active compound

Our latest compounds exhibited promising antibacterial activities not only vs multi drug resistant *S. aureus*, but also on mutated *E. coli* strains, thus interestingly enlarging their spectrum of action not only *vs* Gram-positive but also *vs* Gram-negative bacteria.

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Synthesis and biological evaluation of new chemical entities in the GEBR library PDE4D inhibitors

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In the past we developed a panel of compounds (GEBR derivatives, Fig.1) to obtain selective phosphodiesterase isoforms (PDE4D) inhibitors. In these molecules, we identify three parts: 1) a catechol portion (that interact with the Q2 pocket of the catalytic domain); 2) different linkers; 3) a basic end.
Many compounds showed interesting PDE4D3 selective inhibition, and in vitro and in vivo assays evidenced their great potential as therapeutic agents in pathologies such as Alzheimer Diseases [1,2].

Crystallographic studies identified three major ligand conformational classes (protruding, twisted, and extended [3]), being the protruding ones the most promising candidate for further investigation. We therefore designed and synthesized the new derivatives **1** (Fig. 1), which feature greater steric hindrance, and **2** (Fig. 1), which are characterized by a reduced structure flexibility. Inhibition tests and crystallographic studies evidenced for compounds **1** better enzyme interaction and increased inhibition potency. Whereas, the constrained structures of compounds **2** resulted unable to achieve the catalytic pocket and therefore the series was quite inactive.

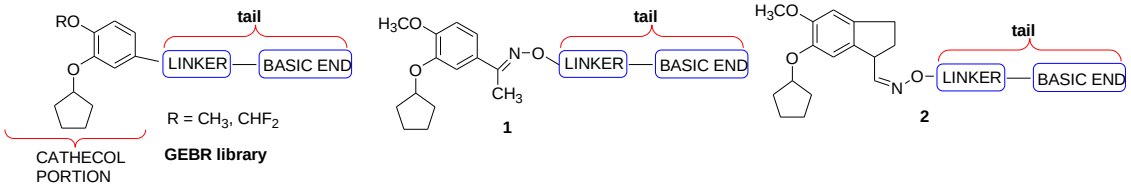

Figure 1: Molecular formula of GEBR library and new synthesized compounds **1** and **2**.

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Novel benzothiazolones and benzoxazolones-based σ receptor ligands: synthesis and preliminary pharmacological evaluation against allodynia

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Millions of people worldwide suffer from a specific form of chronic pain conditions which significantly impairs daily activities, including work. Standard treatments, including opioids and anticonvulsants, are effective treatments. However, these medications possess severe side-effects (*e.g.*, tolerance, respiratory depression, sedation), which mitigate their therapeutic benefits. Therefore, the development of safer painkillers, which might exert their activity through alternative targets, such as sigma receptors (σRs) [1-2], is still a medical need to meet.

In an attempt to develop novel non-opioid drugs to treat neuropathic pain, we designed and synthesized a new set of 6-substituted-2(3*H*)-benzothiazolones, and 6-substituted-2(3*H*)-benzoxazolones as σ receptor ligands. Two of the new high-affinity σ_1 receptor ligands 3-(2-(azepan-1-yl)ethyl)-6-benzylbenzo[*d*]thiazol-2(3*H*)-one (**MCI 77**, K_i σ_1 = 5.41 nM) and 3-(2-(azepan-1-yl)ethyl)-6-(3-fluorobenzyl)benzo[*d*]oxazol-2(3*H*)-one (**MCI 92**, K_i σ_1 = 2.01 nM), were selected for *in vivo* pharmacological evaluation. As a result, both analogs showed anti-neuropathic pain effect in mice (45 mg/kg, i.p.). In addition, no locomotor impairment was observed at the tested dose. Overall, these preliminary data are indicative of the potential for further drug development and optimization of this set of compounds.

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Selective modulators of spliceosome-mutant cancers: a new frontier against hematologic malignancies

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Splicing of precursor messenger RNA, a fundamental step in gene expression, is catalyzed by a majestic multi-megaDalton machinery called spliceosome (SPL). Defects and mis-regulations of this essential biological process are responsible for up to 200 diseases, including several forms of cancer. Indeed, mutations in genes encoding splicing factors, such as SF3b (Fig.1a), are often identified in samples of patients affected by hematologic malignancies. Among the known splicing modulators only H3B-8800 (Fig. 1b), currently in phase I clinical trial, has shown a remarkable selectivity toward cancer cells bearing mutations of SF3b [1]. Recently, we have employed molecular dynamics simulations to obtain an atomic-level understanding of the functional dynamics of the SPL [2] and of the detailed mechanism of action exerted by splicing modulators [3]. Moreover, we are now applying state-of-the-art computational techniques in order to shed light into the mechanism underlying the selectivity exerted by H3B-8800 towards spliceosome-mutant cancers. This novel inhibitor may allow us to move a step forward toward the so-called "precision medicine", with drugs calibrated on specific patient's genetic profiles.

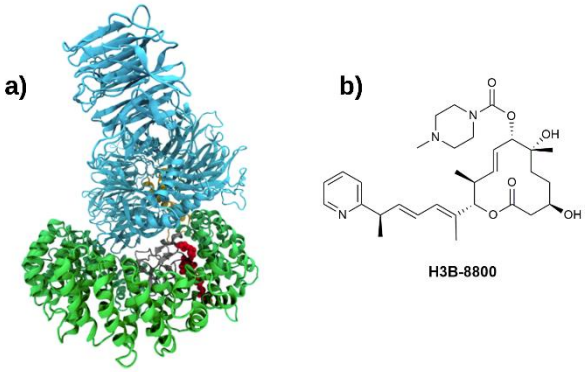

Figure 1: a) Crystal structure of the SF3b splicing factor and b) molecular structure of the splicing modulator H3B-8800.

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(-)-anaferine: an unexpected encounter in a diversity-oriented approach

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Diversity-oriented synthesis (DOS) is a promising approach in drug discovery and development process. It is aimed at generating libraries of compounds as much diversified as possible, usually starting from a common, simple precursor [1]. In this field, a DOS approach was developed in our research group, starting from the cheap and commercially available 2 piperidine ethanol (**1**). In this way a highly diversified library of piperidine-based derivatives has been accessed in the last years [2].

Recently, we were attracted by the structure of **2**, an intermediate already exploited in the synthesis of a new class of potential anticancer agents. The presence of a piperidine ring and of a 2-hydroxypropane motif seemed quite familiar, and we realized that our diversification process had led us to a known natural product, (-)-anaferine. This compound, extracted from *Withania somnifera* plant, is constituted by two piperidine rings connected by a 2-propanone bridge [3]. Therefore, it was sufficient to convert the homoallylic alcohol of **2** into the second nitrogen containing heterocycle, to complete the total synthesis of (-)-anaferine (Figure 1). Biological tests are currently in progress, to verify its neuroprotective properties, so far predicted mainly *in silico*.

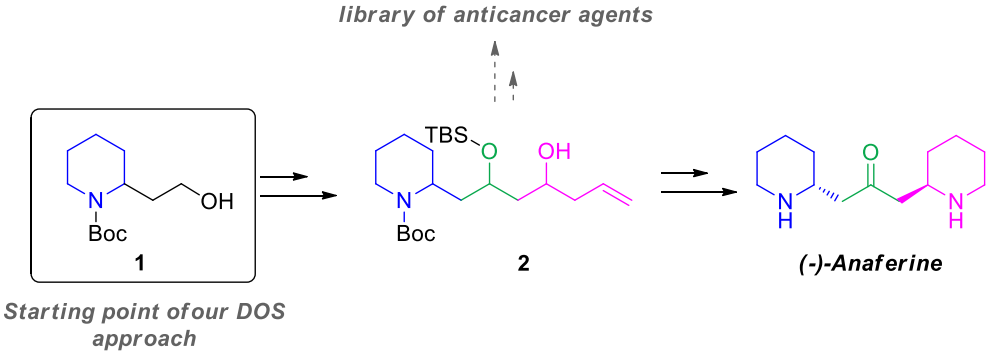

Figure 1: Schematic representation of (-)-anaferine obtainment starting from intermediate **2**.

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Inhibition of NLRP3 ATPase activity: a new strategy to fight chronic inflammatory diseases

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The inflammasomes are a family of intracellular protein complexes, acting as molecular platform for the activation of the innate immune system by cleavage of pro-inflammatory interleukins (IL)-1β, IL-18 and triggering of pyroptotic cell death. NLRP3 inflammasome is the most related to chronic activation of inflammatory processes, leading to progressive loss of tissue functions. Its activation is related with the onset and/or progression of several peripherical and central diseases. The discovery of agents able to prevent inflammasome activation is a promising therapeutic strategy to decrease chronic inflammation and disease-associated damage [1].

The NLRP3 protein possesses ATP-binding potential and intrinsic ATPase activity. Mutations in the ATP-binding region resulted in impaired IL-1β maturation. To successfully target the ATPase activity of NLRP3, we identified a benzo[d]imidazol-1-one sub-moiety as a weak inhibitor of ATPase activity. This fragment was functionalized using structural motifs present in **INF39**, a previously identified compound able to hamper ATPase activity [2]. The new hit compound **INF97** showed 10-fold improved concentration-dependent NLRP3 ATPase inhibition (IC_{50}: 17.2 μM, 15.4 – 19.2 C.L. 95%) with respect to starting fragments and inhibits LPS/ATP triggered pyroptosis. Different modulations of the hit compound allow to develop new refined bioactive compounds and to find best moieties for future development.

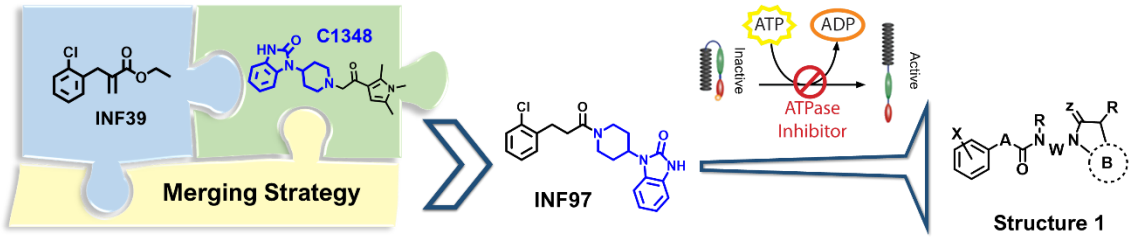

Figure 1: Strategy leading to NLRP3 inhibitor **INF97** and its derivatives

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Multi-target strategy for the identification of IDO1/L-Kyn/AhR pathway modulators

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In last years, the axis IDO1/L-Kyn/AhR has emerged as a fundamental pathway for the establishment of immune tolerance with important implications in tumor immune escape [1]. Indoleamine 2-3-dioxygenase (IDO1) is an intracellular heme-containing enzyme responsible for the first and rate limiting step of L-Tryptophan (L-Trp) degradation along the kynurenine pathway (KP). L-Trp depletion together with increased concentration of L-Kynurenine (L-Kyn) exert crucial immunosuppressive functions regulating T cells activity [2]. L-Kyn, in turn, is able to modulate Aryl hydrocarbon Receptor (AhR), a ligand activated transcription factor mediating fundamental physio-pathological effects in immune system [3].

Recently, IDO-1 inhibitors, currently being investigated in clinical trials, demonstrated the ability to induce AhR transactivation. This evidence led to formulate the hypothesis that their anticancer effects may result from enzyme inhibition, reduction of L-Kyn levels and/or direct modulation of AhR [1].

Grounding on these observations, in this work we investigated the molecular basis of multi-target interactions against AhR and IDO1. After the identification of 20 HITs targeting AhR through an integrated Artificial Intelligence (AI) and Structure Based approach, compounds were screened versus IDO1 applying MicroScale Thermophoresis (MST) technique. As a result, compound VIS8181 was identified as ligand endowed with a good affinity towards IDO1 (K_d = 0.69 ± 0.12 μM) and AhR transactivation activity (F.I. = 12% at 1μM). Hence, this compound may be employed in next hit-to-lead optimization campaigns for the design of IDO1/AhR dual modulators.

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Development and evaluation of the mechanism of action of a carnosine derivative in oxidative stress-based diseases

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Carnosine (β-alanil-L-histidine) is a multifunctional endogenous dipeptide with buffering, metal chelating, carbonyl scavenging and antioxidant properties. Promising activity of carnosine in the prevention and regression of oxidative stress-based diseases (e.g. atherosclerosis, diabetes and metabolic syndrome) have been reported in animal models [1].

The benefits of carnosine supplementation are limited in humans by its hydrolysis upon absorption, which is controlled by a specific enzyme (i.e. serum carnosinase).

Based on the pharmacological properties of carnosine, we have designed carnosinol (e.g. carnosine aminoalcohol derivative) to be as active as carnosine, but metabolically stable in humans.

Some experiments reporting mitigating effects on metabolic disorders have been already published [2].

Alike carnosine, the hypothesized mode of action of carnosinol is the deactivation of reactive carbonyl species (RCS), which under oxidative stress can accumulate in cells as by-products of lipid and sugar oxidation [3]. Carnosinol-RCS binding is therefore expected to prevent cell damages associated with RCS-induced modification of proteins or DNA.

Nevertheless, a complete view of how carnosinol exerts its effects *in vivo* and what is its metabolic fate upon absorption is far from understood.

We are therefore committed to clarify the metabolic pathways and the molecular mechanisms explaining carnosinol activity by *in vitro* and *in vivo* experiments with the support of modern analytical approaches including quantitative proteomics.

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Glycerol carbonate as an innovative alkylating agent for phenolics

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Organic carbonates (OCs) are an important class of molecules with a wide range of applications. Among OCs, glycerol carbonate (GlyC), is increasing its importance thanks to both its wide reactivity and because it is a way to valorize glycerol, the major co-product of the bio-diesel manufacture [1].

Noteworthy, we recently showed the possibility to use catechol carbonate (CC) as an alternative, extremely efficient carbonate source for the synthesis of a wide plethora of OCs, including GlyC, in mild conditions (60°C, 1h, no solvents), obtaining only catechol as coproduct [2]. Also for this reason, GlyC was tested as a pioneering alkylating agent for catechol, by only increasing the temperature from the previous step in a one-pot strategy. In this way, 2-hydroxymethyl-1,4-benzodioxane (HMB), a key intermediate for pharmaceutical industries, has been selectively synthesized for the first time (yields up to 88%), without requiring any reaction solvent or halogenated compounds, in the presence of both homogeneous ($NaOCH_3$) or heterogeneous (MgO, Na-Mordenite) basic catalysts. Moreover, a detailed mechanistic study, supported by kinetics, GC-MS, and HMBC NMR has been performed, underscoring the unique behavior of GlyC related to its multifunctional structure, in particular of the free aliphatic -OH group. The latter plays a fundamental role in obtaining the reactive carbonate intermediate responsible for the intramolecular cyclization to HMB, with only water and CO_2 as benign coproducts [3]. In a similar way, the reaction of GlyC and phenol leads to the formation of a phenoxy carbonate intermediate that can undergo to consecutive nucleophilic substitution obtaining the di-phenylglyceryl ether, the latter being elusive with the traditional synthesis with the exception of the use of epichlorohydrin. In this way, GlyC was proved to be a promising alternative alkylating agent for phenolic derivatives when a double etherification is required.

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Deep Eutectic Solvent (DES): solvent and catalyst for the Henry reaction

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The Henry reaction, also known as nitroaldol reaction, is the coupling of nitroalkane with an aldehyde or ketone to produce β-nitro alcohols, valuable synthetic intermediates of biologically active compounds, such as natural products, insecticides, fungicides, and antibiotics [1]. The Henry reaction occurs using most popular organic bases to catalysed the reaction. In this communication, we report on performing the Henry reaction by microwave using a deep eutectic solvent (DES) as catalyst and solvent media of the reaction.

DESs have emerged as an interesting class of new solvents [2]. They are a eutectic mixture of Lewis and Brönsted acids and bases, which can contain a variety of anionic and cationic species. They are usually obtained by mixing a quaternary ammonium salt (HBA) with a metal ion or a hydrogen bond donor (HBD) species. The 1:2 molar mixture of choline chloride urea, often referred to as reline, is the most representative of the class of these new solvents.

The optimisation of the Henry reaction condition (temperature, heating mode, time, DES...) permits, starting from different aromatic aldehyde, to obtain 1,3 di-nitro derivatives in quantitative yield in one step and in mild conditions [3].

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C–H bond arylations of 1,2,3-triazoles by reusable Pd/C catalyst in solvent-free conditions

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The 1,2,3-triazole ring represents a key structural motif in various applied areas, such as drug discovery, bioconjugation, and materials science. Among the known methods for the regioselective synthesis of fully substituted triazoles, the Pd-catalyzed direct arylation of the easy available 1,4-disubstituted 1,2,3-triazoles turns out to be the most general approach [1]. Only few examples of direct arylation protocols of 1,4-disubstituted 1,2,3-triazoles based on the use of more sustainable conditions have been reported in the literature [2].

In the frame of our studies on triazole-based materials as well as on Pd-catalyzed reactions for the synthesis of heteroaromatic compounds [3], we report here in the first Pd-catalyzed direct arylation protocol of 1,4-disubstituted 1,2,3-triazoles that is performed in (i) solvent-free, (ii) non-anhydrous conditions, (iii) without exclusion of air, and (iv) in the presence of a reusable catalyst (Fig. 1).

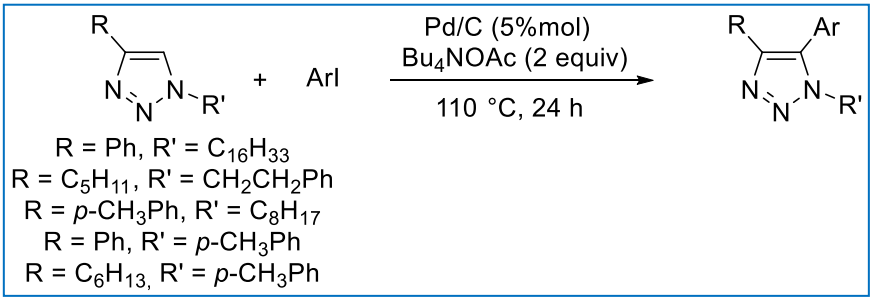

Figure 1

Then, with the aim of making the reaction conditions more sustainable, we evaluated the possibility of using only tetra-n-butylammonium acetate (Bu_4NOAc) as the base and the reaction medium, in the absence of any other additive. Using Pd/C (5 mol %) as the catalyst, we examined the role of the halogen, reaction temperature and catalyst loading.

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About the kinetics of pelargonic acid esterification with 2-ethylhexanol

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Esters are generally used as plasticizers, solvents, flavor chemicals and as precursors for pharmaceuticals, agrochemicals and other fine chemicals.

Esterification of carboxylic acids with alcohols is commonly catalyzed using soluble mineral acids. These catalysts are characterized by high activity, but they show several negative aspects, such as: corrosive nature; the occurrence of side reactions; not easily separated from the reaction mixture. The commercial cation-exchange resins represent an important alternative, as they can be easily removed from the liquid mixture after the reaction, they are not corrosive to the equipment and the side reactions can be almost completely suppressed [1]. Among carboxylic acids, pelargonic acid has a great importance as it can be obtained from vegetable oils. Benessere et al. [2] demonstrated the possibility of using pelargonic acid esters as solvents for bio–based varnishes in combination with a commercial resin. The obtained solvents showed an excellent ability to disperse resins derived from rosin in unprecedented mass percentage, in shorter time and at lower temperature with respect to commonly used solvents.

In the present work, a kinetic study was conducted using both homogeneous (H_2SO_4) and a heterogeneous catalyst (Amberlite IR120), using 2-ethyl-1-hexanol as alcohol in a batch reactor.

Experiments were performed by varying different operative conditions (i.e. stirring rate, temperature, catalyst load and reactants ratio). The collected experimental data were interpreted with reliable models taking into account phenomena involved in the reaction network.

Acknowledgements: Authors wish to thank European Union (FSE, PON Ricerca e Innovazione 2014-2020, Azione I.1 "Dottorati Innovativi con caratterizzazione Industriale") for funding a Ph.D. grant to Francesco Taddeo.

[1] M. Sharma, A.P. Toor, and R.K. Wanchoo, *Int. J. Chem. React. Eng.* **12** (2014) 451-463.
[2] V. Benessere, M.E. Cucciolito, A. De Santis, M. Di Serio, R. Esposito, M. Melchiorre, F. Nugnes, L. Paduano, and F. Ruffo, *J. Am. Oil Chem. Soc.* **96** (2019) 443-451.

(2-Quinolyl)phenylmethanol: new applications as organocatalyst?

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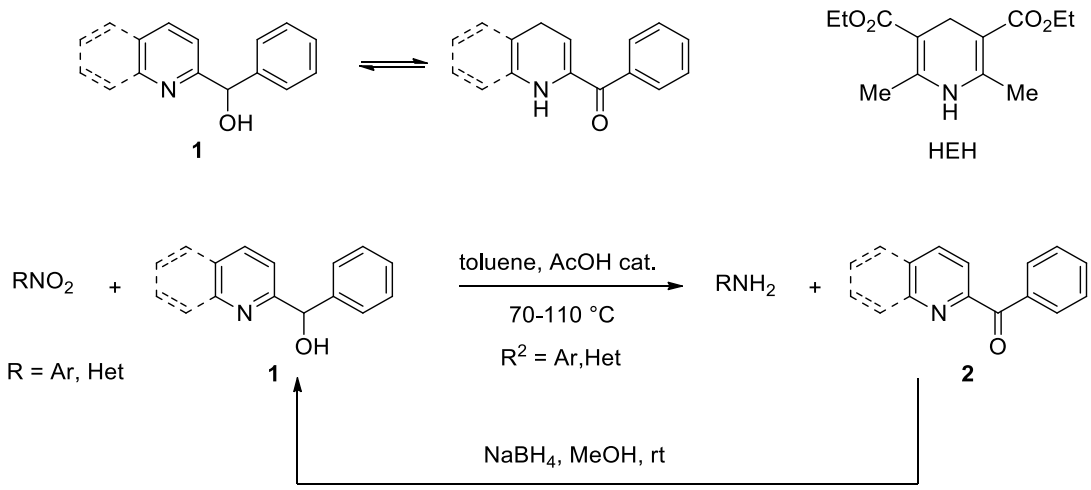
The weak acidity of the 'picoline type' hydrogen atom in 2-pyridyl- and 2-quinolyl-methanols **1** can allow tautomeric equilibria involving 1,4-dihydropyridine species. This behaviour is responsible for their surprising reactivity as hydrogen donor, mimetic of Hantzsch ester (HEH), allowing the metal-free reduction of aromatic and heteroaromatic nitro compounds and imines to the corresponding amines.[1] Moreover, 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.



Scheme 1: Metal-free reduction of RNO_2 with compounds **1**.

Recently, (2-quinolyl)phenylmethanol has been successfully applied as organocatalyst in the reduction of nitro compounds to the corresponding amines, in different reaction conditions.

Mechanistic aspects as well as synthetic applications of these new reactions will be properly discussed [1-3].

[1] D. Giomi, R. Alfini, and A. Brandi, *Tetrahedron Lett.* **49** (2008) 6977-6979.
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Exploiting the Nitrogen nucleophilicity in interrupted Ugi reactions: from indoles to imidazo-pyrazines

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Multicomponent Reactions (MCRs) represent nowadays straightforward methodologies for both medicinal and organic chemists thanks to their convergent nature, atom economy, and efficiency. Recently, we identified a novel interrupted Ugi reaction starting from amphoteric sulfonylamino-arylaldehyde secondary amine and an isocyanide providing *N*-alkyl- 2,3-diaminoindoles [1]. Surprisingly, the use of pyrrolidine as the secondary amine gave an unexpected organocatalytic triple domino process, switching from *N*-alkyl-2,3-diaminoindoles to 2-iminoisatins [2]. Reaction conditions were hence optimized by performing the reaction on water, while irradiating with an ultrasound bath, in accordance with the green chemistry principles. We explored also a novel one-pot multicomponent reaction starting from imidazole *N*-substituted methanamines, aldehydes and isocyanides to give imidazo-pyrazines derivatives [3].

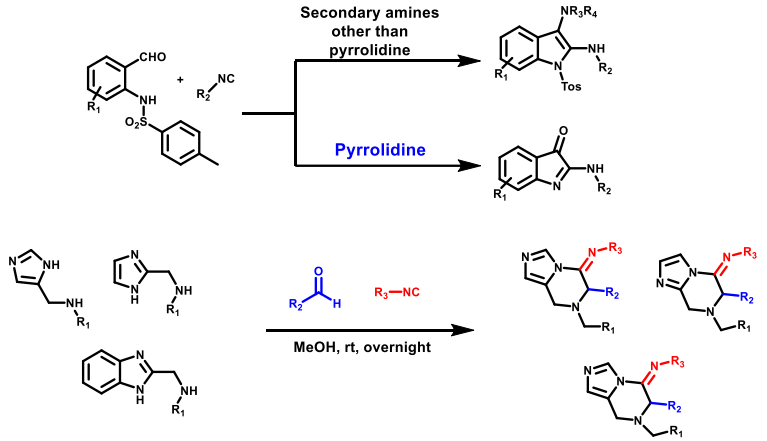

Figure 1: *N*-alkyl-2,3-diaminoindoles, 2-iminoisatins and imidazo-pyrazines

[1] M. Giustiniano, S. Pelliccia, L. Sangaletti, F. Meneghetti, J. Amato, E. Novellino, and G.C. Tron, *Tetrahedron Lett.* **58** (2017) 4264-4268.
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Synthesis of novel chiral ionic organic compounds from Isohexides as potential chiral selectors for Enantioselective Electroanalysis

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Enantioselective electroanalysis (*Ee*) is an analytic technique that, in principle, is able to discern between enantiomers and thus provide qualitative and quantitative information without preliminary purifications.
Nowadays, *Ee* is still regarded as an immature technique, given the lack of chiral selectors of general use and of practical protocols.

Ionic organic compounds are very useful media for electrochemical processes as they can act both as solvents and electrolytes, and organize themselves in well-defined structures at the *electrode-solution interface* [1,2].

In this work, starting from Isomannide (**1**) and Isosorbide (**2**), two inexpensive enantiopure compounds of natural origin, we synthesized a library of new chiral ionic organic compounds through the use of cheap reactants, simple reactions and avoiding tedious purification steps. The leading idea of the project was the use of simple and cheap reactants to enhance intermolecular interactions and to have mono- or di-cationic organic compounds. 6-Quinoline carboxylic acid (**3**) and 6-Hydroxy 2-Naftoic Acid (**4**)were selected to introduce on the sugar-based frame an ester group (*H*-bonds acceptor), an aromatic group (electron-rich or electron-poor for complementary *π-π* interactions) and to have an additional functional group that can be further derivatized to introduce the ionic motif.

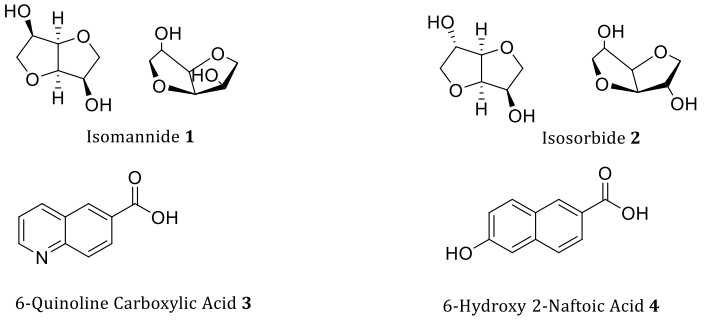

Figure 1: Starting materials used for the synthesis of chiral ionic organic compounds.

[1] S. Arnaboldi, M. Magni, and P. R. Mussini, *Curr. Opin. Electrochem.* **8** (2018) 60-72.
[2] S. Rizzo, S. Arnaboldi, R. Cirilli, A. Gennaro, A.A. Isse, F. Sannicolò, and P.R. Mussini, *Electrochem. Commun.* **89** (2018) 57-61.
[3] J.L. Anderson and D.W. Armstrong, *Anal. Chem.* **75** (2003) 4851-4858.

Enantioselective conjugate addition of stabilized arylzinc halides to enones

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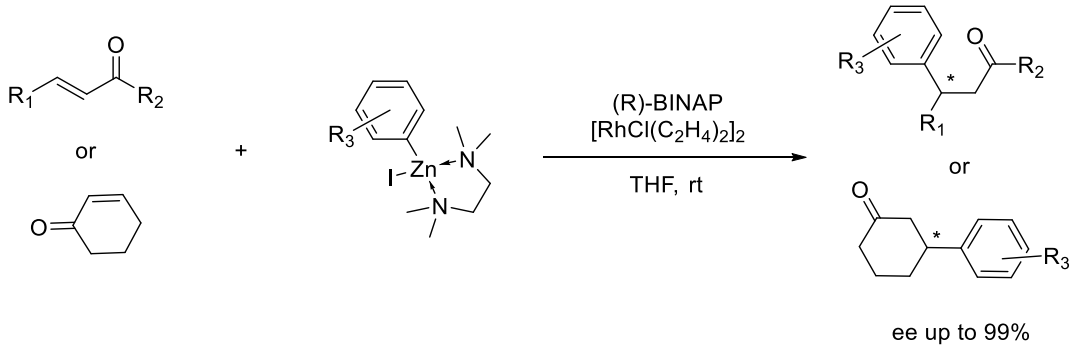
The enantioselective addition of organometallic compounds is particularly important in the field of the total synthesis of natural products. Several organometallics have been used for this purpose but, except for some seminal works, the enantioselective addition of organozinc halides to enones remains undeveloped with respect to the reaction of other organometallics like, for example, organoboron. A few examples of this chemistry with organozinc halides have been reported and, in all cases, the organometallics used in the addition have been made by transmetalation from highly reactive organolithium species. This latter aspect limits the application of the reaction from the point of view of functional group tolerance, environmental friendliness, and general usability. We developed an enantioselective conjugate addition protocol of organozinc halides to enones, both cyclic and linear.



Scheme 1: Arylzinc asymmetric conjugate addition to enones.

The organozinc reagents employed in our protocol have been made by direct insertion of zinc metal into organic halides and have been stabilized with TMEDA to improve the functional group tolerance [1]. Yields and enantiomeric excess are good to excellent and the protocol has general applicability.

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Structure/property correlation in the heterogeneously catalyzed esterification of levulinic acid

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Levulinic acid (LA) is one of the most important platform chemicals as it is a versatile building block for a variety of high value-added agrochemicals, fine chemicals and pharmaceutical intermediates. Catalytic esterification of LA with ethanol leads to ethyl levulinate (EL) which can be used as fragrances, flavouring agents, as well as fuel additives. [1]

Esterification reactions are usually carried out in liquid phase using mineral acids as homogeneous catalysts. However, heterogeneous catalysts are preferable because they are easily to separate from the reaction mixture, recovered and reused. Different catalysts have been already screened for the esterification of LA with ethanol (i.e. ion exchange resins, zeolites, sulfated metal oxides, silica) [1,2]. The cation exchange resin Amberlyst-15 shows good activity, due to the acidity provided by functional -SO_3H groups. Figure 1 shows the activity of Amberlyst-15 in the conversion of levulinic acid compared to the performance of sulfated metal oxides.

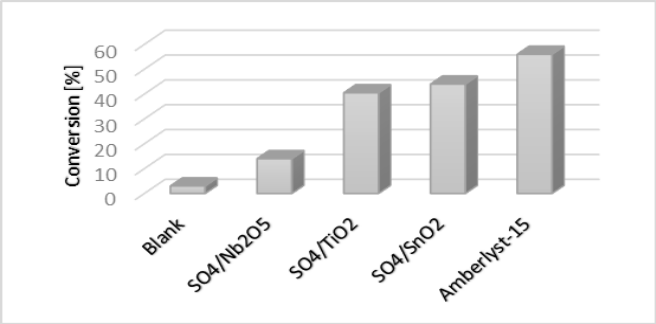

Figure 1. Catalytic screening for levulinic acid esterification.[2]

Starting from the results obtained for ethyl levulinate, the aim of this work was to evaluate and compare the activities of different commercial sulfonic resins (Amberlyst-15 d_p=600μm, Amberlyst-15 d_p=300μm, Amberlite IR-120 and Dowex 50Wx8) in the esterification of levulinic acid with different alcohols, chosen varying molecular weight and steric hindrance.

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Direct and chemoselective synthesis of α,α-difluoromethylketones under transfer of difluoromethyl (CHF_2) unit

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Among the fluorinated compounds, difluoromethylketones play a leading role in synthetic chemistry because of the capability of this moiety to mimic important functional groups (*e.g.* hydroxamic acid) and that of the difluoromethyl group to act as an isoster of the carbinol group (CH_2OH), showing a remarkable hydrogen donor characteristic [1]. The CHF_2 group is weakly acidic and exhibits a natural tendency to make strong H-bonding interactions and, as a consequence, difluoromethylketones act as ideal candidates for the design of pharmaceuticals. Various compounds containing the difluoromethylketone moiety are in development for therapies. Therefore, the need to find new synthetic ways to obtain such structures rapidly and smoothly is becoming crucial.

In line with Pace's group studies on nucleophilic fluoromethylations [2,3], herein we disclose a highly effective difluoromethylation – under nucleophilic regime – for the one-pot, straightforward formal transfer of a CHF_2 motif into a carbon electrophile, and a direct access to α,α-difluoromethylketones.

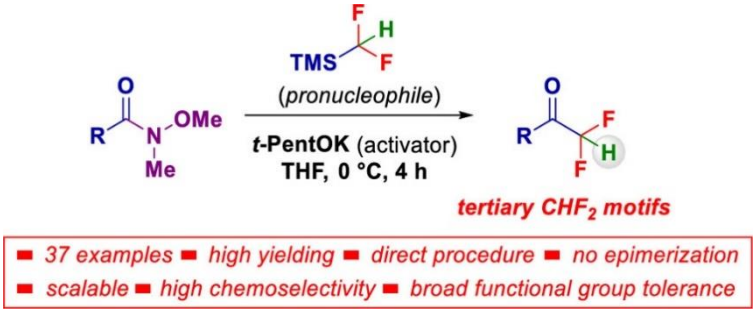

Figure 1: Reaction conditions.

[1] Y. Zhao, W. Huang, J. Zheng, and J. Hu, *Org. Lett.* **13** (2011) 5342-5345.
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Deep eutectic solvents as active reaction media for the aza-Michael addition of amines to 2-vinylpyridine

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The aza-Michael addition is a widely used synthetic reaction for the formation of C-N bonds. In particular, the addition of nitrogen nucleophiles to Michael acceptors is used for the realization of pharmaceutically relevant compounds [1]. Most relevant protocols in literature rely both on the use of Volatile Organic Compounds (VOCs) as solvents and on Brønsted or Lewis acids as catalysts.

In the recent years, the scientific community have been proposing alternatives to VOCs, in order to decrease the environmental impact of these compounds. Deep Eutectic Solvents (DESs) have emerged as a new promising class of green liquids thanks to their favourable physical and chemical properties [2].

Here, we report our investigations on the use of DESs for the conjugate addition of various amines to 2-vinylpyridine, using differently structured DESs as both reaction media and catalysts. Since these novel liquids are formed by inter- and intra-molecular interactions between Brønsted or Lewis acids and bases, this approach avoided the use of further addition of an acid catalyst.

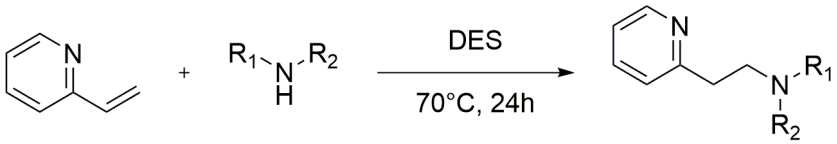

Figure 1: General reaction scheme for the addition of nitrogen nucleophiles to 2-vinylpyridine.

[1] C. Le Guen, M.-L. Tran Do, A. Chardon, C. Lebargy, J.-F. Lohier, E. Pfund, and T. Lequeux, *J. Org. Chem*. **81** (2016) 6714-6720.
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Sustainable leather treatment: a promise of nanomaterials as fireproofing auxiliaries

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The growing awareness on the environmental issues imposes the search of sustainable alternatives to the substances contributing to pollution. Nowadays, the main components of fire-resistance agents used industrially are brominated flame-retardants (BFR's); these substances whether in use or waste, contaminate air, soil, and water [1]. The increased restriction in their use in new consumer goods led to thinking about sustainable, non-toxic, and safer replacements.

The use of nanomaterials as eco-friendly alternative has been widely discussed in literature in recent years, in particular, for their eco-sustainability and for the lower cost in the production [2-3].

In this respect, the aim of the current work is the development of nanomaterials such as nano-hydroxyapatites (nano-HA), nano-SiO_2 and nano-TiO_2 as either inorganic fillers allowing to decrease the amount of synthetic tannins in leather treatment and additives imparting self-cleaning and/or fire-resistance properties, a mandatory requirement, in particular, for automotive leather.

The detailed analysis of the structural (HR-TEM, XRD) and surface features (FTIR, SSA_{BET}, Near-IR) of the nanomaterials was carried out; the effect on the properties of leather, after application of nanoparticles, was investigated using different techniques such as micro-DSC and FTIR-ATR. Moreover, promising results obtained from a preliminary life-cycle assessment of the production of nano-HA at lab-scale give hope for the sustainability of the process at the industrial level.

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[3] Y. Jiang, J. Li, B. Li, H. Liu, Z. Li, and L. Li, *Polym. Degrad. Stabil.* **115** (2015) 110-116.

Bioderived carbonaceous filler for conductive plastic materials production

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Conductive composites represent a very interesting filed due to the many applications as sensors [1]. The main drawback of high performances carbon fillers (*i.e.* CNT, graphene) is represented by their high cost. Recently, Giorcelli et al. [2] showed that pyrolytic solid residue of biomasses, known as biochar, could relevantly improved the conductivity of an epoxy matrix.

In this research, we produced biochar by coffee and tea waste and use it as filler in both thermoset and thermoplastic composite with the aim to increase their electrical properties.

The biochar and biochar based composite electrical conductivity were studied in function of applied pressure and compared with carbon black and carbon black composite. The applied pressure has the aim to investigate the behaviour of filler in powder or dispersed in composite in function of compression. Experimental results clearly showed the better performances of biochar-based composites compared with those produced using carbon black. Composite mechanical properties were tested and they are generally improved respect to neat epoxy resin and poly(propylene) matrix.

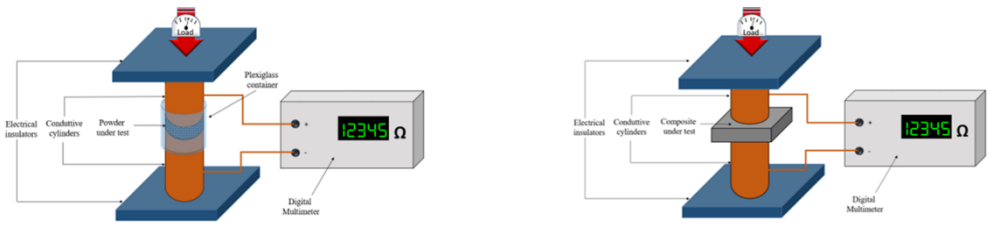

Figure 1: Experimental set-up for the electrical measurement under pressure

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Exploring the structure and dynamics of a novel proton conducting system Aminotris(methylenephosphonic acid) (ATMP)

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An analysis of the complex proton transfer processes in specific cholinium-based, protic ionic liquids has been carried out by us over the last years [1-2]. These systems represent an intriguing and potentially conductive, highly ionized medium. However, the natural tendency of the aminoacid to form stable zwitterionic anions in the bulk liquid limits the practical applicability of these substances. Since these initial explorations, we have shifted our focus to the investigation of a novel system based on Aminotris(methylenephosphonic acid) (ATMP) [3]. The ensuing ionic liquid made of 1, Ethyl-3-methylimidazole (cation) and ATMP (anion) has been explored using ab-initio computation and semi-empirical methods to understand its features. The presence of three phosphoric acidic side chains in ATMP makes this a unique species which can form a vast number of intricate hydrogen bonding interactions and act as a proton donor.

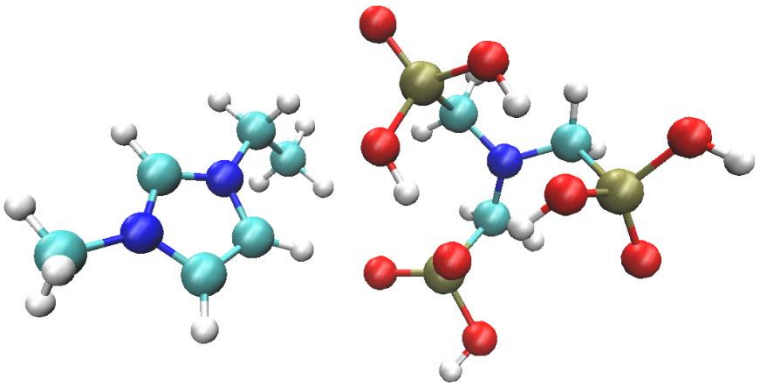

Figure 1: 1, Ethyl-3-methylimidazole (left) and ATMP (right).

Through molecular dynamic simulations we have identified that cooperative hydrogen bonding facilitates proton mobility between the anions altering the charge distribution of the system. This may be a suitable prototype for dry fast proton conduction.

[1] A. Le Donne, H. Adenusi, F. Porcelli, and E. Bodo, *ACS Omega*. **3** (2018) 10589-10600.
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Supramolecular hydrogels based on L-DOPA for $CaCO_3$ crystals growth

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Low-molecular-weight gelators (LMWG) are small compounds with a specific stereochemistry able to self-assemble thanks to weak interactions [1]. It is possible to modify their structure obtaining materials with different properties and a wide range of applications.

The gelation process starts with a trigger and takes place through the slow formation of fibers, which entrap the solvent and all the species inside of it. In this context, hydrogels have relevance in biomineralization, process by which organisms deposit mineral phases in a highly viscous environment, producing for example bones, teeth and mollusc shells [2].

In this work, $CaCO_3$ crystals were grown in hydrogels made with the gelator (S)-N-tert-butoxycarbonyl-3,4-bis(benzyloxy)-phenylalanine [Boc-L-DOPA$(OBn)_2$-OH]. Four hydrogels were prepared varying the base (NaOH or Na_2CO_3), and the trigger (glucono-δ-Lactone or $CaCl_2$): in presence of Na_2CO_3 and $CaCl_2$, the production of $CaCO_3$ crystals was observed.

The viscoelastic behaviour of the hydrogels was analysed through rheological experiments and the corresponding xerogels were analysed by scanning electron microscopy (SEM) and synchrotron X-ray diffraction analysis (XRD). The fibrous structure of the hydrogels has the capability to confine the space of mineralization, to act as a source of Ca^{2+} ions and to preserve its organization once the mineral formation has occurred, confirming the importance of these materials for biomineralization studies.

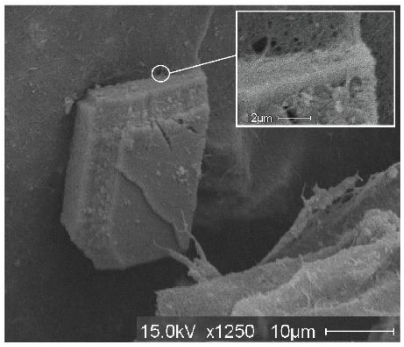

Figure 1: SEM image of a freeze-dried hydrogel with $CaCO_3$ crystals.

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Covalently modified titanium surface trough a combined click chemistry and Atom Transfer Radical Polymerization strategy

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Titanium and its alloys have been extensively used in biomedical devices and components because of their high strength, low density and good inertness to biological tissues, making them very suitable and biocompatible materials. In the continuous search for improving biological and biomedical performance of materials, surface modification - able to enhance interaction of the metal implant surfaces with surrounding tissue while retaining the desirable bulk properties of the materials - is a very attractive tool [1]. In this framework, covalent binding of well-defined polymer allows for precise control over interfacial properties such as wettability, corrosion resistance and adhesion while ensuring long term stability.

Herein the antibacterial and antifouling Poly[2-(Dimethylamino)ethyl Methacrylate] (PDMAEMA) [2] was used to prepare titanium functionalized surfaces. Atom Transfer Radical Polymerization (ATRP) synthesis of PDMAEMA following a previously optimized protocol [3] led to very low polydisperse polymer with "active" chain ends without the need of protection/deprotection procedures. Various characterization techniques, including contact angle measurements and attenuated total reflection infrared spectroscopy were used to ascertain the successful grafting. Polymer thickness and changes in surface hydrophilicity/hydrophobicity, as well as corrosion resistance in physiological conditions as a result of surface graft polymerization were also characterized.

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Effect of organic complexant and UV irradiation on the properties of amorphous TiO_2-based thin films

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Titanium oxide films are employed in sensors, electrochromic devices, solar cells, and as self-cleaning, antimicrobial, protective or anti-reflective layers. Since their production through wet chemical methods requires high temperature treatment, the development of a simple, economic and low-temperature synthesis procedure is an important challenge [1]. Moreover, the knowledge on the properties of amorphous TiO_2 films and on the effect of their functionalization by organic compounds is still insufficient.

We describe a hydrolytic sol-gel procedure coupled with spin coating to prepare TiO_2-based hybrid (inorganic-organic) thin films containing different complexing ligands in their structure (acetylacetone, dibenzoylmethane, citric acid or diethanolamine). We explored the conditions to achieve long-term stability of the precursor sol for each system. The amorphous films dried at 80 °C were studied by microscopic techniques, spectroscopy (FT-IR, UV-vis-NIR, ellipsometry) and resistivity measurements. The nature of the ligand coordinated to Ti and the synthesis process variables determine the thickness, porosity, roughness and hydrophilicity of the hybrid coatings. The electrical conductivity of the films is influenced by the organic complexant, it increases with film thickness and decreases after a low temperature annealing (150 °C) [2].

We investigated the modifications caused by the exposure of the hybrid films to UV light. A short UV irradiation (e.g. 15 min) has a strong impact on their microstructure and wettability, inducing thinning and high surface hydrophilicity. Notably, it also promotes a striking increase in their electrical conductivity (at least one order of magnitude). The changes in the film properties are likely related to the photoinduced decomposition of the organic ligands and concurrent densification; diketones seem to be the most resistant to the irradiation, allowing to retain a hybrid composition [2].

The possibility to tune the structural, morphological and electrical features of spin coated TiO_2 films may turn useful in several applications.

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TiO_2 nanoparticles deposition onto different substrates

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TiO_2 nanoparticles (NPs) with their excellent photocatalytic performance are among the most investigated materials for environmental clean-up applications. The immobilization of NPs is an essential requirement for real application, due to safety and technological applicability [1]. In this work was investigates the impact on photoactivity of two different deposition techniques designed to be suited for a scalable production TiO_2 NPs coating onto different possible substrates, namely, the doctor blade technique and a purposely developed dip coating method, here defined as inverted dip coating. Firstly, the impact of deposition method was studied using a glass substrate, successively the promising deposition technique was used onto unconventional substrate with more active site like stainless steel mesh. To this end, a batch of TiO_2 NPs was synthesized by slightly modifying a reported approach, specifically selected for its scalability [2]. The obtained product was characterized by X-ray diffraction analysis, TEM and SEM microscopy and BET analysis. The photoactivity of the suspended catalysts was investigated following the decolouration of methylene blue (MB) acquos solution containing catalyst under UV irradiation according to ISO 10678:2010. Successively, TiO_2 NPs were deposited by using the two proposed approaches onto glass slides. The TiO_2 NPs were then deposited on stainless steel mesh by using isopropanol suspensions at 6,5% and 13% TiO_2 NPs content. Also, the films deposited onto the stainless steel meshes were thoroughly investigated by SEM microscopy and by measuring their photoactivity. The experimental results revealed that, TiO_2 NPs based coating prepared from the 13% TiO_2 NPs suspension demonstrated to be the most effective in MB photodegradation, under the applied experimental conditions.

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Tuning Pt(II)-based donor-acceptor systems by ligand design and its influence on reactivity

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A novel generation of unsymmetric platinum donor acceptor complexes[1,2] [(pimp)Pt(Q^{2-})] is presented in this work. The focus of the present work lies on the systematic variation of the catecholate ligand in conjunction with the introduction of the novel phenyliminomethylpyridine (pimp) ligand for such systems. The electronic properties of the complexes in various oxidation states have been extensively characterized by means of cyclic voltammetry, UV/Vis-NIR and EPR spectroelectrochemistry. Special focus has been put on the investigation of the complexes featuring diamidosulfonyl-substituted ligands, which show redox-induced linkage isomerism upon oxidation.

(TD-)DFT as well as electron flux density analysis has been employed to rationalize the optical spectra of the complexes and aspects of their reactivity. Compound **1** (see Fig. 1 left) was shown to be an efficient photosensitizer for molecular oxygen, which was subsequently employed in photochemical cross dehydrogenative coupling reactions. Our results thus display new avenues for Pt-based donor-acceptor systems, including their role as photocatalysts and the possibility to introduce redox-induced linkage isomerism.

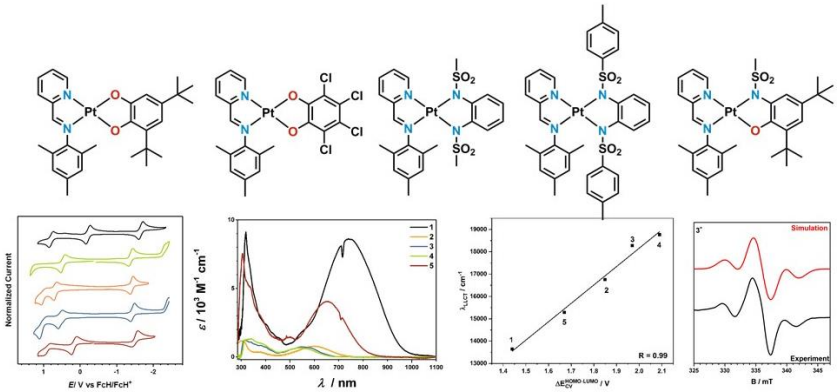

Figure 1: Investigated Pt(II) complexes and characterization.

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Role of polarization and Pauli repulsion effects in non-linear properties of solvated systems

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The response and spectroscopic properties of a molecular system are strongly affected by the presence of the environment. The most general approach to account for such effects is to resort to focused models, where the molecular system is described at the Quantum Mechanical (QM) level, whereas the environment is treated classically, within the Molecular Mechanics (MM) framework [1].

Such models are deeply based on the assumption that electrostatic energy terms dominate the molecular system/environment interactions, therefore non-electrostatic contributions between the QM and MM portions are only roughly modeled. However, non-electrostatic contributions are crucial to get a physically consistent description of any embedded system, also in the case of target/environment interactions dominated by electrostatics.

In this study, it is presented an application of our recently developed polarizable QM/MM solvation model based on fluctuating charges (FQ) [2] and dipoles (FQFμ) [3], enriched by solute-solvent repulsion effects to the calculation of polarizabilities and hyperpolarizabilities of organic molecules dissolved in water. By using linear and non-linear response properties as a diagnostic, we were able to dissect the magnitude and role of each component of the solvation phenomenon as it applies to the set of studied systems.

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Decomposing the forces driving the collagen triple helix wrapping

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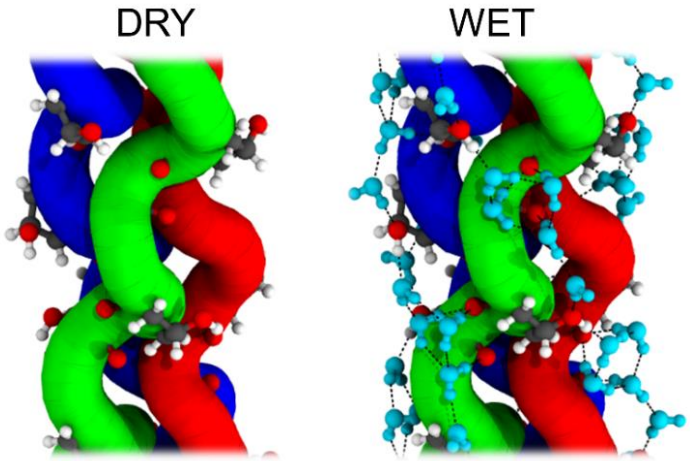
Collagen is the most abundant protein family in the animal kingdom [1]. The structural motif which identifies this type of proteins is the so-called collagen triple helix, see Figure 1. Depending on the amino acidic sequence, collagen has different helical geometries [2]. They vary for small details at the atomic scale which can have large impact on the large-scale. Thanks to accurate hybrid DFT simulations on reliable collagen models, [3] we shed some light on the forces leading the collagen protein to have a specific helical pattern. We demonstrate that inter-strands interactions and solvation effects stabilizes compact helices. Conversely, more elongated helices have more relaxed geometries and they are stabilized by entropic effects.

Figure 1: Dry and wet simplified collagen models.



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Efficient Prediction of Coherent Long-Distance Charge Transport in DNA

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Since its discovery, the ability of singly ionized DNA to provide long-range hole transport (HT) has attracted considerable interest. Apart from the biochemical implications connected with the oxidative damage of nucleic acids, long-range HT makes DNA a potentially well-suited material for nanoelectronics, either by exploiting its self-assembling properties or by using it as the active component in nanocircuits [1], hopefully leading to biocompatible and biodegradable devices.

Herein, we propose a multistep mechanism, in which transient and enduring electronic resonances induce charge transport and solvent relaxation stabilizes the hole transfer products [2]. We show that this mechanism leads to results in excellent agreement with the yields of oxidative damage observed in double-stranded DNA oligomers consisting of two guanines separated by adenine–thymine $(A:T)_n$ bridges of various lengths [3], for both the short- and the long-distance regime (Fig. 1).

Our data are also able to reconcile conflicting experimental results [3] from different groups, shedding light on different facets which characterize charge transport in DNA.

These results are of great importance for the use of DNA in organic electronics, since they provide significant guidelines for the design of novel DNA sequences to be employed in more efficient devices.

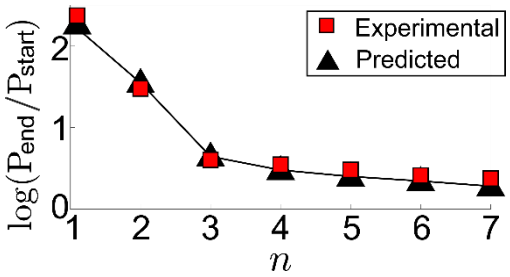

Figure 1: Predicted and experimental yield ratios for the HT in $G(T)_nG$ as a function of the number of T bases.

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Challenges of biomass: valorization of the oil-seed pressing cakes

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Agro-industrial activities result in large amounts of liquid and solid wastes that can be used as raw materials to obtain different products of industrial interest. Among the most common residues available are cakes and sharps from oilseeds treatment, corn steep liquor, and beer waste. These residues are often not fully valorized, even though most of them show good prospectives for several biotechnological applications, mainly because of their low cost, accessibility, and chemical and nutritional composition. Therefore, the use of these agricultural residues could allow the implementation of a sustainable cycle [1].

Oilseed cakes are rich in proteins (up to 35%), in triglycerides of fatty acids and free fatty acids (up to 10%). Therefore, the development of methods for the isolation of these two classes of compounds is particularly interesting from the point of view of their further (bio)catalyzed transformations.

The aim of my research is either to explore new and sustainable extraction methods of lipidic and proteic materials and to develop (bio)catalyzed protocols for the conversion of these intermediates to higher-added value compounds.

Here, as preliminary results, the characterization of the biomasses from Flax, Camelina *sativa*, and Sunflower with different techniques will be shown in order to have an overall view of the complex composition of these raw materials.

In addition, the enzymatic or chemical conversion of the triglycerides into the corresponding fatty acids or esters will be discussed, highlighting the best results obtained and the critical points of the different procedures.

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Model compounds offer insights on the photodegradation mechanisms of complex natural mixtures: the case of dissolved organic sulfur

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Dissolved organic matter (DOM) is a complex mixture thousands of different compounds including proteins, sugars, lignin, cellulose and other aromatic and aliphatic molecules deriving from biological activities or from the degradation of dead plants and animals. DOM is ubiquitous in rivers, lakes, oceans, and in atmospheric aerosols. Studying and understanding the transport and fate of DOM is important to constrain models of biogeochemical cycles, and to be able to predict the fate of anthropogenic pollutants in the natural environment. However, due to the extreme chemical complexity, knowledge on mechanisms of biotic and abiotic DOM transformations are very scarce.

Using as a case study the photodegradation of dissolved organic sulfur (i.e., the fraction of DOM composed of molecules with at least one S atom) [1], we showed that the use of single-molecule model compounds offers a valid approach to study degradation mechanisms of complex organic mixtures. The photodegradation of cysteine sulfinic acid was investigated via steady-state photodegradation experiments under well-defined conditions that allowed to isolate reaction pathways. Using kinetic analyses and knowledge from the available biochemistry literature, we reconstructed the complete photodegradation pathway, allowing to identify sub-reactions that are independent from the nature of the parent compound, and are therefore valid also for mixtures of unknown composition such as DOM.

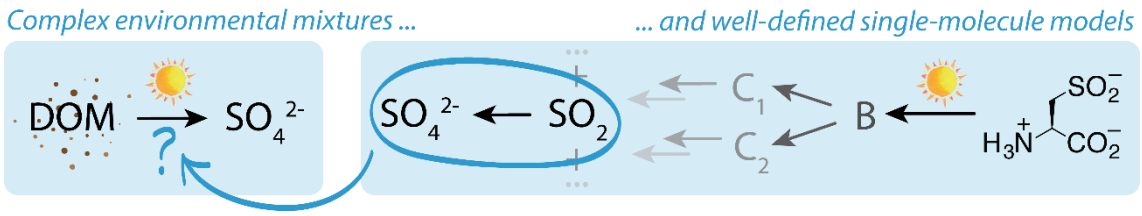

Figure 1: Simple single-molecule model compounds provide insights on the (photo)degradation mechanism of complex chemical mixtures such as DOM.

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Silk fibroin from *Bombyx mori* cocoons: chemical approaches for tunable hydrophobic bioderived materials

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Bombyx mori Silk Fibroin (SF) represents one of the most interesting biopolymers due to its biocompatibility and exceptional mechanical properties and has been elected as one of the most promising biomaterials with applications in biomedical and optical fields [1]. SF is mainly composed by Gly, Ala, Ser and Tyr, whose concentrations are 45.9%, 30.3%, 12.1% and 5.3% in total weight, respectively. Through chemical modifications, SF can be tailored with a large variety of compounds in order to induce peculiar chemical-physical properties to the whole material. Tyr and Ser are the most studied residues for chemical functionalization due to their relatively high abundance and modification easiness [2]. Moreover, these aminoacids are homogeneously located throughout the SF backbone, thus allowing a chemical modification as homogeneous as possible with a certain order and repeatability. One remarkable feature required in bioderived materials is often the modulable hydrophobicity, in order to tune the material durability in aqueous biological media. Moreover, surface polarity plays a key role in specific cell adherence and proliferation and controlling the membrane uptake [3]. A systematic chemical approach is given, exploiting both liquid phase and solid phase SF chemistry, thus creating a new class of bioderived materials with tunable hydrophobic behavior.

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Technology meets tradition: photocatalysts development for self-cleaning Venetian *marmorino*

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Marmorino is a plaster traditionally used in Venice since the 16th century, characterized by the addition of marble powder. The pollution due to human activities can afford to unwanted dirty surface deposits, thus damaging the cultural heritage. In the present work, some oxide-based photocatalysts, namely titania (TiO_2) and zinc oxide (ZnO), were added to *marmorino* as both top coating and within the mortar itself. Two top-coating fining techniques usually used for *marmorino* were also assessed: lime water and Aleppo soap. Methylene blue (MB) was selected as pollutant model molecule, it was applied on the top of the finished *marmorino*, and the self-cleaning properties were measured by colorimetry [1], upon irradiation with light. Despite both TiO_2 and ZnO as top-coating were able to discolor MB, upon introduction within *marmorino* layer, only ZnO was observed to work. X-ray diffraction (XRD) performed on modified *marmorino*, displayed a new phase, namely zinc calcium hydroxide, suggesting that it still could works as photocatalyst. Finally, the fining top-coating techniques had also a huge impact on the self-cleaning properties: while lime water basically kills the performances, Aleppo soap exhibited a huge improvement, even without a photocatalyst. Inductive coupled plasma (ICP) analyses and liquid-phase photocatalytic reactions as check tests, suggested that complexes of metallic ions (Fe and Cu) within the soap, play a crucial role in MB removal, especially if coupled with a photocatalyst. Concluding, we developed a modified high-tech *marmorino*, able to efficiently remove dirty deposit, without affecting its aesthetic properties.

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Synthesis of bio-based ionic liquids for sustainable applications

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Ionic liquids (ILs) are organic salts, liquid at room temperature or below 100 °C, composed by an organic cation (eg imidazolium, ammonium or phosphonium) and an organic or an inorganic anion. Due to their unique physicochemical properties, amongst which negligible vapor pressure, low flammability, high ionic and thermal conductivity, wide electrochemical potential window, excellent thermal and chemical stability as well as remarkable solvent capability, in the last two decades ILs found use in a wide range of applications which span for instance from alternative reaction media for organic reactions, to materials science and biological science.

During the last ten years, questions related to the real green character and even sustainability of ILs have been posed. Therefore, a recent trend in the ILs field is to select more carefully the constituting ions looking with increasing interest to natural and bio-based options [1]. Replacement of petrol-derived ions with natural or bio-based ones, could represent a way to address both issues by reducing ILs toxicity and enhancing their biodegradability.

Figure 1: Potential applications of prepared bio-based ionic liquids and.

Here we present our results in the preparation of ILs and protic ILs comprised of ions with natural origins (eg fatty acids, terpenoids, levulinic acid) [2,3].

Characterization of the obtained ILs as well as potential fields of applications explored thus far will be presented (Figure 1).

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Catalytic systems for the selective transformation of levulinic acid to pentanediols

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Carbon dioxide emission can be reduced using renewable resources such as plant biomass as a carbon-neutral feedstock for commodity chemicals [1]. Levulinic acid (LA) is a useful C_5 resource from lignocellulose. Its catalytic transformations into highly valuable chemicals such as γ-valerolactone (GVL) is quite easily obtained; however, there are few catalytic systems for its further transformation to pentanediols, even when drastic reaction conditions are used [2]. Mo and Pt already showed promising results in this reaction [3]. This work wants to investigate the role of the Mo precursor (Na_2MoO_4 or $(NH_4)_6Mo_7O_{24}$) and the influence of thermal treatments of Pt-Mo catalytic systems for LA hydrogenation to pentanediols. Na_2PtCl_4 have been impregnated on fresh or calcined (in N_2) Mo/C previously prepared by wet impregnation. Pt was then reduced by $NaBH_4$. LA hydrogenation was carried out at 150 °C and 20 bar H_2 in autoclave (Parr Instrument).

1%Pt-10%Mo/C	Mo salt	Heat treat.	LA Conv.%		Selectivity		
			6 h	24 h	GVL	1,4-PDO	1,5-PDO
A	Na_2MoO_4	-	19.6	53.5	100	-	-
B	Na_2MoO_4	400 °C, N_2	66.0	99.8	95	1.5	3.5
C	$(NH_4)_6Mo_7O_{24}$	-	4.4	32.8	100	-	-
D	$(NH_4)_6Mo_7O_{24}$	400 °C, N_2	46.4	97.0	94.8	1.7	3.5

Table 1: LA hydrogenation reaction: conversion and selectivity.

XPS analyses, TEM spectroscopy and acidity characterization allowed to correlate the catalytic results with specific morphological properties of the materials.

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Catalytic transformation of glucose to levulinic acid by using micro meso HZSM5-HMS composites

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The gradual decrease in fossil fuel has urged a shift to biomass valorization as an alternative to secure the energy and chemical supplies. Chemocatalytic conversion can be categorized into homogeneous and heterogeneous reactions. However, heterogeneous catalysts such as zeolites, metal chlorides have attracted increasing attention in the applications for biomass conversion because they are not reactor corrosive and it is easy to separate them from a reaction mixture [1]. However, there still is a significant disadvantage in zeolites associated with microporous structure that limits their application in catalytic conversion of biomass as the macromolecules. As a result, there is a need to modify the zeolite catalysts for solving their problems towards bulky molecules [2]. HMS as a hexagonal mesoporous silicate has larger pore sizes and surface area than zeolites which makes it suitable as a modified support in the catalytic reactions [3]. With that in mind, the aim of the work is optimization of heterogeneous catalyst for hydrolysis of glucose as the most plentiful and approachable monosaccharide unit in the lignocellulosic biomass, in order to produce biochemicals such as levulinic acid (LA). Therefore, HMS was modified by HZSM-5 (Si/Al=15) to obtain HZSM-5/HMS (ZH) composites and derive the benefits of both, HMS in the aspect of mesoporous structure and HZSM-5 in the aspect of acidity, simultaneously. The isotherm and pore size distribution achieved from N_2 physisorption have shown a combination of micro meso and macro pores in the composites. The yield of LA while using only HMS with slight Lewis acid sites was 1.3% while for HZSM-5 with very high acids density was 17.2% because of side reactions. However, in the catalytic tests by ZH composites; the addition of zeolite content in the composites (from 10 wt.% to 40 wt.%) significantly increased the yield of LA from 16% to 29.5%. Furthermore, the best yield of LA (31.2%) was observed for ZH-30 catalyst, that was synthesized by 30 wt.% of zeolite. According to NH3-TPD and Pyridine- FTIR, ZH-40 has shown the highest strong acid sites which led to by-product (humin) production, while ZH-30 as the best catalyst has demonstrated highest strong acid sites (after ZH-40) and also Lewis acid sites among all composites.

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HPLC-MS/MS method for ancient bile acid profiling to characterize stool specimens in soil, mapping antique toilet in the archaeological area of Pompeii

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Steroid and sterols analysis is a well-established tool used in archaeology and related disciplines for detection and source identification of stool specimens also in soil samples. Steroids are relatively stable molecules still preserved in samples that are thousands of years old from Egyptian to Roman era. [1]. Nevertheless, the ubiquitous occurrence of Δ5-sterols and derivatives in soil reduce their specificity as mammalian (human) faecal biomarkers. The commonly used steroids still do not take advantage of the full potential of the steroid spectrum, because they do not consider bile acids (BAs). BAs are likely the most specific and the most stable steroids markers for faecal input, due to their exclusive occurrence in vertebrate faeces. Moreover, common BAs undergo further several metabolic pathways by gut microbiota to produce epimers and oxidized derivatives (oxo-BAs) [2]. We propose therefore these class of molecules as a new specific biomarker of stool collected by latrines or sewage system. In addition, and as a potent peculiarity, BA composition is specie-specific, and their qualitative profile can be used as powerful tool to identify the source of samples. We recently developed and optimized an HPLC-ES-MS/MS method for the analysis of up to 21 BA and their oxo-BAs metabolic products in human faeces. This method was applied to Pompeii's soil samples from a suspected latrine, collected during recent archaeological excavations in Obellio Firmo's House, confirming the presence and the human origin of the faecal input in the archeologic area. To our knowledge, it is the first time that a BA profile, comprehensive of Oxo-BA metabolites, have been determined in ancient samples.

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Biological screening and 2D NMR-spectroscopic analysis of four Sardinian plants

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Secondary metabolites from plants are an inexhaustible source of bioactive molecules with different benefits, including those exerting anti-cancer, anti-microbial [1], and anti-HIV [2].

In the search for new anti-microbial and anti-HIV molecules, in the present work, four plants collected in Sardinia region: *Myrtus communis*, *Plagius flosculosus*, *Helichrysum saxatile*, *Scrophularia trifoliata*, were studied.

Extracts at different concentrations were administered to two hepatic cancer cell lines (HepG2 and HuH-7) by MTT assay. It was performed the anti-microbial effect on selected bacteria with agar diffusion test and microdilution assay. For the evaluation of the anti-HIV potential, it was examined the inhibition of HIV-1 reverse transcriptase-associated ribonuclease H (RNase H) activity and HIV-1 integrase (IN) LEDGF-dependent. In order to identify the principal constituents present in the extracts, a metabolomic analysis using 1D and 2D NMR techniques was performed. As a result, the metabolic profiling of plant extracts revealed a wide range of different species-specific secondary metabolites: feruloylquinic acids derivatives from *H. saxatile* and *P. flosculosus*, iridoids from *S. trifoliata*, flavanols, and phloroglucinol derivatives from *M. communis*. Meanwhile, *M. communis* exhibits a strong inhibition of both HIV related enzymes as well as a marked anti-microbial effect. Myrtle is also the plant in which they have been characterized new phloroglucinol glycosides.

In conclusion, this is the starting point for a more extensive phytochemical investigation addressed to understand the mechanisms underlying the anti-HIV and anti-microbial activities.

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Flow microwave-assisted alkyne semi-hydrogenation on alumina sonochemical loaded Pd nanoparticles

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From the industrial point of view, a selective and sustainable reduction of alkynes is still an open challenge, because the broad synthetic interest toward fine chemicals, pharmaceuticals and vitamins. The typical alkyne semi-hydrogenation relies on batch protocols in the presence of Lindlar catalyst (Pb-doped Pd/$CaCO_3$) [1]. The presence of lead requires a strict and time-consuming purification procedure of the final stream.

Aiming to re-design the process with a highly efficient greener catalyst, well suited for reaction scaling-up, new supported Pd catalysts on ceria and boehmite have been developed [2]. According to this background, the work started from the ultrasound-assisted preparation of Pd nanoparticles loaded on sintered alumina spheres. The homogenous nucleation of crystalline Pd nanoparticles, lead to a highly efficient catalyst with a low metal loading. This newly designed heterogeneous catalyst was applied in microwave-assisted alkyne semi-hydrogenation in a continuous flow reactor.

The semi-hydrogenation of 2-butyne-1,4-diol in ethanol was chosen as a model reaction. High conversion (>90.5%) and selectivity to (Z)-2-butene-1,4-diol (95.20%) have been achieved with a solution flow rate of 10 mL/min, under 7.5 mL/min H_2 flow rate. The chemico-physical features of alumina spheres loaded with Pd nanoparticles have been reported thanks to the full characterization by TEM, HR-TEM, EDX, IR, XRPD and AAS.

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Betulinic acid based self-assembled nanoparticles for cancer therapy

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In recent years the use of prodrugs has become an important tool to improve the pharmacokinetic properties of drugs and overcome a range of different issues, including low bioavailability due to poor absorption and degradation by protective mechanisms after reaching the target site.

Our continuous interest in the field of chemical approaches to target cancer cells [1] moved us to study the preparation of a novel class of betulinic-acid conjugates with cabazitaxel, podophyllotoxin and *N*-desacetyl thiocolchicine. All of them were characterized by the presence of a betulinic-acid moiety that makes them able to self-assemble in water and a linker to allow the release inside the cells [2].

The formation of nanoparticles and their stability was confirmed, and their antiproliferative activity has been investigated on human cancer cell lines.

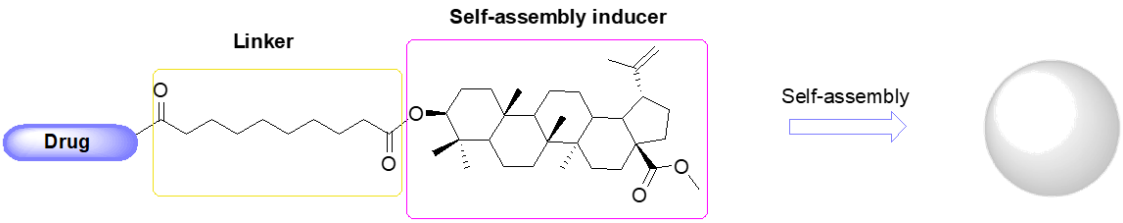

Figure 1: Structure of the synthetized conjugates.

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"Soft" nanocarries for effective brain delivery and targeting

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The blood-brain barrier (BBB) plays a key role as natural selective barrier shielding the brain from exogenous invasive agents (e.g. drugs).

Recently, several approaches by means of nanocarriers have received great attention for brain drug-delivery due to the possibility to increase drug protection against degradation, to enhance drug bioavailability and to perform a targeted drug delivery.

The aim of this work is the study and the formulation of different "soft" nanocarriers for brain delivery using different approaches like different ways of administration and different release strategies.

The nose-to-brain delivery is a non-invasive route to reach directly the brain through the olfactory nerve cells and trigeminal nerve [1].

For this purpose, surfactant vesicles and nanoemulsions have been prepared and characterized. In order to enhance the formulations retention in the nasal mucosa, these formulations were coated with chitosan as mucoadhesive agent.

Another alternative strategy to reach the brain is the non-invasive, localized, and reversible opening of the BBB.

Recently, our laboratory developed new carriers, the "Bubblesomes", able to combine drug and contrast agent delivery (theranostic system). When focused ultrasounds are applied in presence of drug loaded nanobubbles after intravenous administration, inertial cavitation is induced, due to the rapid expansion and violent collapsing of bubbles. This can cause the temporal and fully reversible opening of BBB with a subsequent temporarily leakage due to the enhanced endothelial porosity and vascular permeability phenomenon called sonoporation, resulting in an increased drug uptake [2].

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Droplet-based synthetic biology: chemotaxis and interface with biology

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Liquid droplets (oil in water or water in oil) can exhibit life-like behaviors and have been the subject of many artificial life studies. Life-like behaviors such as fission, fusion and movement [1,2] can be artificially recreated exploiting highly simplified chemical systems. Recently we showed that droplet-based chemotactic systems can be interfaced with biological systems [3]. We developed a chemotactic droplet able to move light cargos such as hydrogel alginate capsules embedded with living cells as a transporter (Figure 1). We transported efficiently and in a sterile way a few types of bacteria and yeast, and we are now modifying our protocols to transport efficiently human cell lines. We recently discovered that some eukaryotic cell lines, can be transported, survive the transport and release surfactants when placed in our artificial transport system, thereby reinforcing the interface between the artificial and living systems. This is an example of not only how the interface between artificial life and biological life could be designed but how the one system can augment the other. In this case the living system produces the surfactants that the droplet needs for cargo transport and the artificial system provides the transport for the otherwise sessile mammalian cells.

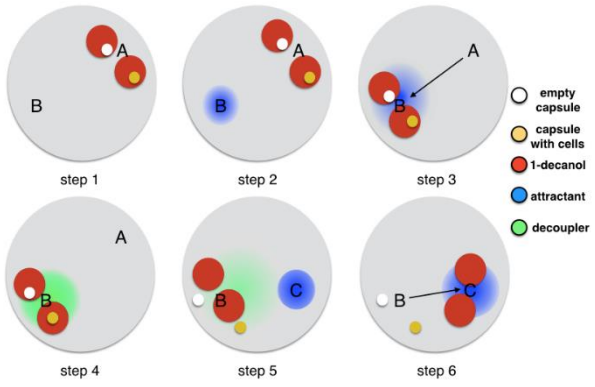

Figure 1: Cartoon of the droplet-capsule transport system.

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Epigenetic toolbox: novel non-hydroxamic HDAC3 isoform selective inhibitors

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The balanced status of hystone acetylation and deacetylation is an epigenetic modification with a critical role in the regulation of gene expression. Modification of histones by acetylation is controlled by the balance between histone deacetylases (HDACs) and histone acetyltransferases (HATs) [1].

Inhibition of HDACs activity has become an important target for therapeutic intervention in the treatment of many diseases including cancer, neurodegenerative disorders and fibrosis-associated diseases. The development of new chemical series, selective for the different HDAC isoforms, is the new mantra in the field to reduce unwanted side effects related to the poor selectivity.

Here, we disclose the evolution of our class I HDACi to generate an advanced set of new non-hydroxamic acid selective HDAC3 inhibitors [2]. In particular, we report the exploration of the zinc-binding group (ZBG) as a key active site binding moiety crucial for selectivity. Furthermore, modulation of potency and metabolic stability were achieved by an extensive SAR in the capping group region and linker units.

These compounds are twenty-fifty fold selective for HDAC3 over the other isoforms (**Figure 1**) and represent an attractive lead compound for the development of novel and optimized HDAC3 selective inhibitors.

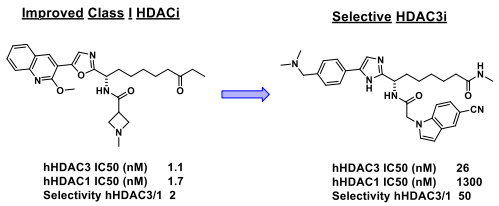

Figure 1: Novel non-hydroxamic HDAC3i.

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* This abstract is dedicated to the memory of our wonderful colleague Dr. Steven Harper.

Study of Cu(II) and Zn(II) interaction with the metal binding domain of ZinT protein

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Understanding the mechanism of metal trafficking at the host/pathogen interface can help designing innovative antibiotic therapies. In fact, bacteria rely on sophisticated systems (e.g. metallophores) to sequester metals from the host environment during infections. In the attempt to investigate these metal-acquisition processes, we studied the complexation of Cu(II) and Zn(II) – two endogenous and competing metal ions – with some peptide fragments of ZinT, a periplasmic protein found in several bacterial species and mostly involved in Zn(II) recruitment. Its most probable metal-binding site corresponds to a domain containing three histidine residues (positions 167, 176 and 178) and one aspartic acid (position 166, Fig. 1). ZinT also possesses a highly conserved histidine-rich loop (HGHHXH, residues 124-129), whose participation in metals uptake has also been suggested [1,2].

By means of ESI-MS, potentiometry, UV-Vis/CD spectrophotometry and EPR measurements, we studied the formed metal complexes with the protected peptides Ac-^{124}HGHHSH^{129}-Am and Ac-^{166}DHIIAPRKSSHFH^{178}-Am (of ZinT sequence from *Escherichia coli)*, and Ac-^{124}HGHHAH^{129}-Am and Ac-^{166}DHIIAPRKSAHFH^{178}-Am (ZinT-*Salmonella enterica)*. We ultimately compared ZinT with some human-defence mediators, e.g. the antimicrobial peptide Calcitermin [3], to evaluate the metal effectiveness in the expression of the pathogenic/antimicrobial activity by the studied systems.

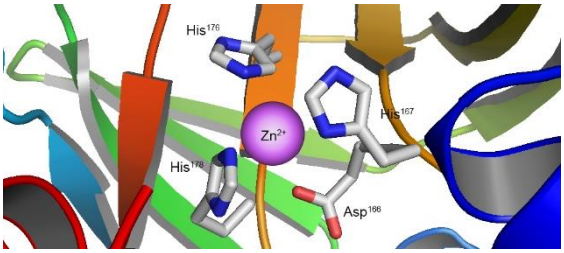

Figure 1: Proposed binding mode for the Zn(II)-ZinT complex at pH 7.4.

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Design, synthesis and evaluation of novel donepezil-hydroxytyrosol hybrids compounds against Alzheimer's disease

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From several epidemiological studies it results the lower incidence of Alzheimer's Disease (AD) in the countries with Mediterranean diet. Recently it was also revealed that poly(phenolic) component of extra virgin olive oil, in particular hydroxytyrosol (HTy) could be neuroprotective against Aβ-induced neurotoxicity in neuroblastoma N2a cells [1]. Considering the multifactorial nature of AD and basing on our previous experience [2], donepezil modifications to develop novel Multi-Target Direct Ligands (MTDL) have been carried out. Then, we propose to combine the antioxidant/free radical scavenging activity of the Hty with the acetyl cholinesterase inhibition activity of Donepezil (Figure 1). Different synthetic strategies were tested in order to conjugate the two different synthons in good yields.

The design, synthesis, characterization and biological tests of new donepezil-Hydroxytyrosol hybrids are described.

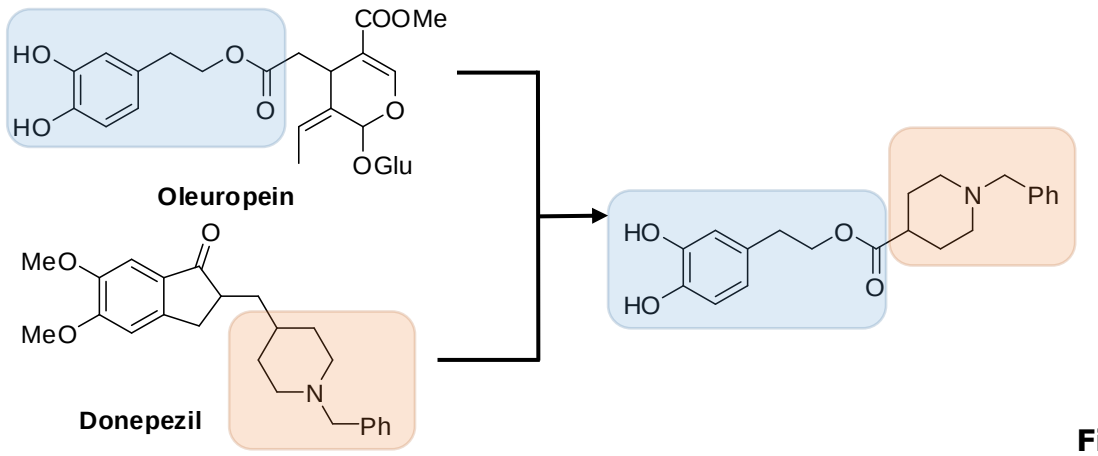

Figure 1: Chemical structure of designed MTDL donepezil-like.

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Spatial metabolomics for biomarkers discovery

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Mass spectrometry imaging (MSI) is a powerful analytical technique suited for simultaneously measuring and assigning functional role of multiple analytes directly from intact tissue sections, and holds potential for bringing metabolomics to the spatial molecular characterization level.

Nevertheless, MSI untargeted metabolomics is not as exploited as expected, mainly because MSI-data analysis still represents a remarkable computational challenge due to the size and analytical complexity of MSI dataset.

To this end, we recently developed LipostarMSI: the first comprehensive and vendor-neutral software for MSI that covers all the steps required for MSI data analysis, including automated metabolite annotation, significantly streamlining biochemical data interpretation.

With case studies in cancer metabolomics and pharmaceutical applications, in this talk we demonstrate that such unique combination of advanced analytical technique [1] with comprehensive and user-friendly data analysis platform [2] pave the way to establish a data-driven histology interpretation of MSI *omics* dataset, to achieve functional interpretation, and ultimately support drug discovery and clinical studies.

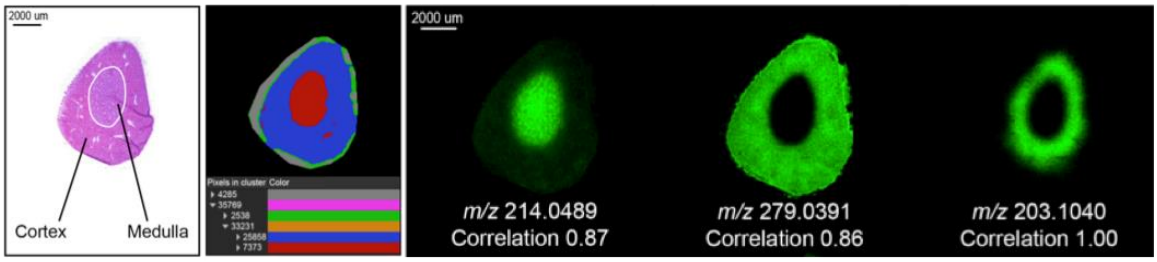

Figure 1: Example of MSI data analysis pipeline of rat kidney tissue: histology characterization, bisecting k-means segmentation, automatic metabolite co-localization and mapping.

[1] S.R. Ellis, M.R.L. Paine, G.B. Eijkel, J.K. Pauling, P. Husen, M.W. Jervelund, M. Hermansson, C.S. Ejsing, and R.M.A. Heeren, *Nat. Methods* **15** (2018) 515-518.
[2] L. Goracci, S. Tortorella, P. Tiberi, R.M. Pellegrino, A. Di Veroli, A. Valeri, and G. Cruciani, *Anal. Chem.* **89** (2017) 6257-6264.

Fluorinated coumarin-based MTDLs against Alzheimer's disease

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Alzheimer's disease (AD), a progressive neurodegenerative disorder, represents the most common cause of dementia. The lack of curative therapies available to clinicians pushed researchers towards the more promising multitarget strategy, which aims at developing rationally designed Multi-Target-Directed Ligands (MTDLs) [1] looking for a synergy of modulating two relevant AD targets through a unique chemical entity. Our contribute to the field has been devoted to discovering dual coumarin-based selective inhibitors of monoamine oxidase B (MAO B) and acetylcholinesterase (AChE) [2], leading to differently balanced dual compounds endowed with outstanding *in vitro* activity and selectivity. In this context, we were intrigued about exploring the effect of fluorine atom(s) and fluorinated motifs on both in vitro potency and drug-like features of our hits. In particular, the bioisosteric replacement of primary alcohols with *gem*-difluoromethyl groups [3] returned equipotent, yet highly active, dual AChE-MAO B inhibitors. A preliminary ADME evaluation was carried out as well.

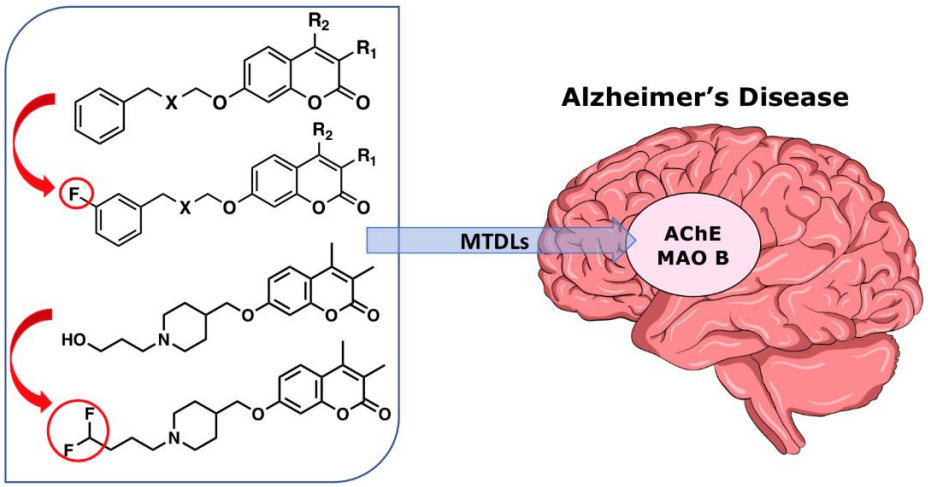

Figure 1: Fluorinated probes as novel MTDLs.

[1] M.L. Bolognesi, *ACS Med. Chem. Lett.* **10** (2019) 273-275.
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From peptidomimetics to smart molecular shuttles: development of reporting drug delivery system (RDDS)

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Construction of small molecule ligand (SML) based delivery systems has been performed starting from a polyfunctionalized isoxazolidine scaffold, whose $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrin affinity has been already established. The synthesis of this novel class of ligands was obtained by conjugation of linkers to the heterocyclic core via Huisgen-click reaction, with the aim to use them as "shuttles" for selective delivery of therapeutics and diagnostics to cancer cells. A development of the system has been obtained with the introduction of a self-immolative linker and a latent fluorophore to achieve a Reporting Drug Delivery Sistem (RDDS). The first is a spacer necessary to link the peptidomimetic and the drug and it should be cleavable under specific conditions to release active molecules such as a drug and/or a fluorophore. The latent fluorophore, instead, is a species with an inhibited fluorescence due to the conjugation with a quencher, that after the cleavage allows to monitoring in a no-invasive manner the localization and dimension of carcinogenic tissues [1,2].

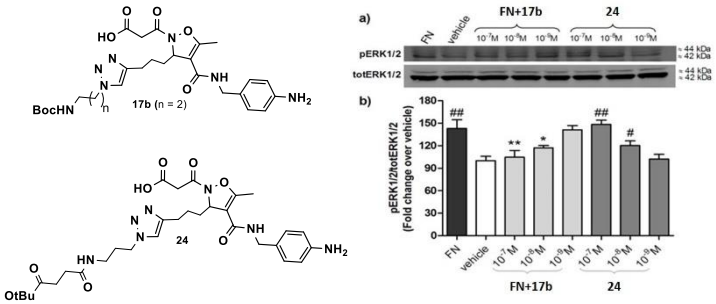

Figure 1: Structure and effect of two compounds on ERK1/2 phosphorylation mediated by $\alpha_5\beta_1$ integrin expressed in K562 cells.

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Hybrid nanoparticles for theranostics: exploring the SPIO@polymer combination

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Within the field of nanomedicine, one of the leading trends is theranostics. We aim to be actors of this revolution, proposing an innovative theranostic nanoplatform based on superparamagnetic iron oxide nanoparticles (SPIO NPs) embedded in a thermo-responsive polymeric scaffold.

The idea is to assembly these species into a nanosystem that acts as a diagnostic tool exploiting ^{1}H-MRI and as a magnetically guided drug carrier for targeted and triggered delivery.

The project has been conceived from the beginning by identifying a suitable synthetic pathway for the synthesis of the SPIO NPs [1], which has been further optimized to obtain these materials with the desired size and shape.

With the nanoparticles available, the next step requires their inclusion in a polymeric scaffold. To this aim, several polymers of different types and lengths have been tested, exploiting the nano-emulsion formation [2-3].

The final nanosystems have been characterized by means of both TEM and NTA to identify respectively the size of the core containing the SPIO NPs and the thickness of the outer polymeric shell. Moreover, these analyses have been performed also to assess the stability of the system and the degree of purity attained, evidencing the best mixture of polymers investigated, suitable for the purposes of the project.

The future research work will focus on the introduction of a model drug in the selected nanosystem and the assessment of its release.

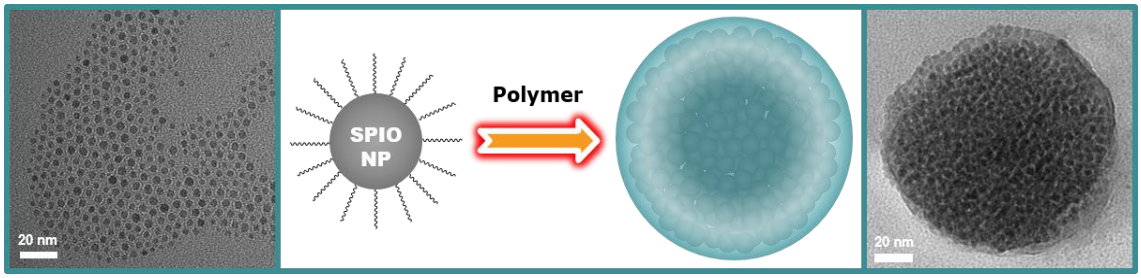

Figure 1: TEM images (left and right) and cartoon representation (center) of SPIO NPs included in the polymeric scaffold.

[1] S. Sun, H. Zeng, D.B. Robinson, S. Raoux, P.M. Rice, S.X. Wang, and G. Li, *J. Am. Chem. Soc.* **126** (2004) 273-279.
[2] H.Y. Huang, S.H. Hu, C.S. Chian, S.Y. Chen, H.Y. Lai, and Y.Y. Chen, *J. Mater. Chem.* **22** (2012) 8566-8573.
[3] H.Y. Huang, S.H. Hu, S.Y. Hung, C.S. Chian, H.L. Liu, T.L. Chiu, H.Y. Lai, Y.Y. Chen, and S.Y. Chen, *J. Control. Rel.* **172** (2013) 118-127.

Chemical functionalization of pyridobenzothiazolones scaffold led to compounds with promising antiviral activity: insight on the mechanism of action

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Nowadays flaviviruses are considered a major threat to human health because in the last twenty years almost 3 billion people have been put at risk of infection and no drugs are available against these viruses [1]. Among the viral proteins, NS5 RNA-dependent RNA polymerase (RdRp) represents a promising target since is essential for viral replication and without a human counterpart [2]. Recently, pyridobenzothiazolones (PBTZs) **HeE1-2Tyr** and **HeE1-17Y** were identified as NS5 RdRp inhibitors endowed with a potent antiviral activity and promising selectivity towards several flaviviruses [3]. Employing **HeE1-2Tyr** as a template, a new set of derivatives was designed and synthesized including a size reduction approach of the central core. Biological evaluation of the new compounds resulted in a 9-40 μM inhibition of NS5 RdRp together with a promising antiviral activity against Dengue and Zika replication in cells. Moreover, aminoacyl PBTZs emerged also as good NS3/NS5 protein-protein interaction (PPI) inhibitors and this activity can be explained by computational simulations that predict the binding of PBTZs to the cavity B of NS5. One of the most active PBTZ **HeE1-2d** was exploited for the selection of resistant mutants and interestingly three relevant mutations were identified on the 3'-UTR that explain the loss of infectivity of viral progeny. Finally, three most potent compounds were also evaluated in *in-vivo* mouse models and from this evaluation **HeE1-2d** was able to ensure 100% of mice survival after 10 days from infection. These results identify the PBTZs as broad spectrum anti-flavivirus agents and inhibitors of both NS5 RdRp and NS3/NS5 PPI. These compounds can be considered as valid candidates for further pre-clinical evaluation.

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Magnetophoresis study of magnetic nanoparticles and their coupling with plasmonic nanoparticles for biomedical application

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The interest of the last years in magneto-plasmonic nanomaterials arises from the demand of a single structure that can be easily manipulated, for example through an external magnetic field, and can act as a sensing substrate, if label with SERS (Surface Enhanced Raman Scattering) reporters [1]. In the field of nanobiotechnology, this kind of nanostructure is very promising for drug delivery, localized hyperthermia and, if properly functionalized with specific biomolecules, selective targeting [2].

A deep knowledge of the response of these nanostructures when a magnetic field gradient is present is the key to control them in a biological system. Therefore, a magnetophoretic model was developed to study the movement of magnetic nanoparticles in a liquid under a magnetic field gradient. It can be followed measuring the optical extinction decreasing of the magnetic nanoparticles' solution. Then, magnetization of the sample can be estimated through the fitting of the magnetophoretic curve given by the decrease of extinction as a function of time.

Magnetic nanoparticles are produced with a top-down approach, called laser ablation synthesis in solution (LASiS). A laser beam was focused on a strontium ferrite target immersed in water and magnetic nanoparticles were produced with an electrostatically surface charge that makes them stable.

In order to realize magneto-plasmonic nanostructures gold nanoparticles are produce using the same LASiS technique and a sol-gel approach was used to assemble the two different materials in a core-shell-satellites structure. A thiolated SERS reporter was easily linked to gold surface and, exploiting the so called hot-spots, its Raman signal is enhanced of several order of magnitude increasing the sensing efficiency.

Finally, targeting activity can be tested through the functionalization with a modified peptide, PEG-KKKGG-GE11, that recognized a specific receptor (EGFR) overexpressed by many cancer cells. A magnetic selection allows to capture selectively those cancer cells targeted by the nanostructures.

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Complex macromolecular design for applications in nanomedicine

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A major challenge in nanomedicine is to enhance drug delivery across biological barriers, which are designed by nature to prevent undesired access of molecules to sensitive organs, tissues and cells. Recent advances in polymer chemistry allow a fine control of key physicochemical properties of polymeric nanocarriers, such as size, drug loading and degree of fuctionalization, in order to overcome these barriers and maximise cell/tissue targeting. A library of linear, comb-like and multi-branched comb-like polymers, based on biocompatible poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL) and poly(ethylene glycol) (PEG), will be presented. PEG and the polyesters PLGA and PCL are common precursors for the preparation of biocompatible and biodegradable nanomaterials. By combining different polymerisation techniques (Ring Opening Polymerization ROP, Atom Transfer Radical Polymerization ATRP and Free Radical Polymerization FRP [1][2]) and further functionalization (*click*-chemistry or Michael-type addition) we developed bioactive self-assembled nanomaterials, which are able to cross specific barriers, and selectively release their therapeutic payload in glioblastoma cells [3].

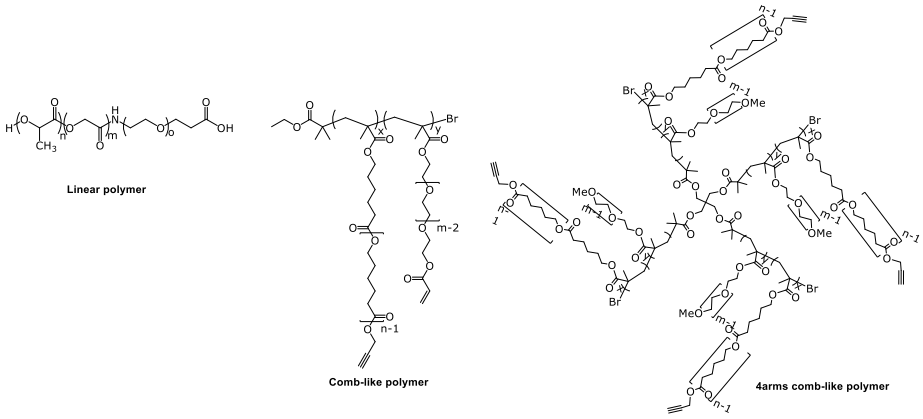

Figure 1: Polymers structure.

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New hybrid NO-donor photosensitizers for photodynamic therapy activable in the NIR region

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Photodynamic therapy (PDT) is a well-established therapeutic modality for treating cancer, exploiting the effects originated by the combination of Vis/NIR light with a photosensitizer (PS) in the presence of molecular oxygen. Nitric oxide (NO) is an endogenous messenger involved in physiological homeostasis and in an extensive number of different diseases, among them cancer. NO photodonors (NOPDs) are compounds able to release NO under the action of the visible light and received an increasing attention as potential new anticancer therapy: NOPDs allow the action of NO to be confined to the irradiated area and its dosage to be controlled by tuning the duration and intensity of the irradiation. Combination of PS with NOPDs is opening intriguing horizons towards new multimodal anticancer treatments entirely controlled by light stimuli. We recently reported a molecular hybrid based on a BODIPY light-harvesting antenna that acts simultaneously as PS and NOPD upon excitation with green light [1]. We report here new molecular hybrids consisting of a nitrosoaniline derivative appendage covalently linked to a phenothiazine light-harvesting antenna activable with the highly biocompatible red light. These NOPD-PSs should originate $O^{2-\bullet}$ as well as NO; the fast reaction between these two species may lead to the highly reactive and toxic $ONOO^-$ [2]. The capability of the phenothiazine skeleton to accumulate in lysosomes both with its intense fluorescence emission is very useful to localize the hybrids in the cells.

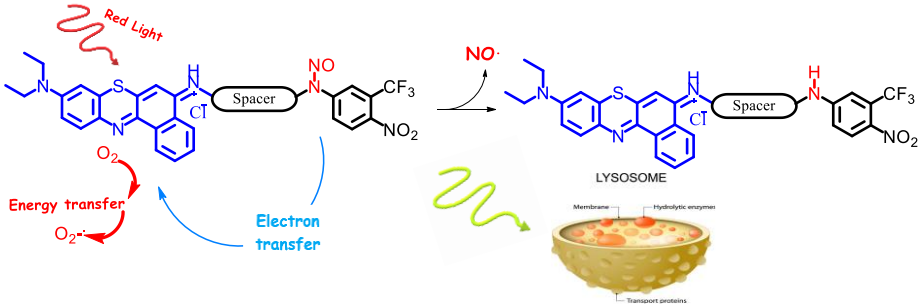

Figure 1: General mechanism for the release of bioactive species.

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Hot-melt Ram extrusion 3D printing: a versatile method for tailor-made orodispersible films

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Orodispersible films (ODF) are a promising alternative to conventional oral dosage forms to therapy personalization and the improvement of patient adherence [1]. Recently, hot-melt ram-extrusion 3D printing (HRP) has been proposed to obtain ODF of different strengths and geometries [2]. In particular, this technology permitted to obtain individually printed ODF in three simple steps starting from a solvent-free mixture. First, solid components of formulation (e.g., drug, maltodextrin, colourants, flavours, sweeteners) are mixed in a mortar and wetted with the plasticizer (i.e. glycerine). The mixture is fed into the chamber of the ram-extruder and heated up to 90°C. Then, melt material is extruded through a 0.8-mm nozzle and ODF are printed directly on the packaging material foil.

To demonstrate the versatility of the technology, three different model drug substances were loaded in printed ODF. The paracetamol (PAR) was used to assess the drug loading capacity of the ODF; the diclofenac sodium (DNa), a thermosensitive drug, and olanzapine (OLZ), a polymorphic drug, were used to determine how preparation steps (e.g., heating, water-free) impacted on the drug physicochemical stability. All printed ODF were also tested in terms of assay, tensile and dissolution patterns. ODF prepared by casting were used as controls.

The prepared ODF (6 cm^2; thickness 150-250 µm) disintegrated in less than 1 min and showed acceptable tensile properties to be handled. Residual water contents were in the 6-8% w/w range. PAR was loaded up to 37.5% w/w in the ODF matrix without altering the film performances. The heating step induced a slight degradation of DNa in ODF, but the impurity threshold was lower than Ph. Eur. limits. Both PAR and DNa dissolution profile of printed ODF (t_{80} < 6min) overlapped with those of casting ODF. On the contrary, printed ODF released about 90% of OLZ was released in ~3 min, while a yellow precipitate was observed in casting ODF, suggesting a change in the OLZ solid state.

This work demonstrated that HRP was a versatile technology to prepare ODF loaded with drugs with different physicochemical properties.

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Nanocomposite PVA films as wound healing material

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We prepared a composite functional material that could be effectively used as wound dressing, consisting of hydrophilic poly(vinyl alcohol) films containing two different kind of nanoparticles, namely silver NPs (from pectin) and gold nanostars, in order to combine the peculiar properties of the two preparations. In fact, AgNPs prepared with pectin (pAgNPs) have remarkable antibacterial and antibiofilm properties as well as promoting fibroblasts proliferation [1]. Gold nanostars (GNS) were prepared by a seed-growth method [2] and coated with different HS-PEGs. GNS have two intense LSPR bands in the IR region, whose position can be finely tuned in the synthesis. We prepared GNS with the Near IR band around 800 nm, that falls in the so-called *biotransparent window* (750-950 nm). Upon excitation with an 808 nm laser source, thermal relaxation is observed.

Different PVA films containing pAgNPs and GNS-PEG were prepared by a *solvent casting* method from a 6% PVA solution [3]. The products obtained are ready-to-use, flexible but quite resistant films, strongly hydrophilic.

Low Ag^+ release from the films has been measured, in agreement with what found for the starting pAgNPs colloid. Dry samples present a fair photothermal response, with a T increase between 5 and 30 °C and a linear dependence on the applied optical power. Preliminary microbiological experiments with two bacterial strains (Gram- *E. coli* and Gram+ *S. aureus*) show a pronounced antibacterial effect of the nanocomposite films, due to both Ag^+ release and a mechanical removal of cells by adhesion on the film surface. Laser irradiation doesn't seem to affect significantly the release of metals or the microbicidal action under the chosen experimental conditions.

We also assessed, by indirect tests *in vitro*, the effect of these materials on NHDF fibroblasts: all samples resulted biocompatible, as no decrease of cell viability is observed, while the promotion of fibroblasts proliferation is not as strong as expected.

[1] P. Pallavicini, C.R. Arciola, F. Bertoglio, S. Curtosi, G. Dacarro, A. D'Agostino, F. Ferrari, D. Merli, C. Milanese, S. Rossi, A. Taglietti, M. Tenci, and L. Visai, *J. Colloid Interf. Sci.* **498** (2017) 271-281.
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Nanocomposite PVA films as wound healing material

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TiO_2-photoanodes from unconventional pastes for aqueous dye-sensitized solar cells

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Within the photovoltaic field, dye-sensitized solar cells (DSSCs) have attracted much attention, due to their low cost, high transparency and possibility of diffuse light conversion, that permits their indoor application [1]. A key aspect to be considered is the stability of the devices, as well as the sustainability of materials and components. In this view, aqueous electrolytes are considered one of the possible breakthroughs toward large-scale diffusion of DSSCs, since they are non-toxic, safe and not affected by the contamination of air moisture [2]. Furthermore, the long-term stability could be increase gelifying the electrolyte solution into a solid polymeric matrix [3]. Consequently, the dye-sensitized TiO_2 photoanode should be wettable and allow the penetration in its bulk, but, at the same time, prevent the water-induced desorption of the dye molecules.

Herein, we report morphological modifications of TiO_2 photoanodes, introduced by adding various kinds of additives, both molecular and polymeric, to the commercial Dyesol TiO_2 paste, typically used for screen printing DSSC electrodes onto conductive glass. It was found out that the addition of polyethylene glycol (PEG) modified both the morphology and the thickness of photoanodes. As a result, PEG-based cells showed an increased short-circuit current density (+18%) and power conversion efficiency (48%) with respect to the pristine counterpart. For this reason, a deeper investigation and characterization of PEG-based electrode and cells were carried out.

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Design of organic based dye-catalyst systems for photoelectrochemical solar fuels

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Clean and affordable solar–based alternatives to fossil fuels are becoming essential as energy source to reduce climate issues. In this scenario, dye-sensitized photoelectrochemical cells (DS-PEC) play an important role. Mimicking nature, they can perform artificial photosynthesis to prepare solar fuels, such as hydrogen from the reduction of water or hydrocarbons from carbon dioxide (Figure 1 left). The strategic center of the device is the photosensitizer-catalyst system, which collects the solar radiation and converts it into the hole/electron couple and then perform the redox process to obtain fuels. Organic dyes have been playing an emerging role as light harvester in photocatalysis and in DS-PEC due to their easy synthesis, low cost, and abundance of precursors [1-3]. This work is focused on the design and the synthesis of new classes of organic push-pull dyes that can be connected to the corresponding catalysts exploiting different types of interactions (Figure 1 right). The first series of investigated dyes is functionalized with a calix[4]arene moiety and will exploit the host-guest interaction to direct the catalytic process (Figure 1a). In the second series, the sensitizer is covalently linked to a graphene layer to exploit π-π interactions with the catalyst (Figure 1b). Finally, catalyst and sensitizer are covalently linked in order to achieve a real artificial photosystem (Figure 1c). These molecular designs can be extended to both anodic and cathodic compartment of the DS-PEC to finally realize a real artificial leaf.

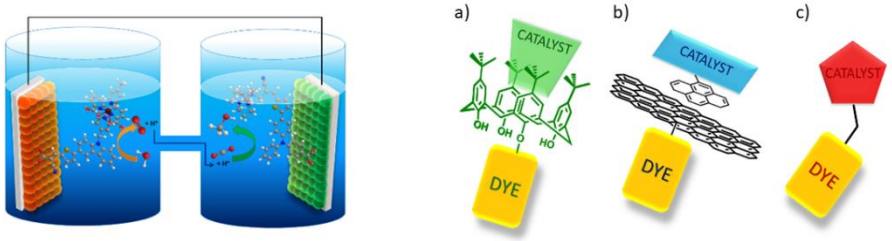

Figure 1: Scheme of a DS-PEC on the left; investigated molecular designs on the right.

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Engineered organic nanowire via nucleobases-pairing supramolecular recognition

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Two appropriately functionalized nucleobases, thymine and adenine, have been covalently linked at the N- and C-termini of an helical peptide foldamers, at a set of selected chromophores and at fully adenine-capped gold nanoparticles. These systems were studied in terms of their self-recognition abilities to generate ordered nano-architectures [1-2]. A crystal-state analysis (by X-ray diffraction) shows that adenine···thymine base pairing, through Watson–Crick intermolecular H-bonding, does take place between either end of each peptide molecule. Evidence for time-dependent foldamer···foldamer associations in solution is provided by circular dichroism measurements. It was found that adenine···thymine binding allowed the formation of precisely assembled nano-systems that depend powerfully on their morphologies from the nature of the chromophores utilized.

Moreover, three building blocks have been designed to chemically link to a gold surface and vertically self-assemble through thymine–adenine hydrogen bonds [3]. Starting from these building blocks, two different films were engineered on gold surface. These films were characterized by electrochemical and spectroscopic techniques, and were very stable over time and when in contact with solution. Under illumination, they generate current with higher efficiency than similar previously described systems.

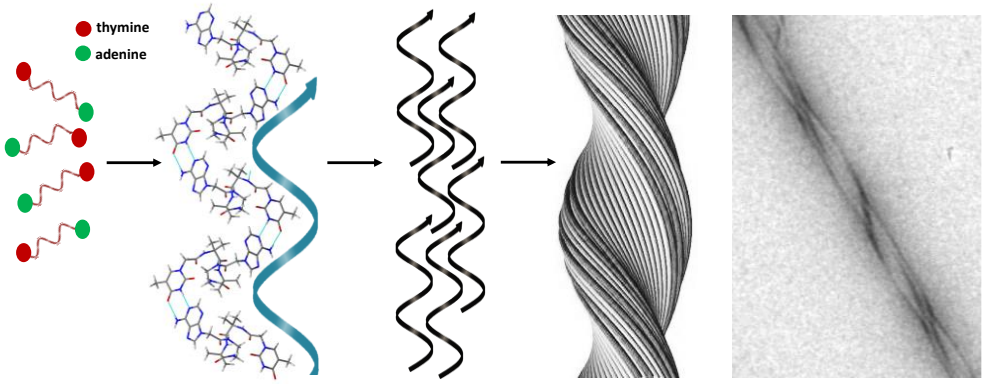

Figure 1: Nucleobase-functionalized foldamers supramolecular assembly.

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Surface effects on a photochromic spin-crossover iron(II) molecular switch sublimate on different surfaces

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The introduction of magnetic molecules in nanoarchitectures is moved to the aim of producing new technology for data storage, sensors and molecular spintronics [1]. Several reports have described the protocols for assembling at the nanoscale Spin Crossover molecules (SCO). To integrate such materials in real functional devices, the understanding of their behaviour when isolated in a 2D nanostructure is a fundamental prerequisite. Here we presents the results obtained by assembling on surfaces a Fe(II) complex flanked by diarylethene moiety. The ligand gives an unusual SCO effect promoted also by light irradiation observable at room temperature in solution and in amorphous powders. We will show that this system can be sublimated in UHV on Au(111) and on HOPG surface while keeping its SCO behaviour at the nanoscale. This work is based on the characterization through X-ray and ultraviolet photoemission, as well as via X-ray absorption. Temperature-dependent studies demonstrated that the thermally induced spin-crossover is preserved. Although the photochromic ligand ad hoc integrated into the complex allows the photo-switching of the spin state of the complex at room temperature both in bulk and for a thick film [2] on highly oriented pyrolytic graphite, this photomagnetic effect is not observed in sub-monolayer deposits [3]. Ab initio calculations justify this behaviour as the result of specific adsorbate-substrate interactions leading to the stabilization of the photoinactive form of the diarylethene ligand over photoactive one on the surface.

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Electrochemical approach for the production of layered double hydroxides with a well-defined Co/Me(III) ratio for oxygen evolution reaction

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The increasing global energy demand on energy grows and renewable resources are the only possible tools to rely for the future. The most relevant problem is that they tend to be intermittent and unpredictable. [1] As a result, there will be an increasing need to store this energy for times when the sun is not shining, and the wind is not blowing. Water electrolysis has drawn a lot of attention to store energy from renewables. In this scenario, layered double hydroxides (LDHs) containing redox active metals are promising materials. Cobalt based LDHs catalysts with iron and aluminum in different molar ratio ranging from 1:1 until 4:1 were synthesized by a newly developed electrochemical potentiodynamic method [2]. The obtained catalysts were characterized by a comprehensive combination of techniques and were evaluated for the oxygen evolution reaction (OER) on classically used rotating disk electrodes and on a stationary system. In all cases studied, an optimal Fe and Al content was highlighted and the performances resulted highly competitive. [3]

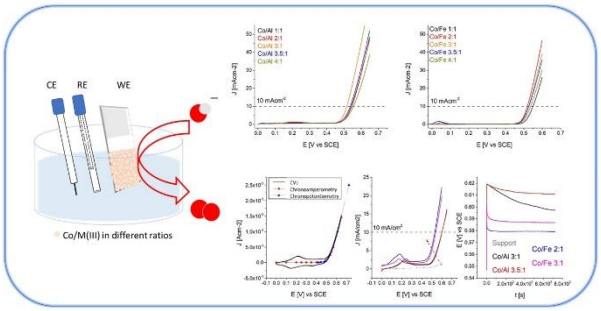

Figure 1: Sketch of the proposed work.

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Graphene-MoS_2 2D heterostructure as electrode for Na-ion batteries: new insights from first-principles calculations

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Graphene and MoS_2 are two single-layer 2D materials that have attracted great interests for their outstanding electronic and catalytic properties [1]. Employed in electrochemical devices, MoS_2 has shown high capacity as negative electrode in Na-ion batteries (NIBs). Still, it suffers from low electron conductivity and huge volume variation upon cycling [2]. These issues have been partially amended by combining MoS_2 with graphene nanosheets [3]. Despite the promising performances of MoS_2-graphene hybrid electrodes, many functioning features are still unclear, especially those concerning the mutual interaction of MoS_2 and graphene and the migration specifics of the Na cation. To fill this knowledge gap, we have investigated the MoS_2-graphene 2D heterostructure and the corresponding Na-intercalated compounds with periodic DFT-based ab initio calculations. In this contribution, we have considered both 1T-MoS_2 and 2H-MoS_2 polymorphs, finding that both phases can be combined with graphene in thermodynamically stable materials. From our calculations, graphene results to be essential for electron conduction, while only MoS_2 plays an active role on hosting Na ions. Such theoretical insights into the Na-adsorption and migration properties help to unveil the subtle structure-property-function relationships in these mixed innovative materials and provide new design principles that can boost their application as negative electrode in NIBs.

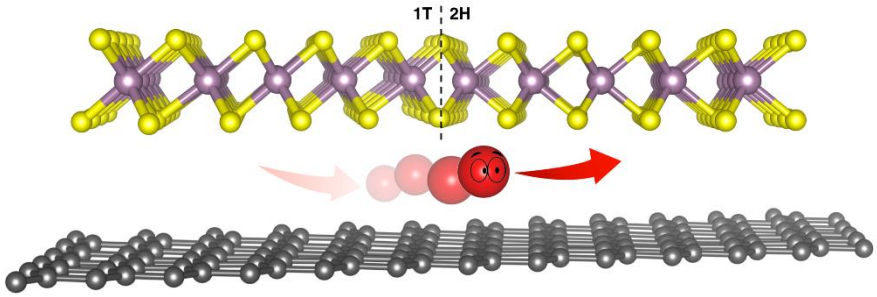

Figure 1: Cartoon of Na diffusion at MoS_2-graphene heterostructure.

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PANI/Au/Fe_3O_4 nanocomposite materials for high performance electrochemical capacitors

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In the present work new supercapacitor components were prepared depositing films made of polyaniline (PANI) modified with gold/magnetite nanoparticles on flexible graphite foils. Three types of composite materials termed PANI/Fe3O4, PANI/Au/Fe3O4 and PANI/Au/Fe3O4@Yne (where @Yne is a propynylcarbamate group) were obtained by electrosynthesis. Galvanostatic chargedischarge (CD) and impedance tests (EIS) were performed to verify their efficiency as supercapacitors: for the gold-containing electrodes PANI/Au/Fe3O4 and PANI/Au/Fe3O4@Yne volume capacitance (CV) values of 25861 and 22860 mF cm-3 were found in 0.5 M H2SO4 + 0.1 M LiClO4 electrolyte at a current density of 0.5 mA cm^{-2}. These values are twofold higher than those found for PANI/Fe3O4 electrodes and threefold greater than those for PANI alone (7846 mF cm-3). In turn PANI/Au/Fe3O4 and PANI/Au/Fe3O4@Yne were employed to assemble gel-state symmetric supercapacitors. CD, EIS and longtime resistance tests were made on the new devices that displayed energy densities of 9538 and 4533 mWh cm-3 (124 and 68 mWh cm^{-2}) and power density values of 131 and 85 mW cm-3 (1.70 and 1.28 mW cm^{-2}) for PANI/Au/Fe3O4 and PANI/Au/Fe3O4@Yne respectively. To our knowledge this is the first time that AuNP–modified magnetite nanoparticles are used in supercapacitors preparation [1-2].

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Graphene oxide derivatives for wearable sensing

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Nowadays, many efforts are devoted to the development of wearable devices as non-invasive alternatives for health monitoring, measuring biomarkers of technological and physiological interest in sweat and in other biological fluids. The painless detection of these analytes, e.g. glucose, cholesterol or lactate, allows their continuous monitoring and a personalized approach to health and fitness goals. To this aim, enzymatic biosensors are routinely employed, exploiting an electrochemical transduction. We are investigating the advantages in the use of graphene oxide (GO) to act as the sensing element of these detection systems. Aiming at improving the performance of these devices at best, we exploited the moieties already present on pristine GO nanosheets to covalently bind organic residues, to provide peculiar characteristics useful for the electrochemical sensing: GO bearing chitosan molecules was chemically synthesized (GO-Ch) [1], aiming at increasing the amount of enzyme anchored on the electrode surface, as well as the stability of its anchoring. To demonstrate the effectiveness of the covalent bonding, the analytical performance of these materials was compared with pristine GO and with GO simply blended with chitosan (GO+Ch), without a stable covalent bond. The physico-chemical properties of the functionalized materials were studied by combining results derived from electrochemical, spectroscopic, and morphological measurements.

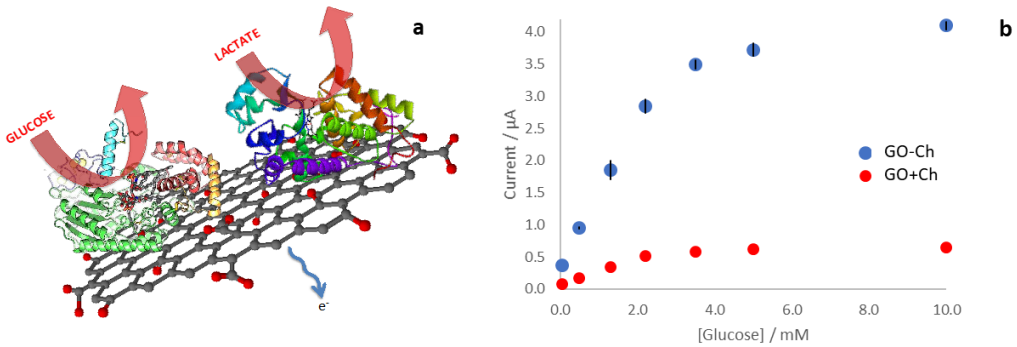

Figure 1: (a) Cartoon illustrating the enzymatic detection involving a GO-mediated electrochemical transduction; (b) calibration plots of glucose at chitosan-blended (GO+Ch) GO and at chitosan-functionalized (GO-Ch) GO.

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A printed miniaturized all-solid state ion-selective electrode for Na^+ monitoring in sweat

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One of the hot topics in bioanalytical field is the development of non-invasive, and easy to use sensing devices for biomarkers monitoring. Highly improved by the use of novel technologies, point of care devices have gained an important role in the continuous and ubiquitous monitoring of people health state [1].

Among the big plethora of point of care sensors, the ones exploiting electrochemical techniques deserve a primary role: the use of potentiometry, amperometry and voltammetry allows for the fabrication of deliverable, disposable, based on a minimal sample requirement and low-cost sensors. Among these, potentiometric ion-selective electrodes (ISE) with internal solid contact (SC-ISE) have attracted high attention in this decade due to their small size and easy fabrication process. Compared to classic ISE, SC-ISE exploits conductive polymers and nanostructured materials for ionic transduction, to replace the liquid contacts of the classic ISE, and a flexible substrate for sensors fabrication, i.e. polyester, polyethylene or paper [2].

Following these principles, we developed a miniaturized all-solid state ion-selective electrode, coupled with a portable potentiostat palmsens 3, for Na^+ detection in sweat sample. The sensor consists of a low-cost fabricated screen-printed electrode (SPE), modified with Carbon Black (CB), in order to effectively convert the ionic signal through the ion-selective membrane into an electronic signal. Two different membranes were exploited: the first one, located onto the CB-modified graphite working electrode surface, contains a sodium ionophore and allows for the selective detection of the ion. Moreover, a reference membrane is placed onto the Ag/AgCl reference electrode to guarantee the acquisition of a stable and accurate potential.

Firstly, several parameters for the sensor optimization were studied, namely volume of CB, volume of selective and reference membrane and conditioning process time. After, a calibration curve was obtained by potentiometric measurements of standard solutions, with a linear response in the range between 10^{-3} M and 1 M and a regression line equation equal to $y = 0.068\ x + 0.262$, $R^2 = 0.984$.

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Electrochemiluminescence microscopy: a powerful analytical technique for sensor applications

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Electrochemiluminescence is a luminescent emission induced by electrochemical stimulus. In the last decades, ECL emerged as a powerful analytical technique applied in different fields thanks to the unique signal-to-noise ratio and spatial control on emission [1].

Recently, the combination of ECL and microscopy resulted in an emerging approach for visualizing micrometer-size objects onto an electrode surface. Herein, we will give an overview about the main applications of ECL microscopy, in particular for sensing and visualization of micro and nano-metric objects and biological materials (like human cells, bacteria) in close proximity of the electrode surface [2]. Moreover, we will present how nanotechnologies, for example dye-doped nanoparticles and functionalized graphene, can further improve the sensitivity and sensibility of ECL microscopy [3].

Thanks to all these improvements and applications, ECL imaging will be used more and more for the surface-confined mapping and quantification of different analytes.

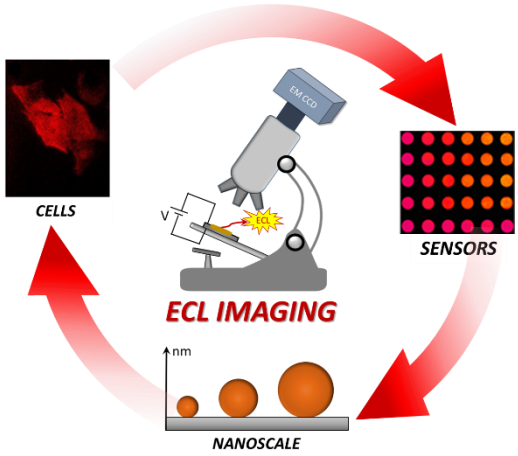

Figure 1: ECL imaging applications.

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Colorimetric sensors for monitoring, modelling and comparing spoilage processes of different meats

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Meat spoilage is a very complex combination of processes, related to bacterial activities. Numerous efforts are underway to develop automated techniques for monitoring this process.

For this purpose, we selected a panel of pH indicators [1] and a colorimetric probe, selective for thiols. Ligands were firstly embedded into an anion exchange cellulose sheets, to obtain coloured spots.

An array of 6 spots were placed over the tray containing a sample of meat, avoiding direct contact with meat. Photos of the array were acquired as function of time (Figure 1a), RBG index were used for monitoring the spoilage, Principal Component Analysis to model the data set (Figure 1b).

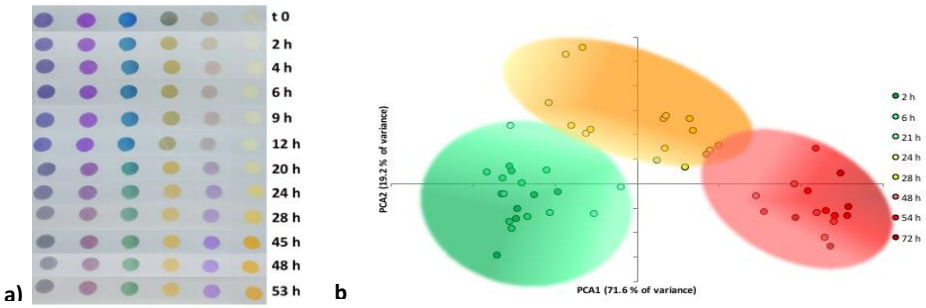

Figure 1: **a)** evolution of sensing spots over poultry meat. **b)** Scores plot of the 2 first component of PCA on RGB evolution on 6 different poultry samples

We used our array for monitoring the overall spoilage process of chicken, beef, pork and fish, obtaining different models that mimic the degradation pathway. The different spoilage processes, clearly followed by the colours evolution, were eventually compared using 3-Way PCA.

After having investigated the applicability of this strategy for monitoring meat spoilage, we decided to change the solid support in favour of a polymeric substrate, more suitable for industrial application, a patent has been deposited on this work [2] and some preliminary results on chicken and fish samples have been already obtained.

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[2] Patent n. 102019000004641 deposited on March 2019 to Italian Ministry of Economic Development.

On the effect of mobile phase composition on thermodynamic properties of zwitterionic teicoplanin-based 2-µm superficially porous particles

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The effect of the mobile phase composition on thermodynamic properties of novel zwitterionic macrocyclic glycopeptide chiral stationary phase (CSP) has been evaluated.

The CSP used has been made on latest-generation 2-µm superficially porous particles (SPPs), functionalized with teicoplanin by means of a proprietary bonding protocol that allows to obtain its zwitterionic version.

The investigation of thermodynamic behavior has been performed by calculating adsorption isotherms in both hydrophilic interaction liquid chromatography (HILIC) and reversed phase (RP) modes [1,2]. The study of absolute and excess adsorption isotherms allowed to gain information on surface heterogeneity in terms of adsorption energy distribution, types of adsorption sites, preferential adsorption of one of the component of the binary mobile phase and to investigate if the mobile phase composition has an effect on both the binding constants of enantiomers and the enantioselectivity of the CSP.

On the one hand, excess adsorption isotherms have been calculated by means of the minor disturbance method [3]. The excess of both methanol (RP) and acetonitrile (HILIC) over water was determined from linear perturbations on a series of equilibrium concentrations, when a steady-state equilibrium between mobile and stationary phase has been reached. On the other hand, adsorption isotherms of Z-D,L-Methionine enantiomers have been studied by using the so-called Inverse Method (IM). Results have revealed that the adsorption mechanism in both RP and HILIC mode can be described by means of a competitive Bilangmuir isotherm, which accounts for the presence of two different adsorption sites: one selective, responsible for the chiral recognition mechanism, and one nonselective, in which the two enantiomers identically behave.

[1] S. Felletti, C. De Luca, O.H. Ismail, L. Pasti, V. Costa, F. Gasparrini, A. Cavazzini, and M. Catani, *J. Chrom. A* **1579** (2018) 41-48.
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Polynorepinephrine as alternative to polydopamine for molecularly imprinted optical biosensors

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Molecular imprinting represents a viable approach for the development of sensing platforms toward a wide panel of analytes [1]. Dopamine (DA) has been widely investigated as functional monomer in non-covalent imprinting. Like dopamine, norepinephrine (NE) is a catecholamine able to easily self-polymerize, by forming adherent films on various type of surfaces [2]. To the best of our knowledge, there are not examples in the use of NE as functional monomer for MIP-based biosensors. The additional hydroxyl group, that distinguishes NE from DA, attracted our attention since the increased hydrophilicity of the surface could reduce the non-specific adsorption of proteins. Here we present the first example on the use of NE as functional monomer for imprinted optical biosensors, and the application in the detection of a biomarker for acute myocardial infarction (i.e. troponin I). The imprinting of PNE was performed on gold sensor chips and the efficiency of the optical biosensors was investigated by SPR transduction. As result, PNE has proved to be an interesting alternative to PDA, improving the analytical sensor performances by reducing the non-specific binding of matrix components to the chip surface, thus favoring the biosensor selectivity.

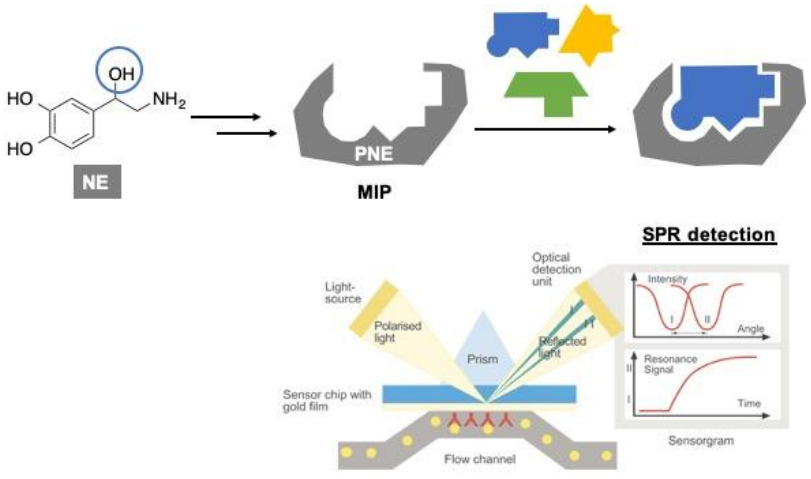

Figure 1: NE as functional monomer for MIP-based biosensors and SPR detection.

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A label free screen printed-based immunosensor for the detection of aflatoxin B_1 in real matrix sample

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In the present work, an indirect competitive immunosensor has been developed with the aim of determining aflatoxin B_1 (AFB_1), classified as carcinogenic, mutagenic, teratogenic and immunosuppressive agent. The method applied involves the use of a disposable screen-printed graphite electrode (SPE) whose surface is modified by the use of AFB_1-BSA conjugate, Nafion®117 and a label free detection technique.

In this approach, to perform the competition step, AFB_1 standard (or diluted sample extract) was mixed with an equal volume of MAb solution (diluted in phosphate buffer solution, PBS). Six µL of this mixture was added onto the working electrode surface and allowed to react with the coated AFB_1-BSA for 30 min at room temperature. Unbound MAb was removed by washing the electrodes. Between each step (coating, and competition), the electrodes were subjected to the 3-cycle washing procedure, each one involving the use of PBS solution.

Finally the determination step was carried out using a label free method (avoiding utilizing the purified goat anti-rabbit IgG alkaline phosphatase conjugate (Ab_2-AP) exploited in the previous work [1]. In particular, this method makes use of the evaluation of the available electrode surface area through the electrochemical reduction of potassium ferricyanide ($[Fe(CN)_6]^{3-}$) using square wave voltammetry technique. The linear range is found to be 10-50 ng mL^{-1}, relative standard deviation (RSD) ranged from 20-30% and the limit of detection was found to be 85 ng mL^{-1}.

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Scanning electrochemical microscopy investigation of 3D bio-printed cellular models

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Three-dimensional printed cellular models have shown great interest both in medicine and basic research because they recapitulate better the real condition of human tissues and organs. The characterization of 3D cell-laden models is also crucial to develop new methods to investigate real tissues.

We 3D-printed a cervical tumor model [1] and grew spheroids characterized by dimensions large as hundreds-microns in order to study cell behavior and signaling in 3D structures. We performed several biological assays to assess the viability of the method.

We are pioneering the use of Scanning Electrochemical Microscopy (SECM) to achieve a chemical characterization of the 3D bioprinted microenvironment. SECM permits to selectively detect (electroactive) species that are involved in biological functions with a high spatial resolution [2]. We are using SECM to characterize 3D bioprinted soft-constructs. In particular, by using nanoelectrodes as probes for SECM, we are able to obtain useful information of the 3D cancer model, such as: diffusion of chemicals, molecular release, oxygen content. As an example, we measured oxygen content inside spheroids (Figure 1), showing that the core of the tumoroids is characterized by a lower oxygen content.

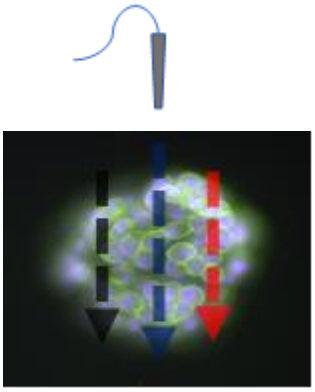

Figure 1: Scheme of the scanning electrochemical measurement of oxygen inside a spheroid of 75 micrometers.

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From preparative batch chromatography to a 2-column Multicolumn Countercurrent Solvent Gradient Purification process for a peptide purification

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Many peptides used for pharmaceutical applications are synthesized through Solid Phase Synthesis. The crude peptide mixture usually contains many impurities chemically very similar to the peptide. Reversed phase preparative chromatography is the preferred choice for downstream purification. However, the separation can be very difficult, resulting in peak overlapping regions not fulfilling the strict purity constraints. To obtain a pool with higher purity, the product collection window must be narrowed, causing a reduction in the product yield [1,2]. This works investigates the possibility of overcoming the purity-yield trade-off through 2-column MCSGP process (a semi-continuous chromatography process) where the columns work alternatively in interconnected or batch mode. While in the first column the gradient method is performed, the overlapping fractions eluting are recycled in the second column, which is also filled with fresh feed. These operations permit to increase the recovery of the peptide, keeping a very high purity. After these tasks are accomplished in the first column, columns exchange position, and half a cycle is completed. Usually, during an MCSGP run, 4 to 6 cycles are carried out [2].

The work started with the determination of batch conditions where the region of the main peak with a purity fulfilling the imposed specifications is as large as possible. From the Pareto (recovery vs purity) curve related to this batch method, a first group of trial values has been established to set-up the MCSGP switching times. The results obtained for the pools collected during the MCSGP run have been compared with those of the batch. By adjusting the times of recycling and collection windows the purity and recovery of the pools as well as the productivity of the method have been significantly modified.

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Selective single-molecule detection of clinically relevant biomarkers with an organic transistor

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The *US National Institute of Health* defines biomarkers *as molecules that can be objectively measured and evaluated as indicators of normal or disease processes and pharmacologic responses to therapeutic intervention*. Among the plethora of biomarkers, the sensitive detection of proteins is of paramount importance in a number of clinical fields. The clinical use of protein biomarkers as indicators of the onset of pathological states requires the measurement of low concentrations of proteins in complex samples. Attempts to develop ultra-sensitive assays for the detection of protein biomarkers have been done by several groups in the last few years. Although in the last decade many approaches to achieve ultra-sensitive detection have been developed, most of them require complicated assay set-ups, hindering their adoption in point-of-care applications. In this perspective, an Electrolyte-Gated Organic Field-Effect-Transistors (EG-FETs) with gate electrode bio-functionalized with trillions of capturing proteins [1], appear as very promising technology. The single molecule with a transistor (SiMoT) biosensing platforms herein presented, able to operate in physiologically relevant fluids such as blood serum and saliva [2,3], will set the ground to a major revolution in biosensing applications for early clinical detection.

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Self-assembled organic nanostructures for photocatalytic CO_2-to-CH_4 reduction

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The conversion of carbon dioxide (CO_2) into useful compounds with the aid of light is an appealing goal. Most commonly, precious metal catalysts (such as ruthenium and iridium complexes) were reported to photo-sensitize the reduction of CO_2 [1]. Recently, also organic sensitizers based on phenoxazines were found to photo-sensitize an iron porphyrin catalyst for the visible-light conversion of CO_2 to CH_4 [2].

Our group has previously reported the formation of a hydrogel, through the crystallization of a chromophore amphiphile, based on perylene monoamide core [3]. This soft material was found to be efficient in the light-driven production of hydrogen, but is not able to drive more energetically demanding reactions, such as the reduction of CO_2.

Here we report the development of an organic chromophore platform for the photocatalytic reduction of CO_2 to carbon monoxide (CO) and methane (CH_4) in aqueous media. The design and synthesis of a new self-assembling amphiphile platform based on the ullazine chromophore was achieved. We characterized the opto-electronic properties and nanostructures of their assembled state, and studied the photocatalytic activity of the obtained hydrogels in CO_2 photoreduction reactions.

[1] H. Rao, L.C. Schmidt, J. Bonin, and M. Robert, *Nature* **548** (2017) 74-77.
[2] H. Rao, C.-H. Lim, J. Bonin, G.M. Miyake, and M. Robert, *J. Am. Chem. Soc.* **140** (2018) 17830-17834.
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pH and reactive oxygen species-sequential responsive nano-in-micro composite for targeted therapy of inflammatory bowel disease

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Oxidative stress and abnormally high levels of reactive oxygen species play an essential role in the pathogenesis and progression of inflammatory bowel disease (IBD) [1].

We designed a nanoplatform for the encapsulation and "on demand" delivery of rifaximin (RIF) at sites of oxidative stress. Nanoparticles (NPs) were formulated from a phenylboronic esters-modified dextran (OxiDEX), that degrades selectively in response to hydrogen peroxide (H_2O_2)[2].

OxiDEX NPs were then encapsulated by microfluidics in hydroxypropyl methylcellulose acetate succinate, a pH-responsive polymer, to produce nano-in-micro structured composites.

The composites were spherical with homogeneous size (53±3 μm) and maintained integrity at acidic pH, preventing the premature release of the NPs in the harsh conditions of the gastric environment, while allowing NPs release in the intestine. The degradation of NPs was highly responsive to the level of H_2O_2, and the release of the loaded drug was sustained in the presence of physiologically relevant H_2O_2 concentrations.

Compared to a traditional enteric formulation, the composites showed ten-fold decreased drug permeability across intestinal cell monolayer, indicating that the produced systems were effective to limit the drug permeation through intestinal epithelium, representing an advantage in terms of unspecific absorption and systemic side effects.

Based on the results, the developed nano-in-micro composite has great potential for selective drug delivery in IBD treatment.

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Tuning the thermal isomerization of phenylazoindole photoswitches from days to nanoseconds

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The growing interest in light-driven oscillators led to the development of molecules able to interconvert from a stable to a metastable configuration upon irradiation and to return to the thermodynamically stable form as soon as the light stimulus is removed [1]. Controlling a wide range of back-isomerization lifetimes in the dark is a crucial goal for the potential application of these compounds as molecular machines [2].

We here present a novel class of azo photoswitches based on the 3-arylazoindole core (Figure 1). Minimal modifications such as methylation, dramatically change the Z-to-E thermal isomerization rate of the switch from days to the nanosecond range. Fine tuning of the Z-to-E lifetimes can be achieved choosing a proper dimethyl sulfoxide-water (or buffered water) solvent mixture [3].

The mechanisms involved in the isomerization have been elucidated by a thorough kinetic, computational and spectroscopic analysis. This allowed to detect three different pathways for the reaction and to identify the hydrazone tautomer of the phenylazoindole switch as the major actor in the fast Z-to-E thermal isomerization of the NH-substituted switch in protic media.

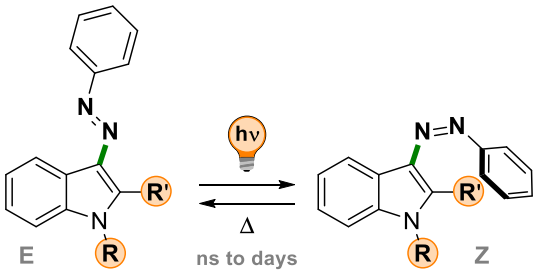

Figure 1: 3-phenylazoindole photoswitches.

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Fluorescent naphthalimide-imidazolium hydrogels for biomedical applications

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Bioimaging and in vivo imaging are cornerstone technologies in support of biomedical diagnosis. However, in some cases imaging methods have increased cancer risks for patients. Moreover, the most widely used diagnostic medical imaging technique, X-ray imaging, is the largest man-made source of radiation exposure to the general population. Thus, the research of new efficient and less invasive materials for imaging is quite urgent.

Supramolecular hydrogels have recently proved to be promising biological carriers to load versatile bioimaging agents for in vitro or in vivo bioimaging, thanks to the ability to undergo reversible swelling and gel–sol transition in response to various physiological stimuli. In addition, the biodegradability and biocompatibility allowed the use of supramolecular gels also for cancer diagnosis, as they can be facilely endocytosed into cells [1].

Remembering the good biological response of some imidazolium derived hydrogels [2], fluorescent imidazolium organic salts, that should own the double function of gelator and bioimaging agent, have been synthesized.

New fluorescent hydrogels with interesting physico-chemical properties (rheology, gel-sol temperature transition and optical properties) have been tested for anti-proliferative activity, in vitro bioimaging on cancer cells and controlled release of gelator in physiological medium. Results evidence how these hydrogels can be potentially investigated as new theranostic media for anticancer research.

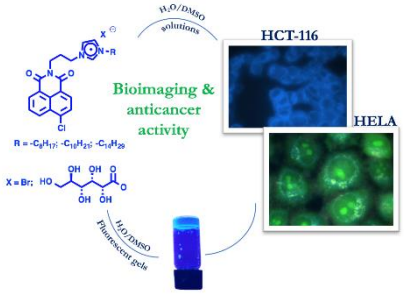

Figure 1: Gelator structure and bioimaging on cancer cells.

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Circularly polarized luminescence and electroluminescence in thin films of novel chiral π-conjugated oligomers

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The development of chiral organic semiconductors with high dissymmetry factors g_{lum} in thin films, which could be employed as active layers in very innovative technological applications such as circularly-polarized organic light-emitting diodes (CP-OLEDs), is a fundamental research goal.

Recently, we reported a family of structurally related benzo[1,2-*b*:4,5-*b'*]dithiophene and 1,4-phenylene-based oligothiophenes, studying their electronic circular dichroism (ECD) properties in thin films [1-3]; unfortunately, all these compounds revealed very low luminescence intensity in the solid state, due to aggregation-induced quenching phenomena.

Here we describe a set of new structurally related 1,4-phenylene and 9*H*-carbazole-based oligothiophenes (**Figure 1**). Circularly polarized luminescence (CPL) features revealed quite large dissymmetry factors g_{lum} values (in the order of 10^{-2}) on a wide wavelengths range, originating from their chiral supramolecular organization in thin film state. In light of the encouraging results, we investigated their electroluminescence (EL) and circularly polarized electroluminescence (CPEL) in organic light-emitting diodes: a multilayer CP-OLED device with dissymmetry factor $|g_{EL}|$ values up to $5.4 \cdot 10^{-2}$ was obtained, which represents to the best of our knowledge the first example of CP-OLEDs based on chiral oligothiophenes as the organic semiconductor.

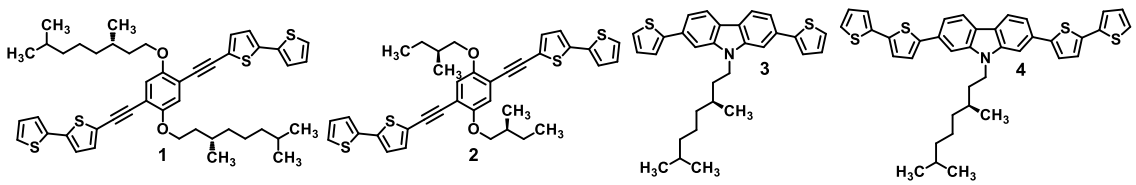

Figure 1: Chiral π-conjugated oligomers **1–4** studied in the present work.

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Functional materials for 3D direct laser writing (sub)microprinting

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Direct laser writing methodologies based on two-photon polymerization (2PP) are powerful tools for the on-demand printing of precise and complex 3D architectures at the micro and nanometer scale, achieving resolutions that can be as small as 40 nm [1]. By carefully designing a material, one can confer specific functional and responsive properties to the printed structures, thus making them appealing for peculiar and novel applications.

In this work, we design and characterize new photoresists and composite materials capable of responding to different external triggers and that can be polymerized via 2PP in micrometric structures: in particular, we will discuss the cases of liquid crystals elastomers and nanocomposites comprising ZnO nanorods which can show anisotropic properties when oriented using an external electric field.

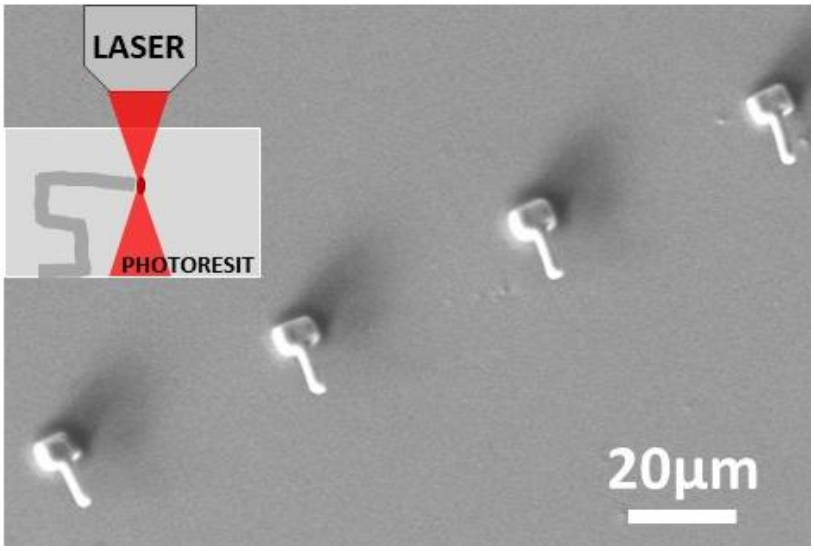

Figure 1: Example of microstructures obtained by 2PP on a homemade functional resist. The cartoon summarizes the principles of direct laser writing which allows for the 3D printing of exceptionally small structures.

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Pinocembrin-GPR120: a new couple in wound healing drug discovery

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Wound healing represents an urgent need from the clinical point of view. Several diseases result in wound conditions difficult to treat, as in the case of diabetic foot ulcer. Starting from there, the medicinal research has involved various targets over the years, including GPCRs as new wound healing targets [1]. In line with this, GPR120, known to be an attractive target in type 2 diabetes drug development, was studied to finalize the development of new healing agents [2]. Pinocembrin(HW0)was evaluated as a suitable moiety for GPR120 interactions, [3] so it was hybridized with fatty acids, endogenous GPR120 ligands, in order to ascertain the wound healing potential and GPR120 interactions. The data demonstrated that HW0 and its 7-linolenoyl derivative (HW3) are interesting wound healing agents, and able to accommodate in the same binding pocket of the known GPR120 agonist TUG-891.

Figure 1: Green approach for the development of new GPR120 ligands.

[1] K.T. Weiß, M. Fante, G. Köhl, J. Schreml, F. Haubner, M. Kreutz, S. Haverkamp, M. Berneburg, and S. Schreml, *Exp. Dermatol.* **26** (2017) 127-132.
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[3] N. Chinthakunta, S. Cheemanapalll, S. Chinthakunta, C.M. Anuradha, and S.A. Kumar Chitta, *Netw. Model. Anal. Health Inform. Bioinform.* **7** (2018) art. no. 8.

Synthesis, physiochemical proprieties and application of hydroxyazole systems as carboxylic acid isoster

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Bio(iso)steric replacement is a widely used approach in medicinal chemistry to improve the bioavailability, selectivity, potency and other properties of a lead compound. Since 2006 the authors have investigated hydroxylated heterocyclic systems in order to create a sophisticate tool able to bioisosterically mimic the carboxylic and other acidic functions. This bioisosteric tool covers a wide range of pK_a and chemio-diversity; its application in drug design led to new optimized molecules [1].

Chemical strategies for the synthesis of hydroxylated pentatomic heterocycles (substituted triazoles, pyrazoles, 1,2,5-oxadiazole, thiadiazole), as well as hydroxylated ring fused systems (pyrazolo[1,5-a]pyridine and benzoisoxazole), are here discussed; each system is also analysed in terms of acidity, lipophilicity and bioisosteric application.

In the following, two successful applications of this tool will be presented: first, some systems were used to modulate the acidic function of lead brequinar led to a library of new and potent *human* dihydroorotate dehydrogenase inhibitors able to restore myeloid differentiation both *in vitro* and *in vivo* Acute Myeloid Leukaemia models [1]. Finally, the modulation of glutamic acid using 4-hydroxy-1,2,3-triazole system led the first selective Glu analogues on AMPA-R2 subtype and NMDA receptors [2].

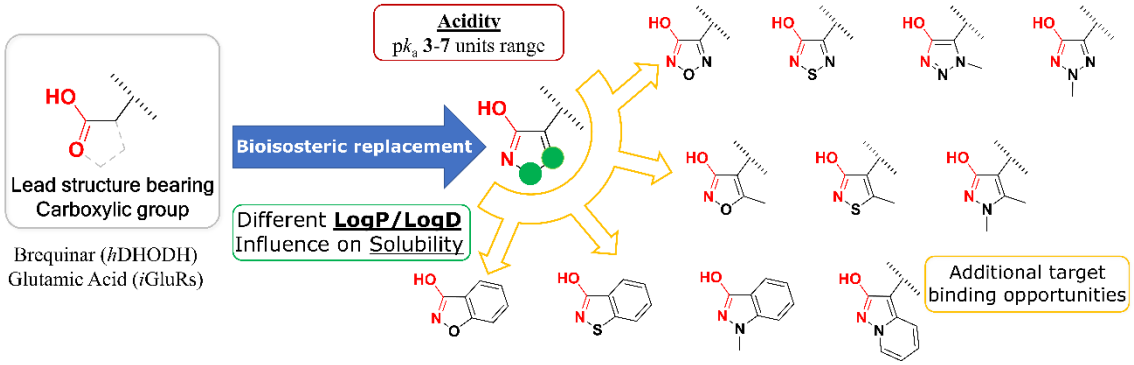

Figure 1: Bioisosteric replacement description and hydroxyazole systems

[1] S. Sainas, A.C. Pippione, E. Lupino, M. Giorgis, P. Circosta, V. Gaidano, P. Goyal, D. Bonanni, B. Rolando, A. Cignetti, A. Ducime, M. Andersson, M. Järvå, R. Friemann, M. Piccinini, C. Ramondetti, B. Buccinnà, S. Al-Karadaghi, D. Boschi, G. Saglio, and M.L. Lolli, *J. Med. Chem*. **61** (2018) 6034-6055.
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Ionic liquids from steroids: a total synthesis approach

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Ionic liquids are molten salts of great interest in organic and analytical chemistry due to their physico chemical properties [1-2]. They have been a subject of intense research in recent years and several ionic liquids with organic cations and inorganic and organic anions have been synthesized and characterized. Among them, chiral ionic liquids are of great importance for enantioselective reactions and chromatographic resolution. An interesting feature lies in the possible modulation of ionic liquids' properties by changing one of its ionic counterparts. Bile acids represent excellent substrates for the synthesis of chiral ionic liquids due to the presence of several chiral centres and functional groups that can be used for selective derivatizations. In addition, they are cheap and available in enantiopure form. Starting from deoxycholic acid, selective esterification reactions of the two hydroxyl groups have been performed followed by the conversion into functionalized terpene ionic liquids (Figure 1).

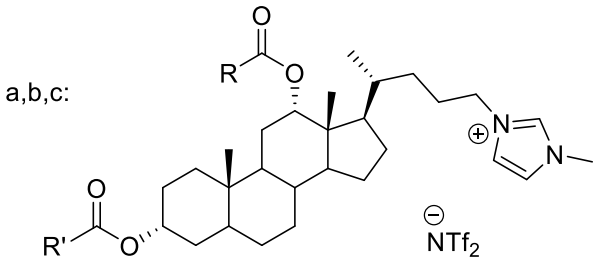

Figure 1: General structure of ionic liquids with a steroidal ion. a: R=R'= decanoyl; b: R=undecanoyl, R'=naphthoyl, c: R=naphthoyl, R'=decanoyl.

[1] J.S. Wilkes, and M.J. Zaworotko, *J. Chem. Soc. Chem. Commun.* (1992) 965-967.
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Amines PEGylation via Ruthenium-catalyzed Hydrogen Borrowing synthesis

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In the last decades, complex organic amines and functionalized *N*-heterocycles, as 5-amino thiazoles, play a key role in pharmaceutical and biological applications making them a valuable target for synthetic chemists in all the world [1]. Among the different methods to achieve nitrogen containing compounds, Hydrogen borrowing is a powerful and atom economical approach for carbon-nitrogen bond synthesis, however, polyethylene glycols (PEG), low toxicity and eco-friendly poly-ether alcohols, are previously unknown to participate in the reaction. In this presentation we report the first direct *N*-PEGylation of aliphatic and aromatic amines via hydrogen borrowing reductive amination using the Williams Catalyst, [Ru(*p*-cymene)Cl_2]$_2$, operating under relatively mild conditions and without exogenous base. A broad scope of amine nucleophiles was tolerated and strong inverse correlation between reaction rate and PEG chain length was observed. The reaction provides a powerful new method for the convenient and mild PEG functionalization of amines of biological and pharmaceutical.

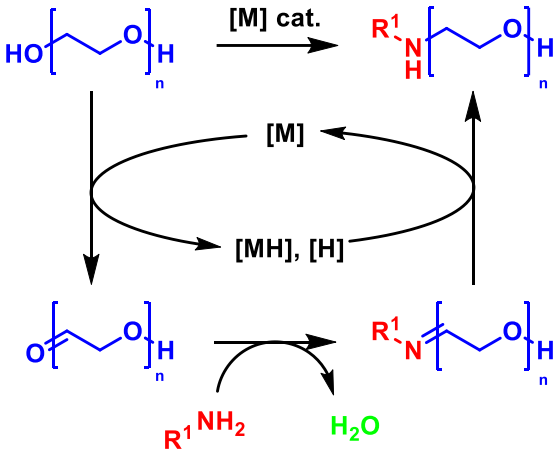

Figure 1: Hydrogen Borrowing method to PEGs.

[1] V.J. Stella, R.T. Borchardt, M.J. Hageman, R. Oliyai, H. Maag, and J.W. Tilley (Eds.), *Prodrugs. Challenges and Rewards*, vol V., Springer, New York, NY (2007).

Site-selective indole oxidation promoted by a peptide-based Mn-porphyrin catalyst

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Indole is a widespread heterocyclic scaffold among natural and bioactive molecules. From a catalytic standpoint, indole oxidation represents a useful model reaction to test the selectivity of a catalyst, since it typically leads to complex mixtures of singly and doubly oxygenated products at different positions of the aromatic ring [1,2].

Here we present the oxidation of indole promoted by a synthetic peptide-based metalloporphyrin catalyst, Mn-Mimochrome VI*a (Mn-MC6*a). Mimochromes are miniaturized proteins that have been designed by targeting the active site of natural heme-enzymes [3].

Differently from most of metalloporphyrin catalysts reported so far, Mn-MC6*a oxidizes indole with unprecedented site-selectivity, leading to 3-oxindolenine as product. Even more significantly, the reaction outcome is altered when methyl-substituted indoles are used as substrates, yielding different products depending on the position of the methyl group.

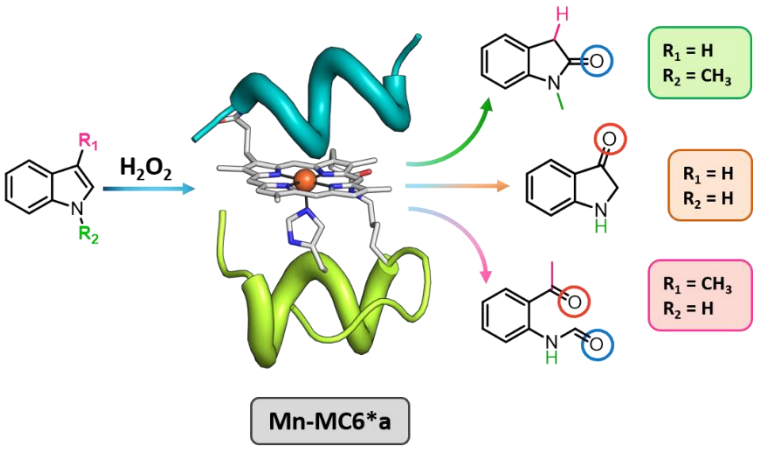

Figure 1: Oxidation of methyl-substituted indoles catalysed by Mn-MC6*a.

A common reaction pathway has been hypothesized to explain the peculiar reactivity of our catalyst and a mechanistic analysis is currently ongoing.

[1] M. Linhares, S.L.H. Rebelo, M.M.Q. Simões, A.M.S. Silva, M. Graça, P.M.S. Neves, J.A.S. Cavaleiro, and C. Freire, *Appl. Catal. A.* **470** (2014) 427-433.
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Oxidation of glucose to glucaric acid using gold-based catalysts

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Our research is focused on the study of Glucose (GLU) oxidation in aqueous phase to produce Glucaric acid (GA) (one of the top 12 added chemicals from biomasses [1]), using molecular oxygen as oxidant agent and gold nanoparticles supported materials as catalysts (**Figure 1**).

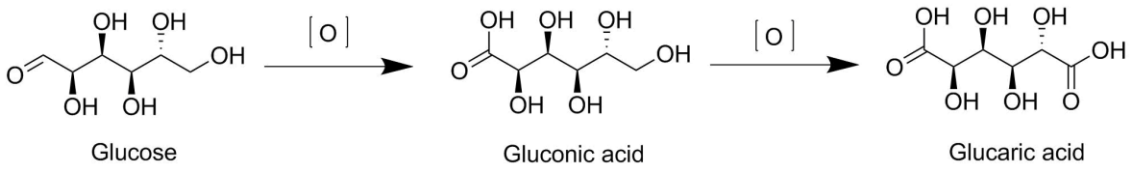

Figure 1: Glucose oxidation pathway.

In order to optimize the previous reaction conditions, several parameters have been changed (stirring rate, reaction time and reagent molar ratio (amount of catalyst)). In this way, the operational conditions were optimized, obtaining 24% of yield of GA, 37% to GO and 27% to byproducts in 1 h, 1000 rpm, 10 bar of O_2 and Glu:Au:NaOH molar ratio of 1000:1:3000. Then, our studies have been focused on the catalyst preparation. Using sol immobilization technique, Au NPs have been supported on AC. At first it has been changed the PVA:Au weight ratio (0-0.3-0.6-1.2-2.4) to study the influence in the formation of the particle size and the influence of PVA in the catalytic performance. The catalytic results showed that after 15 minutes Au/AC PVA0 reached the highest yield of GA (16%) and Au/AC PVA2.4 gave the lowest (8%). It is evident that the presence of PVA influences to a higher degree the reaction rate than the Au NPs size. Hence, the effect of different method for the removal of PVA was investigated. Washing treatment and heat treatment at 120℃ with Air/H_2 may have resulted in the mildest treatments for the removal of PVA while at 200°C -250°C the average crystallite size increased giving a lower yield of GA.

[1] T. Werpy and G. Petersen, *Top Value Added Chemicals from Biomass*, US Department of Energy, Washington DC, 2004.

Flash communications

FL01	Shiva TALI SHANDIZ
FL02	Federica SODANO
FL03	Lorenzo CALUGI
FL04	Serena VITTORIO
FL05	Alessandra RICCIO
FL06	Elena MARTINO
FL07	Francesca ANNUNZIATA
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FL53	Marisa FALCO
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FL56	Francesca TORRINI
FL57	Enrica MECARELLI
FL58	Silvia RADREZZA
FL59	Giovanni RIBAUDO

Exploring FXR selectivity: design, synthesis and characterization of C19-OH-chenodeoxycholic acid

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The Farnesoid X receptor (FXR) is an important bile acid-responsive transcription factor highly expressed in the liver, intestine and kidney. Its activation is responsible of several physiological and pathological processes including lipids and glucose metabolism, inflammation and cancer. Therefore, the development of FXR modulators represents an interesting area of research to disclose novel drugs and clinical therapies [1]. In this context, a semisynthetic bile acid namely 3α,7α,11β-trihydroxy-6α-ethyl-5β-cholan-24-oic acid (TC-100) was discovered as a potent and highly selective FXR agonist (Figure 1) [2]. The insertion of a hydroxyl group at the C11β position was found to be crucial to improve selectivity profile, physicochemical properties and pharmacokinetic behavior, with respect to recently approved drug Obeticholic acid (OCA, Ocaliva™) (Figure 1) [2].

Computational studies have shown that C11β -OH interacts with a polar region at the FXR binding site, which is in close proximity to the C19 position of the biliary scaffold. Based on these findings, in this communication we report the design, synthesis, characterization and biological evaluation of the 'atypical' bile acid C19-hydroxy-chenodeoxycholic acid (Figure 1).

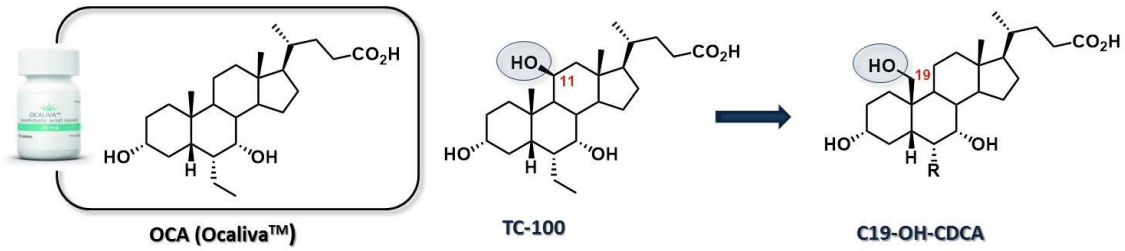

Figure 1: Structure of OCA, TC-100 and C19-OH-CDCA.

[1] V. Massafra, R. Pellicciari, A. Gioiello, and S.W.C. van Mil, *Pharmacol. Ther.* **191** (2018) 162-167.
[2] R. Pellicciari, D. Passeri, F. De Franco, S. Mostarda, P. Filipponi, C. Colliva, R.M. Gadaleta, P. Franco, A. Carotti, A. Macchiarulo, A. Roda, A. Moschetta, and A. Gioiello, *J. Med. Chem.* **59** (2016) 9201-9214.

Combination of PDT and NOPDT with a tailored BODIPY derivative induces an amplified anticancer activity

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Engineering of photosensitizers (PS) for photodynamic therapy (PDT) with nitric oxide (NO) photodonors (NOPD) is opening exciting horizons towards new and still underexplored unconventional anticancer treatment modalities entirely controlled by light stimuli [1]. Pursuing the idea to incorporate a PS and a NOPD within the same molecular skeleton [2], a previously developed boron-dipyrromethene (BODIPY) derivative [3], was appropriately modified in order to act simultaneously as PS and NOPD. Photogeneration of the two key species for PDT and NOPDT such as singlet oxygen ($^1O_2$) and NO was demonstrated by their direct detection upon single-photon excitation with the highly biocompatible green light. Biological studies carried out in A375 and SKMEL28 cancer cell lines and with the aid of suitable model compounds based on the same BODIPY light-harvesting core, unambiguously reveal the combined action of $^1O_2$ and NO in inducing amplified cancer cell mortality exclusively under irradiation with the visible green light.

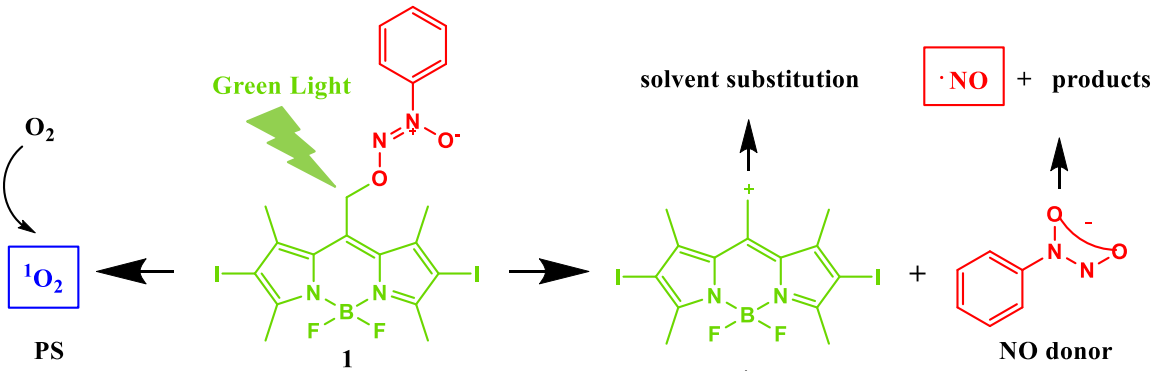

Figure 1: Mechanism for the NO photorelease and $^1O_2$ generation of compound 1.

[1] A. Fraix and S. Sortino, *Photochem. Photobiol. Sci.* **17** (2018) 1709-1727.
[2] C. Parisi, M. Failla, A. Fraix, A. Rescifina, B. Rolando, L. Lazzarato, V. Cardile, A. C. E. Graziano, R. Fruttero, A. Gasco, and S. Sortino, *Bioorg. Chem.* **85** (2019) 18-22.
[3] M. Blangetti, A. Fraix, L. Lazzarato, E. Marini, B. Rolando, F. Sodano, R. Fruttero, A. Gasco, and S. Sortino, *Chem. Eur. J.* **23** (2017) 9026-9029.

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

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Alzheimer's disease (AD) is the most common neurodegenerative syndrome affecting about 47 million people worldwide. One of the main causes is a progressive deposition of insoluble phosphorylated β-amyloid peptide and Tau protein on nerve cells causing difficulties in axonal transport. The pathogenic peptide β-amyloid is generated when the Amyloid Precursor Protein (APP) is degraded by β-secretase (BACE1) instead of α-secretase.

In vivo studies demonstrated that in animals free of BACE1 the presence of amyloid plaques was suppressed, so this enzyme has been one of the most studied targets for the pharmaceutical treatment of AD since its identification in 2000. There are several promising inhibitor candidates in clinical trials, although none of them could pass final steps [1,2].

In this project new BACE1 morpholine-based inhibitors were synthesized by the Castagnoli-Cushman reaction between imines and 1,4-dioxane-2,6-dione and synthetic elaboration of the resulting lactam (Figure 1). A first pool of compounds was evaluated for their biological activity with enzymatic assays, demonstrating the key role of the aryl substituent in modulating the activity profile.

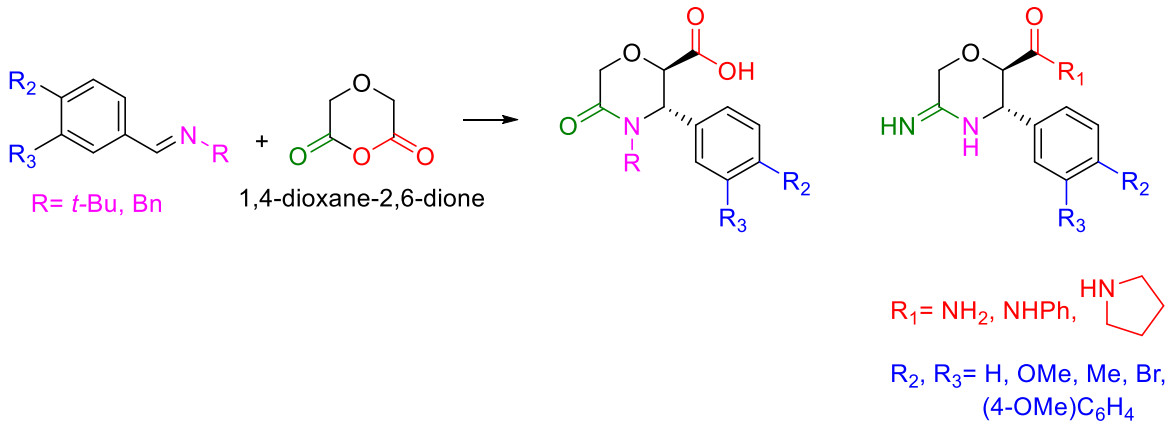

Figure 1: Synthesis of BACE1 morpholine-based inhibitors.

[1] M.G. Kornacker, Z. Lai, M. Witmer, J. Ma, J. Hendrick, V.G. Lee, D.J. Riexinger, C. Mapelli, W. Metzler, R.A. Copeland, *Biochemistry* **44** (2005) 11567-11573.
[2] J. Varghese, *Curr. Top. Med. Chem.* **6** (2006) 569-578.

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In silico screening for the discovery of new α-synuclein aggregation inhibitors

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Synucleinopathies are multifactorial pathologies characterized by the abnormal aggregation of α-synuclein (α-syn) in neurons thus leading to the formation of toxic oligomers and fibrils [1].

Among synucleinopathies the Parkinson's disease (PD) is the most common neurodisorder characterized by the degeneration of dopaminergic neurons causing bradykinesia, muscular rigidity and postural instability. The therapies currently available for the treatment of PD are addressed to reduce the related symptoms; therefore, there is an increasing interest in the development of novel and effective therapeutic tools [2]. The modulation of α-syn aggregation represents a promising disease-modifying strategy for slowing or blocking the neurodegenerative process. In this work, an *in silico* methodology was applied in order to identify α-syn aggregation inhibitors. To this aim, a ligand-based pharmacophore model was built starting from a training set of compounds able to bind the N-terminal region of α-syn (Figure 1). The model was used to screen i) our in-house 3D database CHIME and ii) the MyriaScreen Diversity Library II. The resulting hits were filtered according to the pharmacophore-fit score, the structural diversity and the commercial availability. As results, four hits were tested *in-vitro* in order to evaluate their ability to disrupt α-syn aggregation leading to the identification of a new small molecule able to reduce the formation of α-syn aggregates.

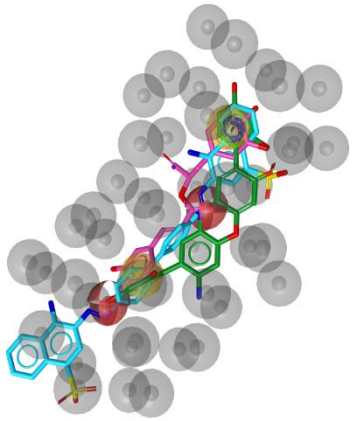

Figure 1: Ligand-based pharmacophore model aligned to the training compounds.

[1] J.Pujols, S. Peña-Díaz, D.F. Lázaro, F. Peccati, F. Pinheiroa, D. González, A. Carija, S. Navarro, M. Conde-Giménez, J. García, S. Guardiola, E. Giralt, X. Salvatella, J. Sancho, M. Sodupe, T.F. Outeiro, E. Dalfó, and S. Ventura, *Proc. Natl. Acad. Sci.* USA **115** (2018) 10481-10486
[2] Oliveri V., *Eur. J. Med. Chem*. **167** (2019) 10-36.

Insights into molecular recognition of PD-1/PD-L1 inhibitors combining *in silico* and biophysical methods

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The programmed death-1 molecule (PD-1) and its ligand (PD-L1) are members of the CD28/B7 superfamily. This protein-protein interaction is involved in regulation of T cells response and in maintenance of peripheral tolerance. Therefore, blocking PD-1/PD-L1 axis has proven to be an effective treatment modality for multiple cancer histologies [1]. Bioactive macrocyclic peptidomimetics and small molecules (SMs) have been reported in patent literature as PD-L1 binders able to block PD-1/PD-L1 interaction and immune checkpoints functions reestablishing an active state of T cells [2]. It has been demonstrated that SMs can induce a compound-dependent dimerization and subsequent internalization of PD-L1, effectively depleting the ligand from the cell membrane, avoiding immune response [3]. However, few information is still available, thus we set up an integrated computational and biophysical protocol to provide insights into the recognition of SMs and peptidomimetics inhibitors. In particular, we performed docking studies and molecular dynamic simulations to unlock the molecular basis of such interactions. Our study allows defining a preliminary pharmacophore model for PD-L1 ligands highlighting the essential residues for specific interactions. As further characterization, the strength of the binding of the selected inhibitors was supported by biophysical assay such as Micro Scale Thermophoresis (MST). We have demonstrated that combining in silico and biophysical methods can be a powerful strategy for the investigation of binding interactions between PD-L1 and inhibitors, where data obtained provides clues for the rational design of new small molecules as functional peptidomimetics. Moreover, the developed strategy can be applied for the screening of chemical libraries in search for new potential inhibitors with drug-like proprieties.

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Synthesis of [^{18}F]Brequinar as PET Imaging probes for *human* dihydroorotate dehydrogenase

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Human *dihydroorotate dehydrogenase* (*h*DHODH), a key enzyme involved in the *pyrimidine biosynthesis*, is a validate target for the treatment of *autoimmune diseases* and recently for acute myeloid leukemia (AML) [1]. In recent years, our group discovered a new class of *h*DHODH inhibitors based on the hydroxypyrazole scaffold [2] (**1**; Fig 1).

For the purpose of in vivo imaging of *h*DHODH activity, we started from *brequinar*, one of the most potent *h*DHODH inhibitors so far discovered [3], to design a novel [^{18}F]brequinar-based *Positron Emission Tomography* (PET) probes (**2**, **3**). During the design of potential F-18 radiolabeling strategies, direct conversion of arylboronate esters, arylstannates and arylheteroaryliodonium salts to aryl fluorides has been investigated.

These F-18 radiolabeled compounds will be further evaluated in animal models. These tools will allow the PET imaging of *in vivo h*DHODH activity, with important implications for clinical practice: assisting in early detection and monitoring disease, assessment of treatment efficacy, or development of new therapies. Based on the outcome of these studies, a similar approach will then be applied to our *in-house* designed *h*DHODH inhibitors.

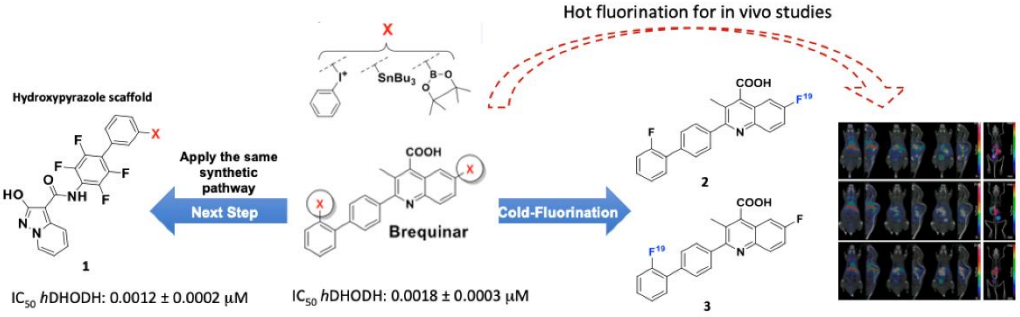

Figure 1: Design of novel *hDHODH* inhibitors probes.

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An innovative synthesis of the antiviral Vidarabine through the dual use of flow chemistry and biocatalysis

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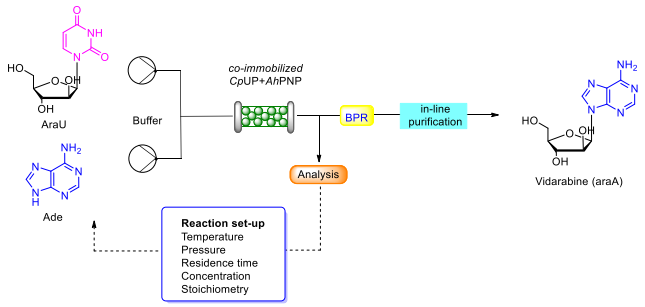
Nucleoside analogues are synthetic, chemically modified compounds that have been developed to mimic their physiological counterparts and act as antimetabolites, thus impairing cellular division and viral replication. Despite the dramatic progress in nucleoside chemistry to date, the preparation of nucleosides by conventional synthetic methods still suffers from low stereoselectivity, multi-step procedures and modest total yields. In this context, we focused our attention on a biocatalysed approach, developing a continuous flow process for the sustainable, efficient and scalable preparation and purification of nucleoside analogues (e.g., Vidarabine) [1]. The use of immobilised biocatalysts in continuous flow reactors, in fact, can help to overcome some of the constraints of batch protocols, such as long reaction times, scalability and productivity.

Uridine phosphorylase from *Clostridium perfringens* (*Cp*UP) and a purine nucleoside phosphorylase from *Aeromonas hydrophila* (*Ah*PNP) were selected to perform a bi-enzymatic transglycosylation reaction (Scheme 1). Both enzymes were efficiently co-immobilised in flow and reaction parameters were optimised. Furthermore, an in-line purification step was added to isolate the pure product.



Scheme 1: Final layout of the flow set-up.

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Acknowledgements: This work has been supported by Fondazione Cariplo, grant n° 2016-0731.

Application of an *in house* bioisosteric approach to the design of innovative inhibitors of aldo-keto reductase 1C3 (AKR1C3)

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The enzyme *aldo-keto reductase 1C3* (AKR1C3) plays a central role in androgen biosynthesis in prostate tissue. Since AKR1C3 was found to be overexpressed in *castrate-resistant prostate cancer* (CRPC), this enzyme has been investigated as an attractive therapeutic target for this disease. At the present, no selective AKR1C3-targeted agent has been approved for clinical use [1].

Some non-steroidal anti-inflammatory drugs, such as *flufenamic acid*, are known to inhibit AKR1C3 in micromolar range, although unselectively toward the other isoforms, C1 and C2, and COX as well. Our group recently employed a *scaffold-hopping* approach based on conformational restriction of benzoic acid group in *flufenamic acid* obtaining compound **1** (Figure 1), a potent and selective inhibitor of AKR1C3 [2]. The aim of the current work is to improve compound **1** potency and selectivity by following two strategies: *modulation of the aniline portion*, and *bioisosteric replacement of the oxygen in the benzoisoxazole ring* (Figure 1).

Here we present the *in silico* design as well as the synthesis and the biological activity of the new designed compounds.

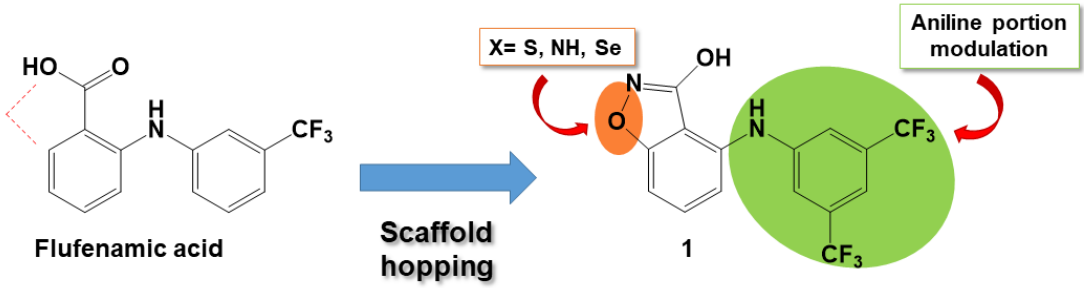

Figure 1: Conformational restriction employed on *flufenamic acid* to obtain compound **1** and the currently proposed modulations of the hit.

[1] A.C. Pippione, D. Boschi, K. Pors, S. Oliaro-Bosso, and M.L. Lolli, *J. Cancer Metastasis Treat.* **3** (2017) 328-361.
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Indazolyl-N-arylbenzenesulfonamides and quinazolinyl-N-arylbenzenesulfonamides as carbonic anhydrase inhibitors

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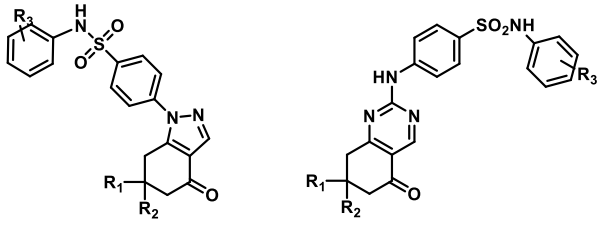
Carbonic anhydrases (CAs) are a superfamily of metalloenzymes, which catalyze the interconversion between CO_2 and bicarbonate. They are ubiquitous isozymes involved in crucial physiological and pathological events, and represent the targets of inhibitors with several therapeutic applications [1]. Primary sulfonamides constitute the most important class of Carbonic Anhydrase Inhibitors (CAIs), but they are usually associated with promiscuous profiles and lack of selectivity amongst the different isoforms.

In this respect, we have recently investigated primary benzenesulfonamides incorporating the bicyclic tetrahydroindazole and tetrahydroquinazoline moieties, that evidence interesting profiles of isoform-selectivity towards II and IX enzymes [2]. Secondary and tertiary sulfonamides have been lately reported in literature as efficient and selective inhibitors of the cancer-related human (h) CA IX and CA XII isoforms [3].

In the present study, bicyclic tetrahydroindazole (1) and tetrahydroquinazoline (2) derivatives featuring a secondary benzenesulfonamide moiety were synthesized and evaluated for their enzyme inhibitory capacity against four physiologically relevant CA isoforms, the hCA I, II, IV, and IX.



1 2

$R_1 = R_2 = H$; $R_1 = R_2 = CH_3$; $R_1 = H$, $R_2 = C_6H_5$;
$R_3 = H$, OCH_3, Cl, NO_2, CH_3

[1] C.T. Supuran, *Bioorg. Med. Chem.* **21** (2013) 1377-1378.
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NMR structural characterization of PHOX-2B

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Phox-2B is a transcription factor that plays an essential role in the development of the autonomic nervous system and the neuronal structures involved in breathing control; indeed, it has an important role in congenital central hypoventilation syndrome (CCHS)[1-2], caused by the presence of a polyalanine (polyAla) region that is the principal mediator of the protein aggregation. Recently, biochemical and structural comparisons of PHOX2B variants containing the correct C-terminal (20 alanines) stretch, one of the most frequent polyAla expansion (+7 alanines) or a PHOX2B variant lacking the complete C-terminal Ala stretch (0 alanines) were carried out by a multidisciplinary approach based on different methodologies (including circular dichroism, spectrofluorimetry, light scattering, and Atomic Force Microscopy studies) [3]. These studies highlight propensity to aggregate for the PHOX2B variant containing the poly-alanine expansion (+7 alanines) especially in the presence of DNA. Here we describe, by means of NMR spectroscopy and computational methods, the first structural characterization of both PHOX2B containing the C-terminal (20 alanines) stretch, and of PHOX2B homeodomain.

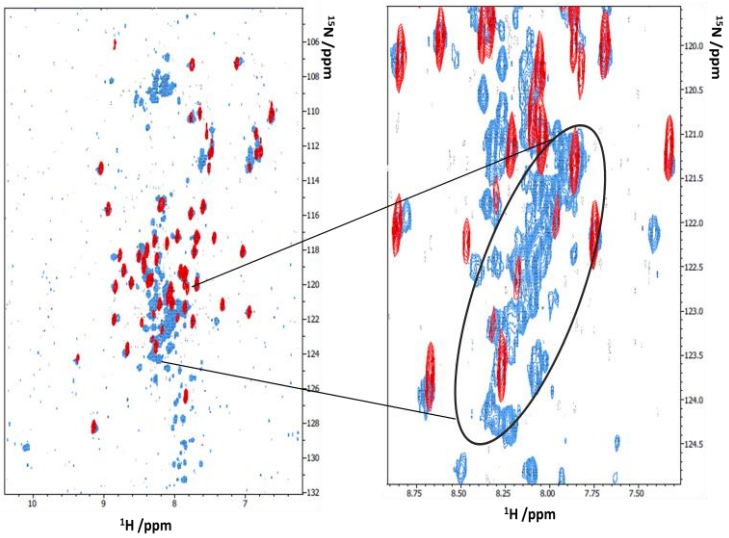

Figure 1: Overlay of 2D [^{1}H, ^{15}N] HSQC spectra of ^{15}N, ^{13}C uniformly labeled Phox2b-HD (red) and Phox2b-Cter (20Ala) (blue).

[1] A. Pattyn, X. Morin, H. Cremer, C. Goridis, and J.F. Brunet, *Nature* **399** (1999) 366-370.
[2] A. Pattyn, C. Goridis, and J.F. Brunet, *Mol. Cell. Neurosci.* **15** (2000) 235-243.
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Oxo-Re(V) promoted catalytic biomimetic cyclization

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The total synthesis of natural products has always been one of the most exciting research areas for organic chemists worldwide; therefore the development of new methodologies with synthetic application still remains a significant challenge. From this perspective, exploring the chemistry and the reactivity of uncommon transition metals such as oxo-Re (V) complexes is an excellent way to achieve positive results in this research field.

Some new procedures related to the oxo-Rhenium(V) catalysis are being developed in our laboratory [1-2], and by taking into account all the previous work, we have developed a new oxo-Re(V) Skurai-type alkylation reaction.

In this work we describe the first example of oxo-Rhenium(V) promoted catalytic biomimetic cyclization reaction between a simple aldehyde **1** as electrophile and the diene allylsilane **2** as soft nucleophile to give the lactone **3** as a single diasteroisomer. Reaction scheme and possible related synthetic targets are shown below (Figure 1).

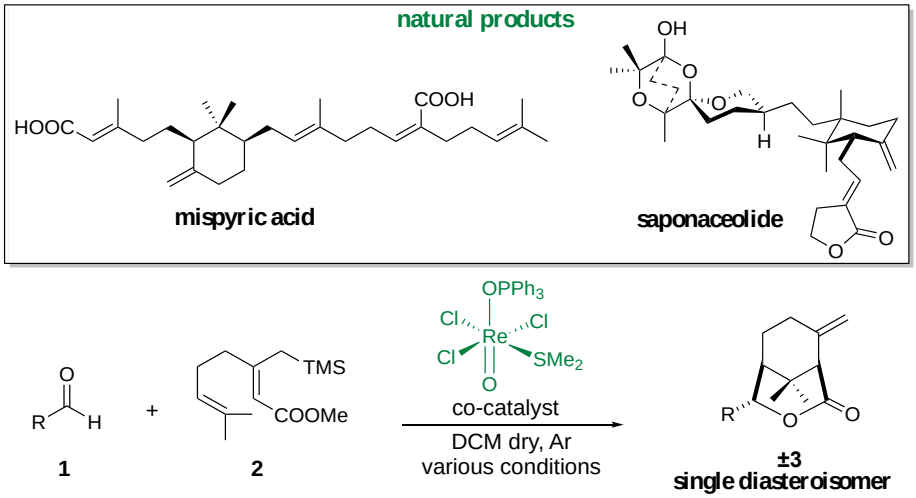

Figure 1: Synthetic targets and general reaction scheme.

The experimental data were supported by DFT modeling and these justify the complete diasteroselectivity that is inedited for this reaction type [3].

[1] E. Mattia, A. Porta, V. Merlini, G. Zanoni, and G. Vidari, *Chemistry* **18** (2012) 11894-11898.
[2] S. Bugoni, A. Porta, Z. Valiullina, G. Zanoni, and G. Vidari, *Eur. J. Org. Chem.* **28** (2016) 4900-4906.
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Advances in the enantioselective organocatalyzed α–azidation of 2-oxindoles derivatives

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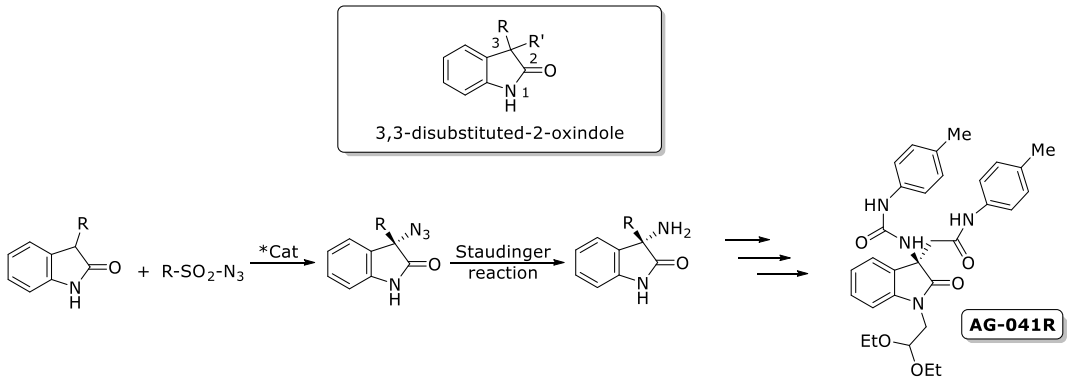
The 3,3-disubstituted-2-oxindole core (**Scheme 1**) is present in a great number of natural products and pharmaceutically active compounds. Many of these molecules show a nitrogen atom directly bonded to the C-3. The simplest way that one could imagine for the formation of the C-N bond is to exploit the natural reactivity of the carbonyl moiety at α-position, using nitrogen electrophilic reagents. This class of reactions is called α-amination (αA) [1]. Furthermore, because the biological activity of the products is often related to the absolute configuration at the tetrasubstituted carbon atom much efforts were spent in developing stereoselective versions of this chemistry (asymmetric α-amination, AαA) [1, 2].

Although the common electrophilic reagents employed for this purpose (azodicarboxylic esters, nitroso derivatives and hydroxylamines) usually give good results in term of conversion and enantioselectivity, the elaboration of AαA products into useful primary amines is often impossible.

To avoid this issue, we recently explored the organocatalysed AαA of 2-oxindole substrates with sulfonyl azides (**Scheme 1**).

To show the applicability of this chemistry, the formal synthesis of the bio-active compound AG-041R is presented.



Scheme 1: Enantioselective organocatalyzed α-azidation and elaboration in the bioactive compound AG-041R.

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Use of deep eutectic solvents for the Belousov-Zhabotinsky reaction

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Deep Eutectic Solvents (DESs) are a novel class of organic liquids that are gaining relevance in the green chemistry framework thanks to their environmental friendly properties [1]. These liquids are formed by weak inter- and intra-molecular interactions occurring between a hydrogen bond donor molecule (HBD) and a hydrogen bond acceptor molecule (HBA).

These forces prevent the formation of regular crystal lattices, favouring the formation of a liquid phase. Their synthesis is performed by simply mixing and heating low cost (often solid) compounds, leading to stable and recyclable liquids with low vapour pressure.

This work presents, for the first time in literature, the Belousov-Zhabotinsky (BZ) reaction in Deep Eutectic Solvents.

This reaction consists of an oxidative bromination of malonic acid by bromate catalyzed by either ferroin, or cerium ions, or ruthenium-tris-bipyridine. This reaction can be used to imitate neural dynamics for the development of Neuromorphic engineering [2].

In this work the "active" (or catalytic) role of DES has been explored by avoiding the use of acids traditionally employed in the BZ reaction.

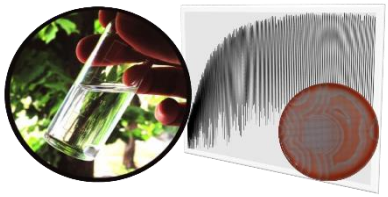

Figure 1: DES system and BZ's oscillation/chemical waves.

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Stereocontrolled synthesis of pyrrolidine iminosugars through asymmetric dihydroxylation reaction

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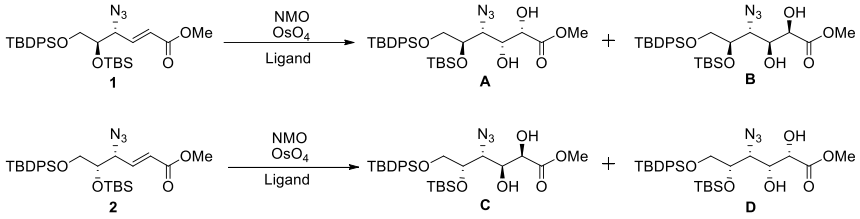
Iminosugars are carbohydrate analogues in which the endocyclic oxygen is replaced by a nitrogen atom [1]. These compounds are nowadays the most attractive class of sugar mimics because of their high glycosidase and glycosyltransferase inhibitor activity and hence their therapeutic potential in a vast array of diseases [2]. The synthetic key step in our approach for preparation of some classes of iminosugars, is the asymmetric dihydroxylation reaction (AD). In this work we conducted a systematic study about AD reaction on the unsaturated azido alchohols 1 and 2 identified in our precedent studies as the ideal precursors of pyrrolidine ring [3] (Scheme 1).



Scheme 2

The conditions were optimized in order to modulate the diastereomeric ratio of the diols depending on which Cinchona type chiral ligand was used, thus allowing to obtain four adjacent stereocentres with full stereochemistry control.

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Central-to-Axial chirality conversion: a DFT evaluation of the oxidative atroposelectivity from enantioselective Povarov cycloaddition

Daniel Pecorari,[a,b] Giorgiana Denisa Bisag,[a] Andrea Mazzanti,[a,b] Luca Bernardi,[a,b] Mariafrancesca Fochi,[a,b] Giorgio Bencivenni,[a,b] Giulio Bertuzzi,[a] and Vasco Corti[a]

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The first stereoselective synthesis of enantioenriched axially chiral indole-quinoline systems was recently achieved [1]. The strategy takes advantage of an organocatalytic enantioselective Povarov cycloaddition followed by an oxidative central-to-axial chirality conversion process, allowing access to previously unreported axially chiral indole-quinoline biaryls.

DFT calculations shed light on the stereoselectivity of the central-to-axial chirality conversion, showing unconventional behavior [2]. Indeed, a complexation arising from the oxidant and the intermediate is involved, leading to an atroposelectivity driven by kinetic quench.

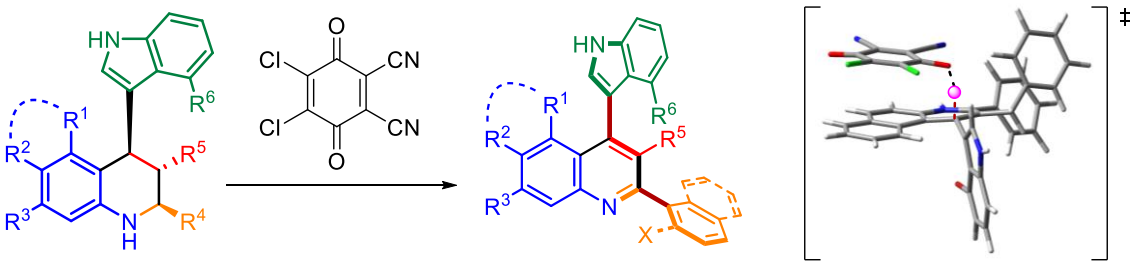

Figure 1: Left: scheme of the oxidative part of the reaction. Right: oxidation's transition state found with DFT calculations.

[1] G. D. Bisag, D. Pecorari, A. Mazzanti, L. Bernardi, M. Fochi, G. Bencivenni, G. Bertuzzi, and V. Corti, *Chem. Eur. J.* DOI: 10.1002/chem.201904213.
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Immobilization of cis-4-hydroxydiphenylprolinol silyl ethers onto polystyrene. Application in the catalytic enantioselective synthesis of 5-hydroxyisoxazolidines in batch and flow

Junshan Lai,[a,c] Sonia Sayalero,[a] Alessandro Ferrali,[a] Laura Osorio-Planes,[a] Fernando Bravo,[a] Carles Rodríguez-Escrich,[a] and Miquel A. Pericàs[a,b]

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A new family of polystyrene-supported *cis*-4-hydroxydiphenyl-prolinol silyl ethers has been prepared, and the resulting polymers have been evaluated as organocatalysts to promote the tandem reaction between *N*-protected hydroxylamines and α,β-unsaturated aldehydes in batch and flow.

Immobilized diarylprolinol **1c**, has afforded the best results while proving remarkably stable under the reaction conditions. This has allowed to run ten consecutive cycles of the same reaction, providing the same enantioselectivity and without significant loss of yield. In addition, eleven flow experiments involving nine different substrates have been carried out over a period of 2 months with the same packed column.

The new PS-supported catalysts compare favorably with well-established immobilized Jørgensen-Hayashi catalysts, affording 5-hydroxy-isoxazolidines as single diastereoisomers with high enantioselectivities and good yields (up to 83% yield, up to 99% ee) [1].

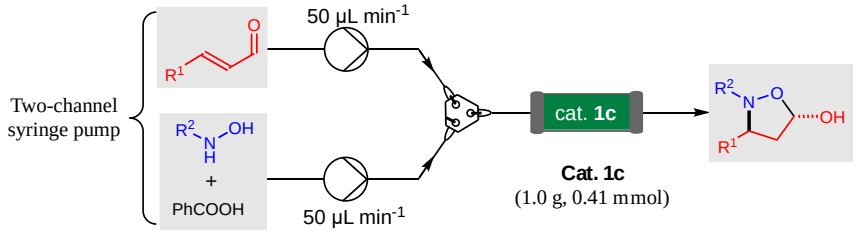

Figure 1

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Designing new artificial neuron models for neuromorphic engineering

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Our societies are profoundly affected by the development of Artificial Intelligence (AI). In fact, AI is applied in many fields: in science, medicine, security, economy, and well-being [1]. There are two strategies to develop AI. One is by writing human-like intelligent programs running in computers or special-purpose hardware. The other is through neuromorphic engineering. In neuromorphic engineering, surrogates of neurons are implemented through non-biological systems either for neuro-prosthesis or to design brain-like computing machines. Surrogates of neurons can be implemented through specific solid materials, in a hardware that can be rigid if made of solid inorganic compounds or flexible if based on organic films. Alternatively, surrogates of neurons can be implemented through solutions of specific non-linear chemical systems, in a wetware [2]. In our group, we are pursuing this second approach: we propose the use of peculiar chemical systems that, in liquid phase and in out-of-equilibrium conditions, can mimic the dynamics of real neurons [3]. We exploit UV-visible radiations as signals and we study their optical communication, giving rise to emergent phenomena of temporal synchronization, analogous to those shown by real neural networks.

In this work, we present the design of new Artificial Neuron Models. They are solutions of two or more photosensitive compounds, which are either photochromic or luminescent or both. The compounds are chosen based on their spectral properties and their mechanisms of relaxation after photo-excitation. They are used to mimic the dynamics of neurons in both oscillatory and phasic excitable regime. The results of numerical simulations are presented.

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Hydrogen-free macrocyclic ligands for the synthesis of a new class of potential molecular spin-qubits

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The obtainment of Universal quantum computers and fault-tolerant quantum processors can be considered a great challenge in the science of quantum information. In this perspective, molecular spin qubits can be an effective alternative to the present ones. Indeed, they guarantee long coherence time (T_2) over a wide range of temperatures, the possibility of a controlled deposition over a surface and a set of addressable and accessible energy levels that can be probed with electromagnetic pulses [1].

The aim of this work is to clarify the effect of peripheral hydrogen atoms on the coherence time of the class of S = ½ metal complexes with macrocyclic ligands like phthalocyanine (Pc) and tetraphenylporphyrin (TPP), that show an appreciable T_2 of some μs at room T [2].

The hydrogen-free ligand *tetrakis*(thiadiazole)porphyrazine (H_2TTDPz) resulted the best choice to the study of the effect of peripheral hydrogen atoms in such systems. In this work, they have been replaced with less active nuclei such as sulfur and nitrogen. The analysis of the magnetization and spin dynamics of the [Cu(TTDPz)] complex is implemented respectively via AC susceptometry and pulsed-EPR. The two techniques highlight some important features of the compound, providing an experimental counterpart of what has been predicted about the influence of hydrogens in [Cu(Pc)] [3].

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An innovative method for quantification of basic sites linked on solid 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 linked on solid matrices (in particular, amino groups). Thanks to the mild operating conditions required by the method, this can also be used to quantify basic sites of matrices already packed in HPLC columns. The procedure is fast and easy to be used, and not destructive towards the analyzed material. The approach is based on the preventive salification of the basic groups linked to the solid by reaction with 3,5-dinitrobenzoic acid (DNBA), and for this reason from now on it will be denoted as DNBA-M. Quantification of the basic functionalities is then performed by an UV-spectrophotometric retro-titration of the salified solid matrix resorting to a preventive either acid or basic displacement of DNBA from the solid material. Alternatively, the displaced DNBA can be quantified by reverse phase HPLC determination. For the development of this method they were employed six samples of derivatized silica, symbolized as AD-CS_n, with *n* ranging from 1 to 6. Consequently, by means of the DNBA-M approach, for each of them it was quantified the relevant Amino Groups Density, AGD.

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A new thiospinel, $MgCr_2S_4$, prepared by Self- sustaining reaction (MSR) induced by ball milling

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The mechanical treatment by ball milling is a powerful processing technique, able to start chemical reactions in a range of reactant mixtures, one of which, at least, in solid-state. Such processes formally occur at room temperature, and no solvent is required.

The literature data indicate that, beside a gradual conversion path, these reactions can occur, in highly exothermic chemical systems, through a self-sustaining processes, and are reported as mechanically induced self-sustaining reaction (MSR) [1]. MSR can often produce unique materials, which are difficult to obtain through conventional techniques [2].

The aim of the present study was to obtain $MgCr_2S_4$ by ball milling, a compound supposed by Liu et al. [3] using DFT and that should have good electrochemical properties and low energy above hull.

To this regard, no literature data are reported concerning the preparation of such chemical system by mechanical treatment, and our efforts were addressed to the synthesis of such composition by ball milling starting from magnesium or magnesium hydride, chromium and sulphur powders.

Experimental results evidenced the occurrence of a MSR, as suggested by a sudden temperature increase of the external side of the reactor wall. This was then confirmed by the structural analyses by XRD of the reaction powders, which indicated that the formation of $MgCr_2S_4$ (space group fd-3m, a=10,137 Å) partially occurs.

Investigation of reaction process was also carried under different experimental condition, i.e. by varying the milling intensity, the ball to powder weight ratio, and the reaction stoichiometry.

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Solid state supramolecular architectures based on calixarenes and halogen bond

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Calix[4]arenes, thanks to their preformed three-dimensional molecular cavity and to their easy chemical modification, are excellent "tectons" to produce solid-state supramolecular architectures also characterized by porosity [1]. In this work we used halogen bonds as the key interactions for the self-assembly of calix[4]arene derivatives. This non-covalent interaction shows important properties like high directionality, modularity and great water stability, thus making it an interesting instrument for the formation of porous networks [2].

A calix[4]arene (**1**) decorated with four halogen bond donor groups was obtained by the functionalization of tetrahydroxycalix[4]arene with four propargyl chains using propargylbromide, followed by the reaction of the resulting tetrapropargyl derivative with N-iodomorpholine hydriodide. The iodine atom was chosen as donor because it is the most polarizable among the halogens, while the triple bond serves to improve the halogen σ-hole thanks to the electronegative effect of the sp carbon atom. Interestingly, the tetraiodo popargyl **1** gives rise to a double layer assembly in the solid state due to sole halogen bonds among the iodoalkyne units. On the other side, the tetraalkynecalix[4]arene (**2**) lacking iodine atoms on the triple bonds, originates a compact 3D network. The capability of the tetra(O-iodopropargyl)calix[4]arene **1** to act as halogen bond donor at the solid state was confirmed by the crystal structure of the 1:2 co-crystal of **1** and 4,4'-bipyridine, where the halogen bonds between the iodine atoms and the nitrogen atoms of bipy lead to the formation of linear ribbons of calixarenes (Figure 1).

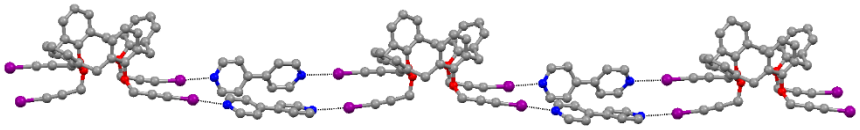

Figure 1: Co-crystal structure of 25,26,27,28-tetra(O-iodopropargyl)calix[4]arene **1** with 4,4'-bipyridine.

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Immobilization of ephedrine-based ligands on magnetic nanoparticles for applications in heterogeneous phase asymmetric catalysis

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Heterogeneous phase catalysis has attracted scientific community in the last few decades because, supporting chiral catalysts on solid supports, it is possible to easily recover and reuse them for several catalytic cycles. Especially the use of magnetic nanoparticles is highly advantageous, both for their high dispersibility in organic solvents that the simple and non-expensive recovery by magnetic decantation [1].

Our attention has been focused on the modification of known efficient chiral ligands' structure, in order to let them be anchorable on Fe_3O_4@SiO_2 nanoparticles. We have chosen ephedrine, that has showed excellent catalytic activity in various asymmetric reactions [2,3]. Two ephedrine-based ligands have been synthetized, with a different linker between the catalytic site and the anchoring function, that have been tested in the addition of diethylzinc to aldehydes. Having obtained promising results, we started the heterogeneous phase tests.

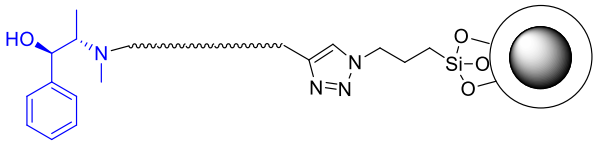

Figure 1: Ephedrine-based nanocatalyst.

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Enables: European infrastructure powering the internet of things

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The mission of EnABLES [1] is to open up key research infrastructure in powering the IoT to all European researchers, from both academia and industry. Six research institutes together with five knowledge hubs are providing access to researchers to enable them to create 'self-sustaining' energy solutions to 'power the IoT'. This encompasses providing free-of-charge access to external academic and industry stakeholders, as well as fostering collaborations between the project partners to develop standardised and application-optimised materials, devices and systems.

The ultimate goal of EnABLES is to create a 'starting community' to foster collaborations to accelerate technology development. This contribution outlines why EnABLES is needed, particularly for enabling researchers address key challenges of modern society, such as extending battery life of wireless IoT edge devices.

[1] www.enables-project.eu

Determination and qualitative characterization of microplastics in Ocean Arctic waters

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One of the most persistent and abundant types of marine pollution is represented by microplastics, small plastic debris less than 5 mm in size. Plastics are cheap, lightweight, strong, durable and corrosion resistant. All these features together arose the investment in plastic manufacture, leading to massive production and application. Therefore, the amount of plastic-based waste sharply increased. When the plastic debris enter the marine environment, they undergo photochemical, mechanical or biological degradation, which cause their division even in smaller pieces. These plastic fragments are so small that they are no longer discernable from the surroundings so that they are easily ingested by marine organisms. Furthermore, the reduced size of these plastic wastes make their transportation via ocean current and wind very simple, even in the most remote areas of the planet [1]. The aim of the present work was to qualitatively characterize the microplastics found in the marine area of the Northwest Passage during the Arctic Expedition conducted by Gyres in 2016. The samples were collected using a Manta trawl and 20 micron pump and successively stored in isopropyl alcohol until analysis. Six water samples were examined: they were first sieved using 5 mm, 2 mm, and 0.3 mm sieves to separate solid material in two different class sizes, 5-2 mm and 2-0.3 mm, respectively. Sieved materials were then dried and subjected to wet peroxide oxidation in the presence of Fe(II) to digest the organic matter [2]. The resultant solution was filtered, and solid residues were analyzed using Attenuated Reflectance Fourier Transform Infrared spectroscopy (ATR FT-IR) and Field Emission Scanning Electronic Microscopy (FESEM) [3]. It was found that the 80% of microplastics contained in water samples were identified as polyethylene (PE), polypropylene (PP), polystyrene (PS), polyvinyl chloride (PVC), nylon, polyurethane (PU) and mixtures of PE/PP.

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Supercritical CO_2 extract of *Commiphora myrrha on a pilot scale* focused on sesquiterpenes

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Exenia is a company working on the supercritical fluids from 25 years and, in its history, has dealt with many different supercritical carbon dioxide's ($scCO_2$) fields of application: from pasteurization to supercritical fluid extraction (SFE). In particular, Exenia is set on the research and development of new $scCO_2$ industrial applications, feasibility studies and process optimization.

This work aims to show the first results obtained with supercritical fluid extraction of the myrrh through a pilot scale machine. Moreover, it lays the foundations for the evaluation of the scale-up for an industrial scale production of $scCO_2$ extracts.

The myrrh is well known for its healing properties. In accord with literature it could be used as an ingredient for cosmetic and nutraceutical products. [1]. The myrrh is the exudate of *Commiphora myrrha* plant, a gum-resin made up of waxes (40-50%), resin (23-40%) and volatile oil (2-8%) [1]. The fractions of essential oils and waxes contain many different sesquiterpenes, more than 33 were characterized in a single plant variety for essential oil fraction [2]. Furthermore, SFE was focused on selected sesquiterpenes extraction: **furanoeudesma-1,3-diene, furanodienone, curzerene** and **β-elemene** [2]. In this framework, the extracts resulted enriched in these molecules and, after the post processing, were concentrated even more, in fact in example, the concentration of **furanoeudesma-1,3-diene** reached the 10.48% (w/w).

Therefore, myrrh essential oil extraction, through SFE, leads to yield results perfectly comparable with those deriving from traditional methods [3], without the usage of toxic and undesired organic solvent by the pharmaceutical and cosmetic industry.

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Selective air-photooxidation of sulfides to sulfoxides: a green approach

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Sulfoxides are key moieties in pharmaceutical (omeprazole and omeprazole-like compounds for the treatment of gastroesophageal reflux disease, peptic ulcer disease, and Zollinger–Ellison syndrome) and broad-spectrum insecticides like Phenylpyrazole chemical family.

The oxidation of sulfides to sulfoxides is a challenging reaction due to the overoxidation to sulfones in common organic solvents [1].

To overcome this issue, we recently proposed a highly efficient, complete chemoselective in-water air-photooxidation of sulfides to sulfoxides mediated by Tetraphenyl Porphyrin Sodium Tetrasulfonate (TPPS) supported on core-shell PMMA NPs, followed by an innovative membrane-mediated electrocoagulation (MM-EC) separation technique [2].

As mayor limitations, in-water oxidation is only limited to water soluble sulfides, while MM-EC showed low throughput and time demanding operations.

The scope of this research has been the identification of suitable experimental conditions for the sulfoxidation water-insoluble sulfides (Fig. 1).

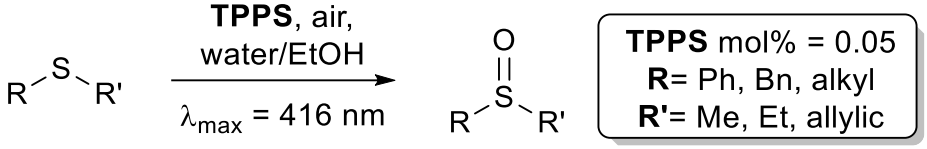

Figure 1: Typical reaction conditions for the sulfides oxidation.

This work offers an innovative, fast and reliable approach to the synthesis of sulfoxides from a variety of sulfides (with electron-poor and/or electron-rich substituents), with complete chemoselectivity, high yields and efficient isolation of the target products from the reaction crudes.

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Innovative materials for As(III) and As(V) removal in water treatment

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Aquatic environment contamination due to heavy metals and their potential toxicity and accumulation is a serious concern for humans and ecosystem. Usually, metal contamination derives from the run-off of agricultural lands, contaminated soils and mineral deposits. Other contamination sources could be industries, agricultural and livestock farming. Arsenic contamination in groundwater is a big issue that involves about 140 million people in over 50 countries worldwide. In natural water, arsenic is in the inorganic form, most commonly as arsenite As (III) and/or arsenate As (V). The main reclamation processes currently available to remove arsenic from water are based on: i) oxidation, ii) coagulation, iii) precipitation and filtration, iv) adsorption, v) membrane technologies, vi) bio-reclamation and vii) ion exchange [1]. In this paper it was decided to exploit, as an alternative technique for the removal of As(III) and As(V) in water, plant biomass biochar and nanosponges synthesized from starch derivatives. Biochar is a carbonaceous substance usually resulting from vegetable essences, highly resistant to biological decomposition. Biochar is the product of a thermochemical conversion of biomass with a reduced or zero supply of oxygen. An important feature of biochar is the heavy metals break down. Biochar could be suitable for metals removal in aqueous matrices but could be also fundamental for contaminated soils treatment. In this context of unconventional techniques, the use of synthesized nanosponges could be an interesting alternative to the traditional methods for arsenic removal. In order to be able to evaluate the adsorbent capacities of biochar and nanosponges, solutions of As (III) and As (V) at different concentrations were prepared and were placed in some batch system respectively with biochar and nanosponges. The arsenic reductions recorded were considerable, from 90 to 100% for both types of materials. It can be said that biochar and nanosponges can represent an effective alternative to traditional methods for arsenic removal in water treatment, more sustainable and more economically convenient.

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Sprinkler irrigation: a golden bullet to minimize the bioaccumulation of As and Cd in rice grain?

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Among the factors affecting the bioaccumulation of toxic elements (like As and Cd) in rice, a key role is played by the nature of the irrigation methods. Sprinkler irrigation (SP), optimized for rice exclusively in Sardinia [1], Italy, and applied to several tens of rice genotypes over many years, has produced no reductions in yields, leading also a conspicuous water savings and a collapse of emissions of greenhouse gases. In addition, SP has proven to be effective in reducing the amounts of both As (-98%) [2] and Cd (-20%) [3] in rice grain in comparison to the amounts measured in the same conditions using the traditional irrigation (i.e. the continuous flooding, CF). In this contribution, original ICP-MS and HPLC-ICP-MS methods have been developed and validated in order to study changes in the bioaccumulation level of total As and Cd, as well as the distribution of four As species (i.e. As(III), As(V), MMA and DMA), in parts of rice plant (i.e. grain, roots, stems, leaves, and panicles) as a function of the nature of irrigation method, as well as the nature of the soil or the genotype of rice. SP is able to minimize contemporary the amounts of As and Cd in rice grain, and this allows to always produce – also on soils heavily polluted by As and/or Cd (ca. 50 mg kg-1 each), an healthy rice, where the amounts of both toxics in grain are well below the very strict limits posed by EFSA and EC (0.2 mg kg-1 for both elements). Dynamics of translocation of As and Cd along the soil-plant system have been studied in order to gain insights on the influence of the irrigation technique in their bioaccumulation phenomena. Finally, As(III) and DMA are the main species in CF rice, whereas As(V) sharply prevails in SP rice.

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Preparation of biowax esters in continuous flow conditions

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The term "wax" concerns to naturally solids and amorphous substances at room temperature that become liquid quite easily around 50 °C. Biowaxes synthesized from vegetable fatty acids are an alternative to petrochemical paraffins. A simple way of access to these compounds is the esterification of long-chain acids with fatty alcohols to obtain wax esters with chains longer than C30 [1].

In this study, biowax esters are prepared under flow conditions cutting dramatically both reaction times (from 12 h to 30 min) and temperature conditions, with respect to batch procedures (from 90 -120 °C to 55 °C).

With the goal of obtaining a suitable method for industrial applications [2], the flow chemistry procedure for the esterification of margaric, stearic, oleic and palmitic acids with an array of alcohols to produce the corresponding ester waxes, is developed.

Optimization of reaction conditions has been performed by response surface methodology (RSM).

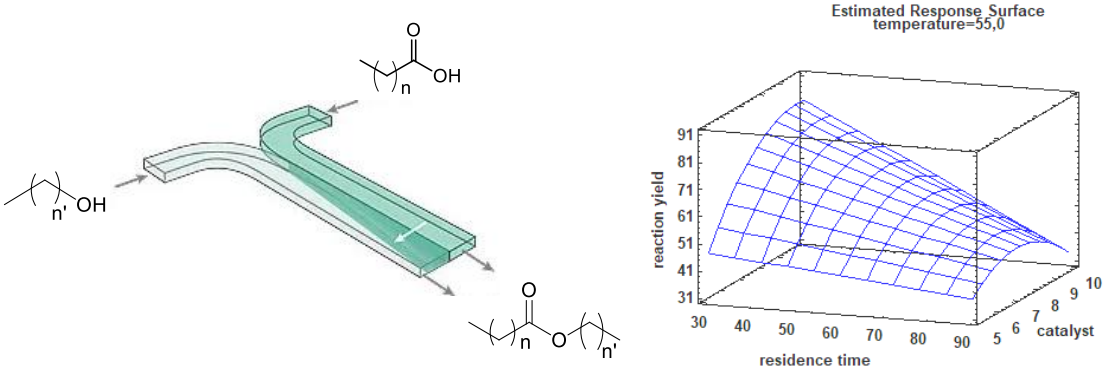

Figure 1: Fisher-type esterification of long-chain acids with alcohols under flow conditions optimized by response surface methodology.

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Tuning mesoporous carbon materials with nitrogen content for CO_2 up-take

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The increase of global greenhouse gases concentration, mainly due to anthropogenic emissions, is responsible for severe environmental issues, in particular global warming. This urgent problem is leading to the development of new strategies to reduce the emissions of CO_2, which is the main greenhouse gas produced through human activities. At present, functional materials based on amines are the most promising for CO_2 capture, thanks to the possibility to realize a reversible adsorption [1].

Nitrogen-containing ordered mesoporous carbons (NOMCs) are interesting materials with large surface area and functional CO_2-filic groups. OMCs can be synthesized as nano-replica of an ordered mesoporous silica hard template (in our case SBA-15 silica in Fig. 1a), using a three-step procedure: i) infiltration of a carbon precursor inside the pores of the silica material (Fig. 1b), ii) pyrolysis and iii) template removal (Fig. 1c). Starting from SBA-15 silica template and sucrose as carbon source, a high specific surface area CMK-3 type material (see Fig. 1d) was prepared [2]. Carbon material based on sucrose was used as a model in order to explore different strategies to obtain nitrogen-rich porous carbon materials (Fig. 1e) as an efficient CO_2 adsorbent.

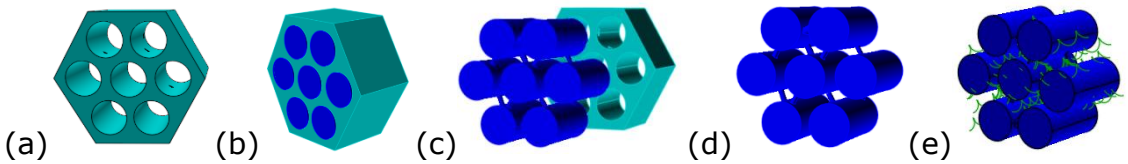

Figure 1: Schematic illustration of SBA-15 silica template (a), infiltration process of a carbon precursor into a silica template (b), template removal after pyrolysis, CMK-3 type carbon material (d) and nitrogen-rich porous carbon material (e).

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A new synthesis of (*S*)-1-(5-fluoropyrimidin-2-yl)-ethanamine catalyzed by immobilized ω-transaminase from *Vibrio fluvialis* under flow and green conditions

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It is estimated that at least 40% of APIs and drugs in development contain chiral amines [1]. Typical constraints associated with reductive amination (e.g. low efficiency/selectivity and high environmental impact) make biocatalytic routes an attracting alternative for the preparation of chiral amino compounds.

ω-Transaminases (or aminotransferases, ω-AT, EC 2.6.1) are pyridoxal-5'-phosphate (PLP)-dependent enzymes that catalyze the transfer of an amino group from the amino donor to a prochiral ketone acceptor, thus yielding a highly enantiomerically enriched amine through a greener and more concise route compared to conventional chemical reactions [2].

Herein we report on the covalent immobilization of the (*S*)-selective ω-AT from *Vibrio fluvialis* (Vf-AT) and its use in the synthesis of (*S*)-1-(5-fluoropyrimidin-2-yl)-ethanamine, a key intermediate of the JAK2 kinase inhibitor AZD1480 [3]. The reaction was performed in batch and then transferred in a flow system. Coupling of the *in continuum* biotransformation with an *in-line* purification step resulted in a highly productive and straightforward bioprocess.

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Novel Hydrophobic Deep Eutectic Solvents (DESs) as Green Water-Separable Extraction and Reaction Media

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The environmental impact of chemical applications can be reduced by using novel solvents with green properties. In this field, Deep Eutectic Solvents (DESs) are promising liquids thanks to their unique characteristics [1].

DESs are mixtures of a hydrogen bond donor molecule (HBD) and a hydrogen bond acceptor molecule (HBA) at the proper molar ratio. Those novel liquids are showing excellent green properties for their non-volatility, their low or absent toxicity and for their recycle capabilities. Moreover, if the HBD and the HBA are natural-source molecules, these liquids have increased bio-availability and bio-compatibility.

In this work we present the preparation of novel hydrophobic deep eutectic solvents and the studies of their properties. In this study, the role of the components of the liquids has been revealed. The HBD compound properties, in particular its hydrophobicity/hydrophilicity, showed to be fundamental for an efficacious separation from water and for an effective removal/extraction of organic phenol polluting molecules from it. The phase separation and the extraction efficiency of these mixtures were not dependent on the pH of the water phases; this revealed these liquids to be effectively separated under these conditions and still active in their extraction capabilities[2],[3].

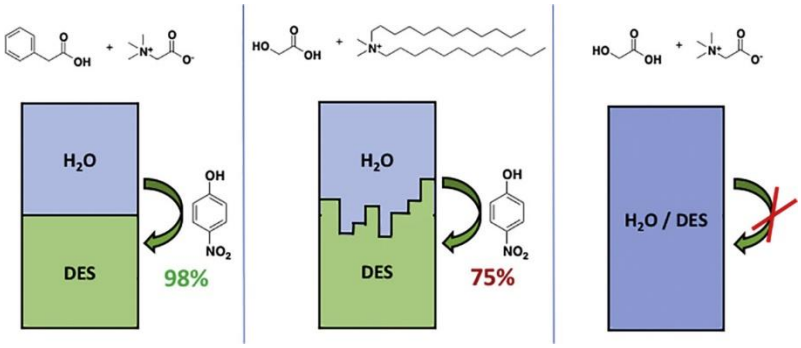

Figure 1: Extraction capabilities of novel Hydrophobic DESs.

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Computationally driven design and chemical synthesis of a novel library of VX-809 hybrids derivatives as F508del-CFTR correctors

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Cystic fibrosis is caused by mutations in the CFTR gene. The deletion of phenylalanine 508 (F508del) is the most prevalent mutation and leads to an incomplete folding of protein [1]. Hereto, small-molecule to be used in therapy requires compounds that correct the CFTR misfolding, such as the well-known corrector VX-809, its retention in the endoplamastic reticulum (ER) or, its defective channel gating by means of potentiators [2]. At this time, corrector compounds like VX-809 partially rescue the protein misfolding and have to be administered in tandem with other modulators or potentiators, such as VX-770. Recently, a number of correctors exhibiting key chemical features of VX-809 merged with the aminoarylthiazole scaffold have been synthesized (Figure 1) [3], showing promising and sometimes ameliorated activity as F508del CFTR correctors. Starting from these data, initially we scouted the binding mode of these hybrids on the NBD1 site of the CFTR protein using computational methods. Results obtained from molecular docking simulations around the hybrid derivatives have shown comparable positioning with respect to that of the prototype VX-809. In particular, these studies highlighted a number of key residues supporting the corrector binding and allowed to guide the rational design and the chemical synthesis of a novel small library of analogues, herein discussed.

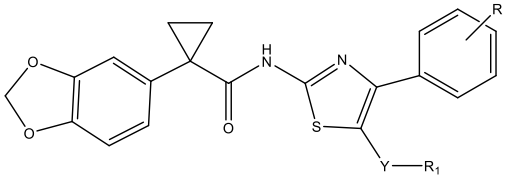

Figure 1. Scaffold of the VX-809 hybrid compounds.

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Innovative synthetic approach based on the native chemical ligation for development of new dual PET/OI peptide imaging probes

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Dual Optical/PET peptide imaging probes are considered as efficient tools for disease diagnosis and/or monitoring. Their preparation is still a challenging task due to the complicated synthetic protocols requiring fully-protected peptide segments (in solution) or the use of orthogonal protection groups (solid phase) to achieve the dual site-specific labelling. An advantageous strategy for peptide site-specific modification of unprotected peptide in solution, overcoming most of the above mentioned limitations, relies on the use of native chemical ligation (NCL) [1].

Targeting peptide AE105 (reported antagonist of uPAR) was synthetized using a solid phase peptide synthesis approach and functionalized with a cysteine to allow the condensation with AAZTA-C4-COOH, pre-activated as thioester with 2-Mercaptoethanesulfonic acid sodium salt (MESNA). After the reaction between the free thiol of the cysteine and the AAZTA thioester derivative, a rearrangement gives a stable amide bond between the N-terminus of the same cysteine and the carboxylic group of the arm of AAZTA-C4-COOH. The transposition of the chemical bond on the amine, made the thiol accessible to the subsequent reaction with a maleimide pre-activated fluorophore (i.e. cy 5.5). The desired product was afforded from preparative HPLC with a chemical purity over 95%. Final complexation with ^{nat}Ga was performed at pH 4, in order to evaluate the labelling efficiency with the metal and to demonstrate, by *in vitro* binding evaluations monitored by Flow Cytometry, that all the above modifications on the native peptide structure, did not affect the affinity for the uPAR receptor. Herein we developed a standard synthetic strategy to easily obtain a targeting molecule functionalized with a fluorophore to be employed in optical imaging applications and a cage, to allow the complexation with PETs radionuclides.

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Purine nucleotides as potential ligands of G protein-coupled receptor 17 (GPR17): molecular modelling and synthesis

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The GPR17 receptor, phylogenetically related to both purinergic P2Y and CysLT receptors, is involved in various brain disorders and demyelinating diseases such as multiple sclerosis, stroke, schizophrenia, and depression. GPR17 is a promising therapeutic target; thus, molecules which can bind specifically to this receptor are actively being sought [1].

The evidence that GPR17 is responsive to nucleotides [1] prompted us to synthesize few molecules addressed by docking studies on a GPR17 homology model based on the $P2Y_1$ receptor experimental structure.

Chemical synthesis of 8-methylaminoinosinic acid (**1**) and N^2-alkyl/acyl derivatives of guanylic acid (**2**-**4**) (**Figure 1**) was performed either by phosphorylation of 8-methylaminoinosine, or by N^2-alkylation/acylation of guanosine, followed by phosphorylation. In the case of **2**, position N^2 of the purine ring was activated as a bromo derivative and subjected to displacement with octylamine. N^2-Acylations were performed by N^2 functionalization with the proper acyl chloride or anhydride through a transient protection strategy. Compounds **2**, **3** and **4** were obtained as 2',3'-*O*-isopropylidene adducts of the corresponding nucleotides.

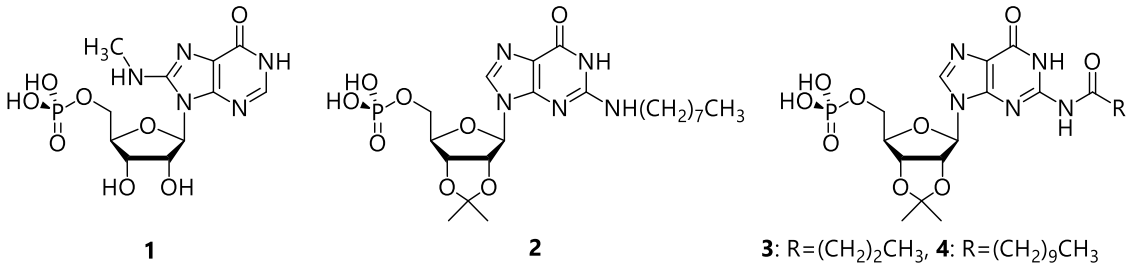

Figure 1: Purine nucleotides (**1**-**4**) as potential ligands of GPR17.

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Coordination of an alpha-synuclein c-terminal fragment to non-heme iron: effect on dopamine oxidation and oxidative stress

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Alpha-synuclein (αS) is a small protein of 140 residues, very abundant in the brain. Its biological role is not fully understood, but probably it is implied in cellular membrane binding, pre-synaptic vesicles recycle and dopamine metabolism [1]. The native sequence of αS can be divided into three different domains: (i) the N-terminal domain (residue 1 to 65), which contains KTKEGV repetitions; (ii) the non-amyloid-beta component (residue 66 to 95) and (iii) the C-terminal domain (residue 96 to 140) [1]. This last region has an high concentration of negative charged residues, which makes it possibly implicated in iron(II)/iron(III) coordination [2].

In order to have further insights regarding the effect of iron-synuclein complexes in dopamine metabolism and oxidative stress, two representative sequences of C terminus have been synthesized: Ac-α-$Syn_{119-132}$ (Ac-^{119}DPDNEAYEMPSEEG^{132}-NH_2) and its monophosphorylated analog at S129 (Ac-α-$SynpS_{119-132}$). This region was chosen because it contains the ^{119}DPDNEA^{124} motif, which is thought to be the main binding site for iron [2]. Furthermore it contains the Tyr125 and Ser129 residues, whose phosphorylation could enhance the iron-binding affinity [3].

Preliminary studies on iron binding and catalytic oxidation of dopamine have been performed. Our data suggest that Ac-α-$Syn_{119-132}$ and, particularly, Ac-α-$SynpS_{119-132}$ delay the initial formation of the $[Fe(DA)_2]^-$, main representative species at physiological pH, and its decay over time. Furthermore, our data suggest that Ac-α-$Syn_{119-132}$ does not influence the catalytic oxidation of dopamine, instead Ac-α-$SynpS_{119-132}$ seems to depress the reactivity, although to a modest extent.

Future perspectives are directed toward the synthesis of the Tyr125 and Tyr125-Ser129 phosphorylated analogues, in order to evaluate the effect of increased affinity on catalysis.

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Exploring the conformational space of IDO1 with the available experimental data in PDB

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Indoleamine 2,3-dioxygenase 1 (IDO1) is a heme-containing enzyme which is responsible of the oxidative cleavage of the indole double bond of L-Tryptophan (L-Trp) along the Kynurenine pathway [1]. IDO1 exerts not only a catalytic activity, but is also important for its signaling pathway [2]. Because of its involvement in the alteration and dysregulation of the immune response during cancer development, IDO1 is considered an important druggable target [3]. Since 2006, thirty-five crystal structures of IDO1 have been released in RCSB Protein Data Bank (PDB) in holo- or apo-state. Being a dynamic process, ligand-protein interaction often goes hand by hand with conformational modifications.

Hence, in this work we performed a study using all deposited IDO1 structures with the aim of exploring similarities and differences in the conformational landscape defined by these entries. Firstly, a secondary structure analysis was carried out to assess structural differences among the crystals at level of secondary motifs. Secondly, docking studies were conducted to study whether differences exist in conformations of binding site residues that, affecting binding scores and predicted binding modes, may eventually impact on the outcome of structure-based virtual screening campaigns (SBVS). In particular, a Principal Component Analysis (PCA) was carried out to identify groups of different crystallographic entries that, representing an enriched ensemble of IDO1 conformations, may be used for future SBVS aimed at capturing the widest array of chemical diverse scaffolds in small molecule libraries as novel enzyme ligands.

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Exploring the substrate-*Staphylococcus aureus* NorA efflux pump recognition pathway through a Supervised Molecular Dynamics approach

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The excessive use and abuse of antimicrobial agents in humans and animals has contributed to the growing of antimicrobial resistance (AMR), which is currently a public health threat. In this context, bacterial efflux pumps play a key role in AMR development, being able to effluxing a wide spectrum of compounds. The co-administration of an antibiotic with a compound able to restore the effective antibacterial activity may be a winning strategy. In particular, the identification of efflux pump inhibitors (EPIs) holds promise for new antimicrobial resistance breakers (ARBs) [1]. NorA efflux pump contributes to *Staphylococcus aureus* (*S. aureus*) resistance against fluoroquinolone antibiotics (e.g., ciprofloxacin) by promoting their active extrusion from the cells [2]. Even though NorA efflux pump is known to be a potential target for EPIs development, the lack of protein structural information and the limited knowledge available on its mechanism of action have strongly limited rational drug discovery efforts in this field.

To provide a comprehensive understanding of the antimicrobial drug extrusion mechanism, a NorA efflux pump homology model was built. Next, the possible recognition pathway between NorA and its substrate ciprofloxacin was investigated by using a Supervised Molecular Dynamics approach (SuMD) [3]. SuMD aided for the first time the identification of possible key sites explored during the extrusion pathway. Future directions will regard the validation of the obtained results for a deeper comprehension of the mechanisms of action of both NorA efflux pump and related EPIs.

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[3] D. Palazzotti, M. Bissaro, G. Bolcato, A. Astolfi, T. Felicetti, S. Sabatini, M. Sturlese, V. Cecchetti, M.L. Barreca, and S. Moro, *Int. J. Mol. Sci.* **20** (2019) 4041.

Towards new small-molecule peptidomimetics as selective $\alpha_V\beta_6$ integrin ligands

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Integrins are heterodimeric cell surface receptors used by cells to communicate with the extracellular matrix; they play key roles in different physiological processes and, for this reason, their altered activity is related to different pathologies including cancer development, metastasis spread, autoimmune diseases and fibrosis, rendering these receptors attractive targets in biomedical research [1]. The $\alpha_V\beta_6$ receptor, belonging to the RGD-recognizing integrin family, is overexpressed in many epithelial tumors as well as in liver and pulmonary fibrosis, and has emerged as a biomarker of the epithelial-to-mesenchymal transition, which in turn sustains metastatization, tumorigenesis and fibrosis. Along this line, $\alpha_V\beta_6$ is an ideal target for both therapeutic and diagnostic purposes, provided that potent and selective $\alpha_V\beta_6$ ligands are available. In this context, our purpose was to synthesize a library of cyclic peptidomimetics where a 4-aminoproline scaffold (Amp) is flanked by variable tri-, tetra- and pentapeptide sequences, and functionalized for the covalent conjugation to bioactive or imaging-active units (Figure 1). Inspired by the known $\alpha_V\beta_3$ integrin ligand **1** [2], we synthesized a collection of 18 cyclopeptidomimetics of type **2-5** by solid phase synthesis, followed by in-solution cyclization reactions. These compounds have been evaluated for their binding affinity toward the isolated $\alpha_V\beta_6$ receptor giving promising results that will drive us in the development of potent and selective $\alpha_V\beta_6$ ligands as new pharmacologically relevant agents.

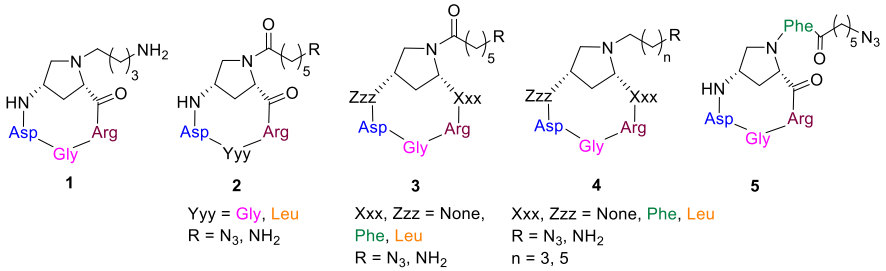

Figure 1: Library of cyclic peptidomimetics.

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Development of novel 7-Deazahypoxanthine derivatives as potential antitripanosomal agents

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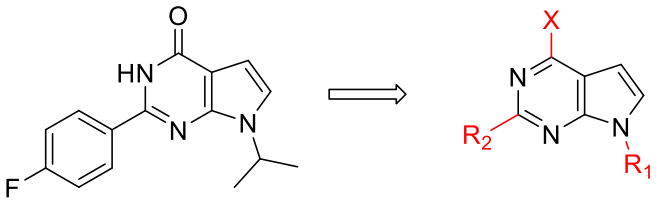
The currently available therapy for the treatment of Human African Trypanosomiasis (HAT) is unsatisfactory due to unacceptable toxicity, poor efficacy and drug resistance [1], therefore there is an urgent need to develop new safe and effective drugs.

A scaffold-hopping approach was performed by replacing the chemical core structure of NPD-2975, which is a potent antitrypanosomal hit compound (pIC_{50} = 7.1), in order to identify new promising heterocyclic systems with enhanced pharmacokinetic, pharmacodynamic and physicochemical properties.

In this way, a collection of close analogues with different scaffolds was obtained. One of these, presenting the 7-Deazahypoxanthine core (NPD-3632), showed promising inhibitory activity *in vitro* against *Trypanosoma brucei* (pIC_{50} = 5.9), thus a Structure-Activity Relationship (SAR) study was performed (Figure 1). From this study, several new promising antitripanosomal compounds emerged, which are endowed with submicromolar IC_{50} values.



NPD-3632
T. brucei pIC_{50}: 5.9

Figure 1: SAR study on NPD-3632.

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Preliminary ADME/PK studies of new *h*DHODH inhibitors effective for treatment of acute myeloid leukaemia (AML)

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The *human* Dihydroorotate Dehydrogenase (*h*DHODH) plays a pivotal role in *de novo* pyrimidine biosynthesis, controlling vital cellular functions and survival. Recently, *h*DHODH, a validated target for treatment of autoimmune diseases has related to acute myeloid leukaemia (AML), being *h*DHODH inhibitor able to restore the myeloid differentiation. We developed a new class of *h*DHODH inhibitors [1], being M433 (IC_{50} = 1.2 nM) the most interesting.

In this occasion, we profiled these compounds for their physicochemical properties as drugs, i.e. lipophilicity, solubility, biological fluids stability, protein binding and *in vitro* metabolism. Compound M433 was also studied *in vivo*, in order to determinate its *pharmacokinetic profile*. We quantified plasma concentration of M433 by LC-MS/MS in MRM mode in female and male CD-1 mice, after a single intravenous dose (5 mg/Kg).

Moreover, *in vivo* toxicity was evaluated in Balb mice, treated the animals for 35 days with two different doses of M433 (10 and 25 mg/Kg), all mice tissues were evaluated and compared to controls. *Drug-like* properties, pharmacokinetic and toxicity profile are presented and discussed. The data obtained will be useful for planning the design of the next generation of inhibitors, while future tests to determine the complete ADME-Tox profile.

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Giant Unilamellar Vesicles (GUVs) as highly sensitive MRI contrast agents

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The last ten years have witnessed the development of a large variety of nanosystems for applications in MRI, to overcome the intrinsic low sensitivity of the technique in Molecular Imaging protocols.

Pushing further the same reasoning, in this work we have explored the potential of microsystems such as Giant Unilamellar Vesicles (GUVs) as T_1, T_2 and CEST MRI agents. In particular, we optimized a procedure reported in literature [1] in order to design the most suitable probe for Molecular Imaging purposes. The newly developed vesicles, loaded with Lanthanides complexes, have been characterized in terms of dimensions, millimolar relaxivity at different magnetic fields and CEST potential. As the mean diameter of GUVs ranges between 1-2 μm, the payload of complexes in the inner cavity could be up to three order of magnitude larger than nanosized liposomes whose typical diameter is about 100-200 nm. It follows that the sensitivity per particle has been increased accordingly.

Fluorescence microscopy *in vitro* targeting experiments have been performed incubating fluorescent Folate-targeted GUVs with IGROV-1 cancer cells. After the binding with the target receptors on the cell surface giant liposomes are not internalized contrary to nanosized liposomes.

To the best of our knowledge this is the first time that GUVs have been developed as Molecular Imaging agents.

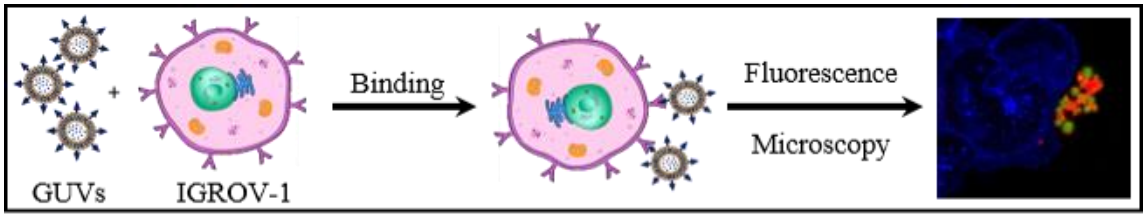

Figure 1: Fluorescence miscoscopy image of the external binding of Folate-targeted giant liposomes to IGROV-1 cancer cells.

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1-Benzylpiperidine derivatives: design and synthesis of new compounds as tyrosinase inhibitors from Agaricus bisporus

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Tyrosinase (Tyr, EC 1.14.18.1) is a widely distributed metallo-enzyme responsible for melanogenesis. Tyr displays a conserved bi-copper active site able to bind molecular oxygen. To date, several natural and synthetic tyrosinase inhibitors (TyrIs) have been developed for treatment of hyperpigmentation, melanoma, lentigo and freckles. To improve the pharmacological profile of currently used TyrIs, there is a growing interest in development of new synthetic and semi-synthetic inhibitors. Over the past few years, we developed a series of compounds bearing the 1-benzylpiperidine fragment as structural motif for inhibitory properties. Our efforts resulted in the identification of molecules showing inhibitory effects up to IC_{50} = 0.48 μM toward Tyr from *Agaricus bisporus* (TyM) [1-3]. These promising data inspired us the synthesis of newer series of TyrIs. We chose to maintain the benzylpiperidine fragment and modify the remain portion of molecule as suggested by docking analysis (Figure 1).

All synthesized compounds were studied to evaluate their inhibitory effects against TyM as well as the mechanism of enzyme interaction.

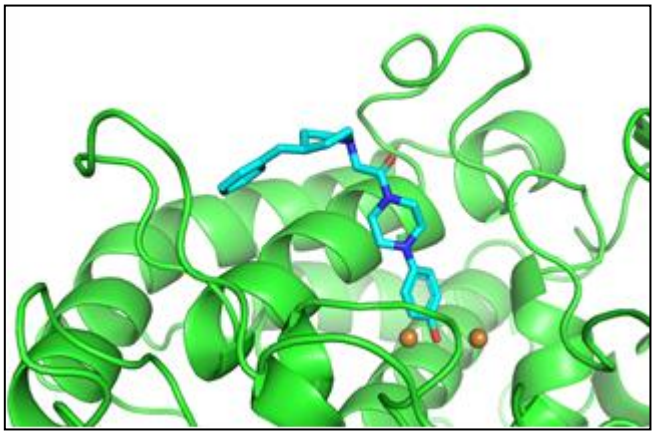

Figure 1

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[3] L. Ielo, B. Deri, M.P. Germanò, S. Vittorio, S. Mirabile, R. Gitto, A. Rapisarda, S. Ronsisvalle, S. Floris, Y. Pazy, A. Fais, A. Fishman, and L. De Luca, *Eur. J. Med. Chem.* **178** (2019) 380-389.

Design, synthesis and co-crystallization of new *Plasmodium falciparum* dihydroorotate dehydrogenase inhibitors based on hydroxypyrazole scaffold

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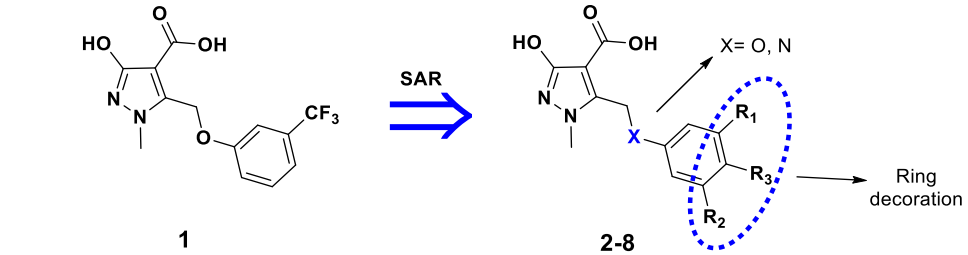
Dihydroorotate dehydrogenase (DHODH) is an enzyme involved in the *de novo* biosynthesis of pyrimidines. In humans, cells can acquire pyrimidines using two different pathways: the *de novo* biosynthesis and the *salvage pathway*. *Plasmodium* species, responsible for the transmission of Malaria, can gain pyrimidines only from the *de novo* pathway and, by reflex, blocking this biosynthesis offers a therapeutic opportunity to kill the parasite. *P.falciparum* DHODH (*Pf*DHODH) has been validated as a drug target and, nowadays, two inhibitors are tested in clinical trials for Malaria [1]. Starting from compound **1**, a *Pf*DHODH inhibitor recently designed by our group [2], we here present a SAR study involving seven new analogues. Among them, compound **5** shows higher activity than **1** on *Pf*-infected erythrocytes. In this work, beside the design, synthesis, co-crystallization with *Pf*DHODH protein, biological activities of new *Pf*DHODH inhibitors are fully discussed.



1
EC_{50} 67.1 μM on *P.falciparum* 3D7 cells

2-8
Cpd 5: X=O R_1,R_2=H R_3=SF_5
EC_{50} 18 μM on *P.falciparum* 3D7 cells

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Hydrogen cyanide adsorption and reactivity on TiO_2 nanoparticles

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HCN is a very toxic (acute oral LD_{50} *ca*. 4 mg/Kg), rapidly acting poisonous substance. It has been utilized in the past as poison and chemical weapon.

HCN can be released in the atmosphere in gaseous form also because of much common activities than the above, like industrial processes, combustion of fossil fuels and of some plastics, vehicle exhaust emissions, and biomass burning. The need to prevent its release in the environment has prompted the research of strategies for its capture and neutralization. Among them, hydrolysis and oxidation over heterogeneous catalysts (i.e. metal oxides) have been found to be effective, even at very low concentrations [1].

The investigation of the heterogeneous chemistry of HCN has recently received a renewed interest, also because of the research in some completely different contexts, *i.e.* in prebiotic chemistry and astrobiology. The presence of HCN and its derivatives in interplanetary and interstellar media has been evidenced. These compounds adsorption and reactions on solids like ice, silica, silicates, and other minerals are supposed to play a role in the synthesis of a variety of biomolecules in prebiotic era [2].

The aim of the current research is to add new insights to the above fields. The starting point is the evidence that the surface Lewis acidity and basicity of TiO_2 combined with its redox properties cause an interesting surface chemistry in the case of interaction with unsaturated hydrocarbons like H-C≡CH [3]. In this respect, we decided to investigate the adsorption and the chemical behavior of H-C≡N on titania samples with controlled morphology and surface composition (hydroxylation degree). The investigation was performed *in situ* in dark conditions as well as under UV illumination using vibrational (FTIR and Raman) spectroscopies as main experimental techniques.

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[2] J.P. Ferris and W.J. Hagan Jr., *Tetrahedron* **40** (1984) 1093-1120.
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Highly oriented enamel-like hydroxyapatite nanorods: the effect of citrates on the structure and surface properties

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Nowadays, the field of biomaterials becomes very advanced and competitive with more and more biocompatible and efficient materials resembling natural ones. The prominent class of inorganic materials is hydroxyapatite, being the major part of mineral content of a bone tissue.

Here, the formation of high-oriented columns of enamel-like hydroxyapatite (HA) on amorphous calcium phosphate (ACP) supports prepared with and without citrate is demonstrated. The ACP and Cit-ACP pellets were soaking in a growing solution at 37°C with different maturation times from 30 minutes to 24 hours, consequently, the formation of HA nanorods was achieved. That was confirmed in both cases by FE-SEM. By XRPD measurements, a preferential orientation of growing along the c-axis of the HA domains was observed. As well as a delay in the kinetics of growth of the HA nanorods in the presence of citrates.

The study of the surface properties of the nanorods after 24 hours of maturation was done by infrared spectroscopy in DRIFT mode under a controlled atmosphere. The comparison between the normalised spectra of nanorods grown on ACP and Cit-ACP in the region of the νOD band of the first hydration layer conditions, evidence that the presence of citrates causes a decrease in the hydrophilicity of HA. In addition, the presence of columnar OH groups in the nanorods overgrown on ACP was detected, instead these species were not detected in the case of the Cit-ACP.

Synthon-approach starting from amino-azaheterocycles to obtain new compounds with potential antiproliferative activity

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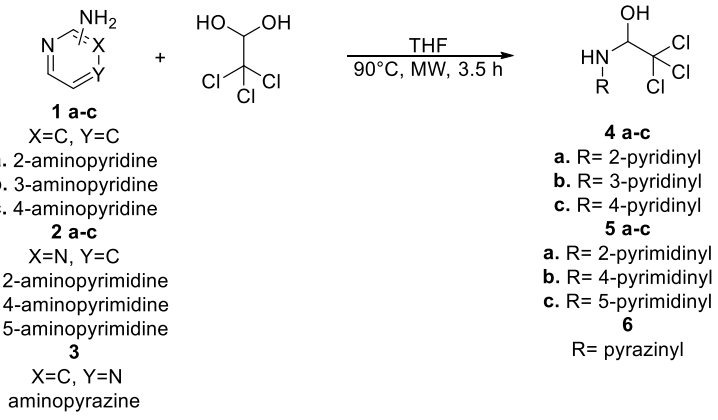
The trichloromethyl group plays an important role in many biologically active compounds such as pesticides and anticancer drugs. Recently among them [1], it was discovered a new molecule called Apcin that showed an inhibitory activity towards APC/C-CDC20 complex into cells afflicted by AML (acute myeloid leukemia). Molecular docking calculations predicted a biological activity similar to that of Apcin for some azaheterocycles bound to the α-trichloromethyl-hemiaminal group.

This suggested us to synthesize a series of α-trichloromethyl-hemiaminals from amino-azaheterocycles as useful scaffolds for further derivatizations. In this context, we prepared pyridine-, pyrimidine-, and pyrazine derivatives under MW conditions with yields ranging from 70 to 90% (**Scheme 1**).



Scheme 1. Synthesis of α-trichloromethyl-hemiaminals.

The hydroxy group will be useful for further functionalizations with other heterocyclic compounds with known biological activity. Starting materials and novel derivatives will be tested against AML and other human cancer cell lines.

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A novel tetrameric gadolinum-based contrast agent for molecular imaging of tropoelastin by MRI

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Dysfunctional matrix turnover in atherosclerosis leads to the accumulation of monomeric tropoelastin rather than cross-linked elastin [1]. Hence, tropoelastin may represent a novel promising imaging biomarker for MRI non-invasive detection of atherosclerosis progression and lesion instability. However, the density of the molecular target might be inherently low, limiting the amount of the contrast agent at the target site and eventually the sensitivity of the imaging technique. An interesting approach to increase the concentration of the contrast media is to insert a pre-formed Gd(III)-multimer to the targeting vector, in order to accumulate multiple copies of the contrast agent within a single target-binding event.

Thus, the aim of this project is to upgrade a pre-existent tropoelastin-specific MRI contrast agent (Gd-TESMA) [2], with the purpose of achieving a higher vessel wall enhancement in pathological conditions (Fig.1). In particular, we developed a tetrameric version of Gd-TESMA (Gd_4-TESMA).

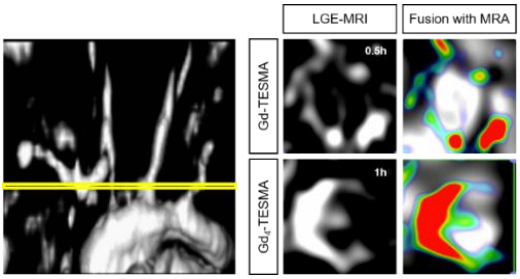

Figure 1: *In vivo* MRI using TESMA and Gd_4-TESMA in apolipoprotein E-deficient mouse.

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Different setups of ascorbic acid a-cellular assay for measuring PM oxidative stress potential

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The oxidative potential (OP) has been proposed as a biologically relevant metric for assessing the toxicity of ambient particulate matter (PM), as there is increasing evidence that the mechanism of adverse effects caused by inhaled PM is mediated by the generation of reactive oxygen species (ROS), [1,2]. Among the most widely used acellular assays to quantify PM oxidative potential, in this work we characterize the ascorbic acid assay (AA), that uses AA as a target molecule oxidized by redox-active species present in PM. It is an inexpensive and user-friendly method based on spectrophotometric measurements [2].

We investigate different experimental conditions in order to mostly represent the physiological fluids encountered by PM in lung, i.e., an artificial respiratory tract lining fluid (RTLF). In addition to ascorbate (AA), we include typical lung concentrations of reduced glutathione (GSH) and urate (UA), which are naturally occurring in the lung fluid, and citrate (Cit), that is a good proxy for proteins that mobilize iron in the lung fluid [3].

The study was performed on 20 real $PM_{2.5}$ samples collected at an urban and rural site in the Po Valley. The obtained results clearly show that the OP^{AA} responses change with the composition of the synthetic RTLF, as they significant decreased by adding other antioxidants to ascorbate.

Although each antioxidant shows a different effect, a general order is followed for all the analyzed samples:

Asc > Asc + CIT > Asc + UA > Asc + GSH > Asc + CIT+GSH ~ Asc + CIT + GSH + UA.

All the investigated surrogates generate linearly correlated responses, indicating that the effect of the various RTLF surrogates on OP^{AA} responses is similar for all the samples. This suggests that all the tested assay set ups are useful for measuring OP^{AA}.

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[2] M. Visentin, A. Pagnoni, E. Sarti, and M.C. Pietrogrande, *Environ. Poll.* **219** (2016) 72-79.
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Towards new concepts in the design of Gadolinium based magnetic resonance contrast agents

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Gadolinium based contrast agents (GBCAs) for magnetic resonance imaging (MRI) are in clinical use since 1988 [1]. Although they are considered to be highly stable and safe, concerns about their repeated use were recently raised [2-3]. The efficacy of GBCAs to generate contrast in a MR image is based on their local tissue concentration and their relaxivity (r_1) [3]. In order to decrease the dose, it is necessary to go for systems endowed with higher relaxivities. Herein we report the synthesis and the in vitro characterization of a novel q=2 Gd(III) complex (Gd-ISDO3A) based on the introduction of several hydroxyl functionalities on the outer surface of Gd-DO3A. The presence of hydroxyl groups is expected to i) increase the outer sphere contribution to the relaxivity and ii) limit the accessibility of bidentate anions to the inner coordination sphere of Gd(III) ion.

In summary, although the relaxivity of Gd-ISDO3A (r_1=12.1 $mM^{-1}s^{-1}$, at 0.5 T, 25 °C, in water) is markedly higher than the one observed for the parent Gd-DO3A (r_1=6.0 $mM^{-1}s^{-1}$, at 0.5 T, 25 °C, in water), the results obtained in serum indicate that the hydroxyl containing moieties are not sufficient to prevent the access of endogenous anions into the Gd(III) ion inner sphere. Work is in progress to insert more sterically encumbered groups into the ligand branches in order to prevent the displacement of the coordinated water molecules. Conversely, the hydroxyl containing moieties resulted a very good choice to generate a marked enhancement of the second sphere contribution to the observed relaxivity.

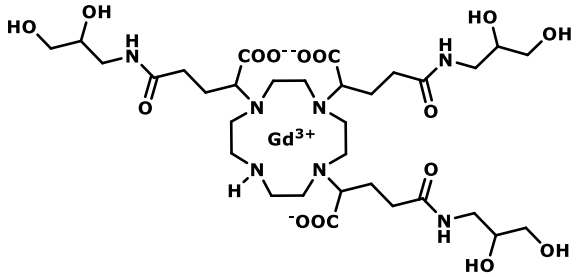

Figure 1: Chemical structure of the novel MRI contrast agent Gd-ISDO3A.

[1] J. Lohrke, T. Frenzel, J. Endrikat, F.C. Alves, T.M. Grist, M. Law, J.M. Lee, T. Leiner, K.C. Li, K. Nikolaou, M.R. Prince, H.H. Schild, J.C. Weinreb, K. Yoshikawa, and H. Pietsch, *Adv. Ther.* **33** (2016) 1-28.
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[3] M. Le Fur and P. Caravan, *Metallomics* **11** (2019) 240-254.

In silico design of novel organic hole transport materials for perovskite solar cells

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Hole transport materials (HTMs) based on conductive organic molecules are crucial components to prepare highly efficient perovskite solar cells (PSCs).
Currently, the Spiro-OMeTAD is the most used HTM allowing for a conversion efficiency above 23%.

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 (TPA) moieties have been proposed as alternatives to Spiro-OMeTAD.

In this work, the *in silico* design of four new triphenylamine and phenothiazine-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 Spiro-OMeTAD [2] and other TPA-based HTMs, e.g. PTZ2 [3], already present in literature.

The results suggest that HTM1-4 fulfil all the requirements that enable hole extraction and transport processes in PSCs and they can be considered as suitable alternatives to Spiro-OMeTAD in the construction of potentially efficient PSCs.

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[2] S. Fantacci, F. De Angelis, M. K. Nazeeruddin, and M. Grätzel, *J. Phys. Chem. C* **115** (2011) 23126-23133.
[3] R. Grisorio, B. Roose, S. Colella, A. Listorti, G. P. Suranna, and A. Abate, *ACS Energy Lett.* **2** (2017) 1029-1034.

Sustainable synthesis of non-fullerene acceptors for bulk heterojunction solar cells

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In the Bulk Heterojunction solar cells (BHJ) scenario, fullerene derivatives have been widely used as acceptor material due to their photochemistry proprieties, however, they have shown some disadvantages such as high cost, low stability and a narrow absorption spettra [1]. Recently, a new class of no fullerene Acceptors (NFAs) 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 for the synthesis of novel NFAs, using cascade or one-pot methodologies such as multicomponent reaction or Domino Direct Arylation-Cross Aldolization [3].

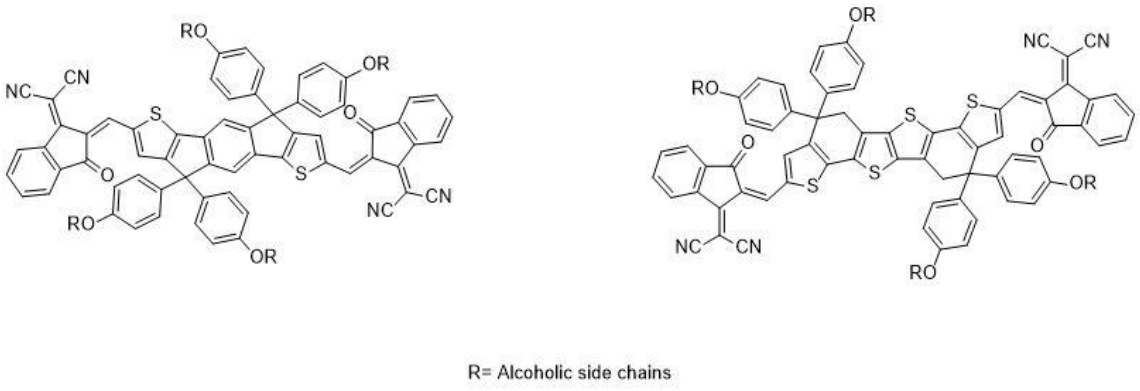

Figure 1: New NFAs materials.

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Si-DRIVE: European Li-ion battery technology for Electric Vehicles

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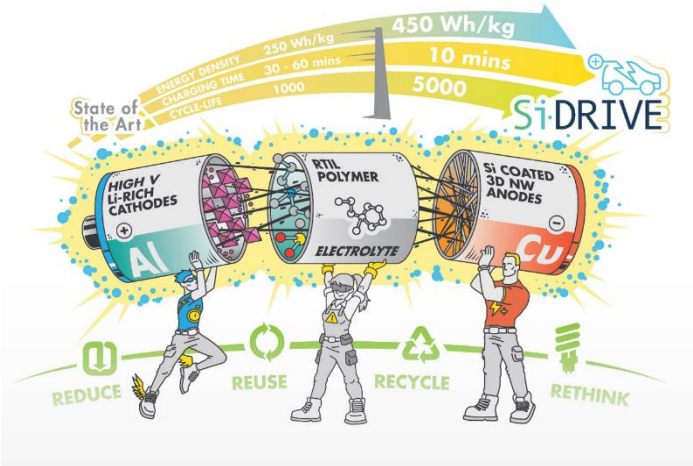
Si-DRIVE is a European project aimed to develop rechargeable Li-ion batteries with enhanced safety and energy density for cost competitive EVs mass market [1]. Comprehensive theoretical and experimental studies will probe and control interfacial processes that currently limit Li-ion technologies, tailoring materials design and eliminating capacity fade. Cost effective materials recycling and suitability for 2nd life applications, consistent with a circular economy, will be also demonstrated. The technology encompasses amorphous Si coated onto a conductive copper silicide network as the anode with polymer/ionic liquid (IL) electrolytes and Li-rich high voltage (Co-free) cathodes via processes that are scalable within Europe.

In this framework, in GAME Lab we develop solid-state polymer electrolytes (SPE) and composite polymer electrolyte (CPE) with superionic ceramic materials, combined with high performing ILs mixtures. The all solid electrolytes are aimed to improve safety, energy density and compatibility with electrode materials.

Preliminary results with Si anodes and IL-based all-solid-state crosslinked polymer electrolytes are herein presented.



[1] www.sidrive2020.eu

SNAPtide-based sensor for botulinum neurotoxin detection

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Botulism is a potentially fatal disease caused by accidental or intentional exposure to botulinum neurotoxin (BoNT) which is mainly produced by *Clostridium botulinum* an anaerobic, Gram-positive, spore-forming bacterial species. *C. botulinum* is widely spread in the environment, in both soil and water sediments, and its toxin is primarily transferred to humans through contaminated foods. This neurological disease manifests clinical syndrome of symmetrical cranial nerve palsies that may be followed by descending, symmetric flaccid paralysis of voluntary muscles, which may progress to respiratory compromise and death [1]. Given the rapid onset of disease symptoms, it is of great importance to offer a rapid screening instrument to improve food safety and medical diagnosis. Unfortunately, diagnosis of botulism often relies on the mouse lethality assay or ELISA tests, which require a turnaround time of 2-5 days [2]. Herein, we propose preliminary results of an antibody-free alternative for the detection of BoNT/A, which allow a more rapid diagnosis. We developed a screen-printed electrochemical sensor based on the proteolytic function of BoNT/A against the soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) causing muscle paralysis [3]. For the detection, we used a short peptide, SNAPtide, which mimics the synaptosomal-associated protein 25 (SNAP-25, a component of the trans-SNARE complex) with a cleavable site. SNAPtide was labelled with methylene blue as electroactive molecule and it was immobilized on gold nanoparticles modified electrode thanks to the formation of disulfide bond between the AuNPs and the peptide. The methylene blue allows for an electrochemical signal only when the SNAP25 is entirely linked to the gold electrode surface and we demonstrated that the presence of BoNT/A is able to cleave the peptide leading to a decrease of the signal, demonstrating the capability for a fast measurement by only dropping the sample on the working electrode surface.

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[3] B.R. Singh, *Neurotox. Res.* **9** (2006) 73-92.

Deferoxamine and a tris-hydroxypyridinone ligand (KC18) as receptors in new polymeric devices for Fe(III) sensing

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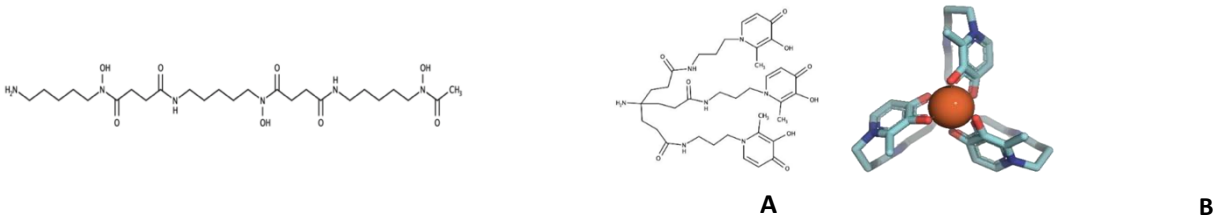
Iron is a metal essential for life, involved in many strategic metabolic pathways, such as in the oxygen transport system and in the electron transfer chain. The presence of Fe(III) in biological systems must be monitored since both its deficiency and overloading can cause serious disorders [1].

In our group, we already developed probes for Fe(III), based on DFO as receptor and using silica and paper as solid phase [1,2].

In the present research, we explore the possible usage of ethylene-vinyl alcohol, EVOH, as sensor solid support to obtain an extrudable material, which in principle is much more convenient for a practical application as sensor. DFO was used as model receptor, while the target receptor was a tris-hydroxypyridinone, a hydroxamic acid derivative, named KC18, synthetized in Lisbon by Maria Amelia Santos group. Their structures are shown in Figure 1.



A **B**

Figure 2: Structure formulae of DFO (**A**) and KC18 (**B**); molecular model of [Fe(KC18)] (**C**)

The final devices are characterized studying their sorption properties and affinity constants towards Fe(III).

In perspective, new strategies will be developed to increase sorption capacity always focusing on a plastic material as final device.

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Molecular imprinting as a new bioanalytical tool for small peptide hormones detection in the anti-doping field

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Nowadays, there is a lack of miniaturized, prompt and robust bioanalytical methods to detect small peptide hormones, such as Gonadorelin, Buserelin, and Leuprolide, in the anti-doping protocol. These peptides are improperly used by male athletes to enhance sports performances stimulating the endogenous secretion of testosterone in the bloodstream via the hypothalamic-pituitary-gonadal (HPG) axis. For this reason, low molecular weight peptide hormones (< 2000 Da) were banned by the World Anti-Doping Agency (WADA) and represent a new frontier in antidoping research. Primarily, we focus our attention on the development of an efficient and selective molecularly imprinted polymer (MIP)-based assay to detect and quantify Gonadorelin (peptide sequence: pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2, MW 1182,33 Da) level in biological fluids, such as urine or plasma. Many efforts were dedicated to synthesizing non-covalent MIP.

The process of molecular imprinting involves the synthesis of a 3-D polymeric matrix (polydopamine or polynorepinephrine) with binding sites complementary in shape, size, and functional groups to the template molecules. The interaction between Gonadorelin and "tailor-made" synthetic polymers, as biomimetic receptor successfully used for other biological analytes [1], was preliminarily characterized by a surface plasmon resonance (SPR) sensing platform. Then, a biomimetic competitive assay in 96 micro-welled plates was designed (biomimetic enzyme-linked immunosorbent assay BELISA, Fig. 1), so that the analyte competes with a conjugated analyte for the same binding site, by recording a colorimetric output. Promising results were recorded for Gonadorelin in the μM-range and future work will be devoted to embedding an amplification strategy to improve the sensitivity.

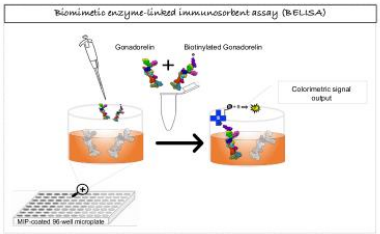

Figure 1: Sketched representation of a MIP-based competitive assay.

[1] P. Palladino, M. Minunni, S. Scarano, *Biosens. Bioelectron.* **106** (2018) 93-98.

Characterization and quantification of endogenous proteins and peptides with Nano-LC-HRMS in biological fluids and tissues

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The characterization and quantification of endogenous proteins and peptides in biological matrix for clinical studies with immunochemical technique, is an expensive and not sensitive process. Using coupled techniques such as LC-MS the determination may be greatly improved. GnRH (Release Hormone for Gonadotropin) is an endogenous neuro deca-peptide and its increase in hypothalamus-pituitary gland system is involved in reproductive system disorders such as infertility and PCOS (Polycystic Ovary Syndrome) [1]. Recombinant EGF (Epidermal Growth Factor) is a 6kDa protein used to grow in vitro stem cells [2]; once the growth cycle is completed, the Quality Control for their use requires the absence of this protein. The aim of this work was the development and validation of two analytical methods based on nanoHPLC-HRMS for the characterization and the quantification of: 1) GnRH in human, sheep and mouse biofluids and tissues; 2) EGF in stem cells. For this purpose, we used a nanoHPLC chromatograph with C18 PepMap® pre-concentration and C18 Easy Spray separation column. The separation system with integrated nanoESI source was coupled to an Orbitrap Fusion HRMS (high resolution mass spectrometer) for both methods. Some samples clean-up steps were required: deproteinization and C18 solid phase extraction (SPE) for GnRH; cell lysis and successive filtrations with 40kDa and 3kDa filters for EGF. 1 µL of reconstituted extracts was injected into the nanoHPLC instrument. Acetonitrile/water (8:2) with 0.1% FA were used as eluents. Full mass (300-2000 *m/z* range) and Data Dependent Acquisitions (dda) of fragments by CID (Collision Induced Dissociation), ETD (Electron Transfer Dissociation) and HCD (High-energy Collision Dissociation) activation modes were used for analytes characterization; 591.7944 *m/z* (z=2) and 1058.6385 *m/z* (z=6) were chosen as precursor ions for GnRH and EGF respectively. The CID system guaranteed the best sensitivity for both molecules quantification in the analysed biological matrices. A calibration curve with Internal Standard (LHRH III) in human plasma was used to quantify GnRH. A calibration curve in FBS (Fetal Bovine Serum) was used to quantify EGF. Online SPE-Nano-HPLC-HRMS technique allowed to use reduced volumes, to concentrate the analytes and to uniquely characterize the analyte ions thanks to high resolving power.

[1] B. Tata, N. El Houda Mimouni, A.-L. Barbotin, S.A. Malone, A. Loyens, P. Pigny, D. Dewailly, S. Catteau-Jonard, I. Sundström-Poromaa, T.T. Piltonen, F. Dal Bello, C. Medana, V. Prevot, J. Clasadonte, and P. Giacobini, *Nat. Med.* **24** (2018) 834-846.
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Hyaluronic acid at low-molecular-weight in human dermal fibroblasts: study by LC-MS/MS quantitative proteomics

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The hyaluronic acid (HA), involved in several biological functions, is a widespread ingredient of pharmaceuticals and cosmetics products [1]. Despite its extended use, the intra- and extra-cellular effects of HA at low-molecular-weight (LWM-HA) are currently undefined. The aim of this study is to in-depth identify and quantify proteome's changes after 24 hours treatment of human dermal fibroblasts with 0.125, 0.25 and 0.50 % LMW-HA respectively, vs controls.

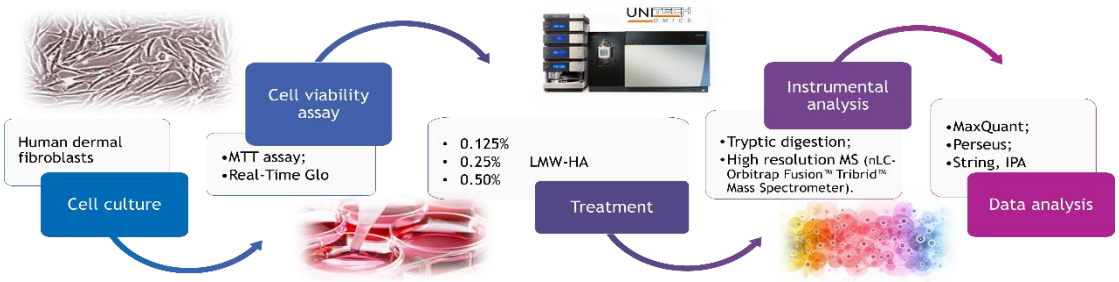

Figure 1: Graphical description of methods.

Overall, 2328 proteins were identified of which 39 significantly altered by 0.125 % LMW-HA, 149 by 0.25 % LMW-HA and 496 by 0.50 % LMW-HA. Both intra- and extra-cellular pathways were modified and extracellular matrix reorganization, proteoglycans and collagen biosynthesis enhanced. Moreover, cell's wellness was confirmed despite the inflammation and immune response induced by the highest concentration. The more complete comprehension about molecular effects of LMW-HA here provided by the LC-MS/MS quantitative proteomics paired to protein network analyses will be useful to further exploit its features and improve current formulations.

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Probing the selective binding of small molecules to G-quadruplex DNA by mass spectrometry

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G-quadruplex DNA stabilization mediated by small molecules is an attractive approach to modulate the transcription of guanine-rich sequences and contrast unregulated cell proliferation. Synthetic small molecules as well as natural compounds with specific structural features have been reported to target this macromolecular arrangement [1].

In this communication, the potential of electrospray ionization mass spectrometry (ESI-MS) in probing the interaction of small molecules with different DNA structures will be exemplified. Compounds with a planar scaffold, such as anthracenes, anthraquinones and flavonoids were tested against a G-quadruplex-forming sequence containing the telomeric TTAGGG repeat [2,3]. A double stranded DNA oligonucleotide was used as control and G-quadruplex/duplex selectivity ratio was estimated on the basis of binding affinity (BA) values.

Collision-induced dissociation (CID) experiments were used to investigate the relative gas-phase kinetic stability of the complexes, highlighting osajin among the most promising compounds of the experimental set (Figure 1). MS fragmentation pattern, combined with molecular docking, provided insights on the interaction motif of the compounds with G-quadruplex.

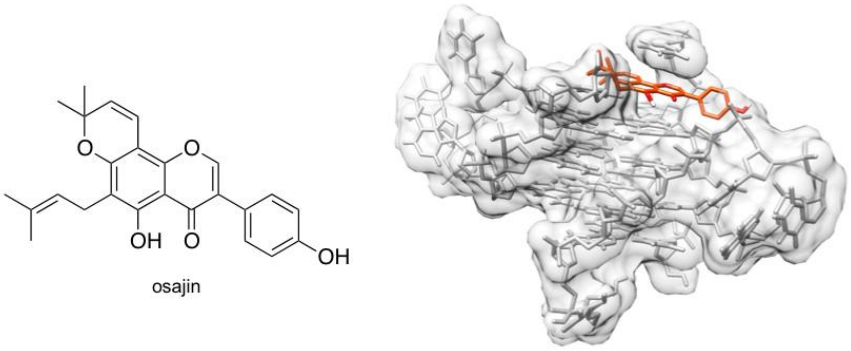

Figure 1: Chemical structure of osajin, a natural isoflavone, and its predicted interaction pattern with G-quadruplex DNA (PDB ID: 3CE5).

[1] D. Halder and P. Purkayastha, *J. Mol. Liq.* **265** (2018) 69-76.
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[3] G. Ribaudo, T. Vendrame, and S. Bova, *Nat. Prod. Res*. **31** (2017) 1988-1994.

Poster presentations

PO01	Marta ALBERTI
PO02	Rebecca APPIANI
PO03	Claudia ARDINO
PO04	Matteo ATZORI
PO05	Andrea BALDI
PO06	Lorenzo BALESTRI
PO07	Luisa BAUDINO
PO08	Federico BELLA
PO09	Irene BRUSA
PO10	Federica CAPONE
PO11	Alice CAPPITTI
PO12	Matteo CAPRIOLI
PO13	Alessia CASO
PO14	Michele CASTIGLIONI
PO15	Rosella CRISAFULLI
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PO32	Filippo MONCALVO
PO33	Luca NUVOLI
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PO36	Paolina PASCALICCHIO
PO37	Francesca PICARAZZI
PO38	Cecilia PINNA
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PO49	Lorenzo SUIGO
PO50	Emanuele TERRANOVA
PO51	Sebastiano TIEULI
PO52	Veronica TORRESAN
PO53	Mauro TRAPANI
PO54	Mariarosaria TUCCILLO
PO55	Vitantonio VALENZANO

Improvement of *in vivo* pharmacokinetic profile of M433, a potent and innovative *h*DHODH inhibitor

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Human *dihydroorotate dehydrogenase* (*h*DHODH) has been found to be associated with acute myelogenous leukaemia (AML), a disease for which traditional medical treatment and molecules involved have not changed over decades. We developed new potent *h*DHODH starting from structure, SAR and x-ray crystallography of *Brequinar*, one of the most potent known *h*DHODH inhibitors. This compound, named **M433**, showed a very high *in vitro* activity (IC_{50}=1.2 nM), comparable to that of Brequinar (IC_{50}=1.8 nM) in the enzymatic assay [1]. Despite its high selective on target activity, however, this emergent compound has found to have a really low solubility that does not make it an ideal candidate for *in vivo* studies. In this occasion, we present a new series of **M433** analogues which have been designed in order to improve the solubility and to avoid some metabolic alteration. More polar functional groups were introduced in the original scaffold without losing the Brequinar-like binding mode such as the replacement of ring C with several aromatic rings or the total replacement of the biphenyl moiety (rings B and C) with a substituted biaryl ether. On the other hand, we modulate also ring A by inserting substituents in different positions with the purpose to reduce a possible *in vivo* metabolism.

Theoretical design, modelling, synthesis, SAR, X-ray crystallographic data, biological assays, are here presented and discussed.

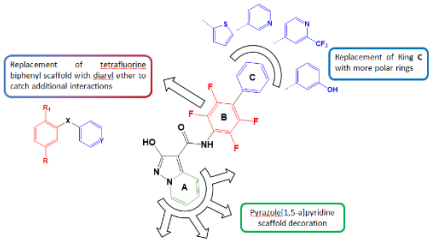

Figure 1: Some examples of structural changes.

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One-pot reductive amination of carbonyl compounds with a recyclable catalyst and sodium borohydride

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A one-pot reductive amination method was developed to convert aldehydes and ketones into primary and secondary amines under more sustainable and safety conditions.

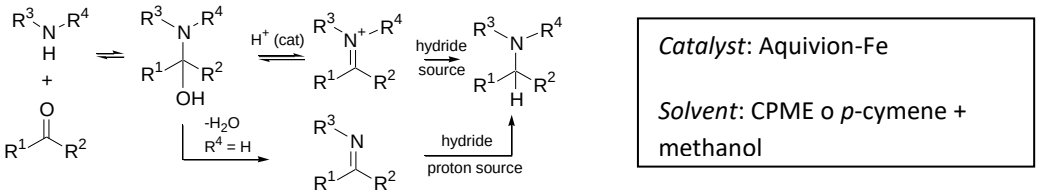

Figure 1: Reaction mechanism.

For this method were used solvents with acceptable EHS (Environment, Health & Safety) properties, such as TAME, CPME, Me-THF and *p*-cymene, and a cheap and non-toxic reducing agent ($NaBH_4$), which is activated by the addition of methanol after the formation of the C=N bond. In this way, it was possible to implement a one-pot procedure without using more selective but expensive and less sustainable hydrides ($NaBH_3CN$, $Na(OAc)_3BH$). For this purpose, the use of a new catalyst was decisive. The ferric salt of Aquivion-H it is a perfluorosulfonic ionomer, which was recently used as an efficient and recyclable Lewis catalyst, in Friedel-Crafts acylations [1]. Aquivion-Fe promotes imine formation, and it is removed by simple filtration and can be reused for several cycles. The reaction protocol was used for 41 different reductive aminations with generally excellent conversion degrees, and 18 amination products were isolated by chromatography in order to verify the consistency between yields and previously observed selectivity. In the end, it was used for the amination of 3(3-trifluoromethylphenyl)propionaldehyde, prepared according to a new method, with (R)-1-(α-naphthyl)ethylamine to obtain the active ingredient Cinacalcet [2].

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Targeting the viral envelope: synthesis and biological evaluation of novel broad-spectrum antivirals

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Some of the most infectious emerging and re-emerging viruses are endowed with a lipid membrane called envelope. Despite the viral envelope derives from the lipid membrane of the host cell, several differences can be highlighted between them, such as the lack of biogenic and reparative pathways that makes these viruses vulnerable to envelope's injury.

In our previous papers [1,2], we reported some rhodanine and aminothiazolone derivatives endowed with submicromolar activities against HIV-1 infected cells. The compounds were found to be only moderately active on HIV-1 integrase and HIV-1 gp120, but their submicromolar activity in vitro on HIV-1 replication and time of addition experiment suggested a diverse mechanism of action.

New thiobarbituric derivatives [3] displayed a broad-spectrum antiviral activity against different enveloped viruses (i.e. HSV-1, HCMV, RSV, ZIKV, INFLUENZA A, VSV) and resulted to be completely inactive against non-enveloped ones (i.e. Ad5, HPV and HRoV), suggesting that their mechanism of action could involve the viral envelope, affecting the dynamics of viral fusion and altering the fluidity and integrity of the lipid bilayer.

We gratefully acknowledge use of the facilities provided by Lead Discovery Siena S.r.l. This work was partially supported by the European Union's Horizon 2020 Research and Innovation Programme under ZIKAlliance Grant Agreement no. 734548 and by POR-CREO project PANVIR.NET.

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Strong magneto-chiral dichroism in enantiopure chiral molecule-based magnets

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Magneto-chiral dichroism (MChD) is a non-reciprocal manifestation of light-matter interaction that can be observed in magnetized chiral magnetic systems [1]. It features an unbalanced absorption of unpolarized light on dependence of the applied magnetic field direction and the chirality of the systems and has been observed only rarely [1]. Aim of this communication is to report on the recent investigation of the magneto-optical properties of paramagnetic enantiopure Ni^{II} and Co^{II}-complex and two magnetically ordered molecular materials: a $Mn^{II}Cr^{III}$ chiral heterometallic 2D-layered molecule-based ferrimagnet [2,3] and a Mn^{III}-based 1D coordination polymer showing weak ferromagnetism.

Magneto-optical measurements on enantiomeric crystals of the three compounds in the Vis-NIR range show various strong MChD signals, with opposite signs for enantiomeric crystals and equal absolute values. The frequencies of the observed signals correspond to precisely defined electronic absorption of the metal ions involved, that have been detected by single-crystal electronic absorption spectroscopy at low temperature (down to 4K) [3]. Interestingly, the MChD signals are clearly observed up to 8 K for the 1D Mn^{III} compound and up to 40 K for the Mn^{II}-Cr^{III} 2D compound, thus just above the ferrimagnetic and ferromagnetic ordering temperature of the two materials [3].

These studies open the door for the first systematic structure/properties investigations of MChD in chiral magnetized systems and are expected to provide useful insights for a better understanding of this effect proposed as one of the possible origins of homochirality of life on Earth.

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Plastic ingestion by the mediterranean *scyliorhinus canicula*

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The presence of plastic debris in the environment, especially in water bodies, is nowadays a problem of major concern. Plastics are widely diffused in the oceans and their possible ingestion by marine organisms can potentially cause adverse effects [1]. In this work we assessed the occurrence of plastic ingestion by the small-spotted catshark (*Scyliorhinus canicula*), one of the most abundant elasmobranchs in the Mediterranean Sea.

One hundred catsharks were collected during the Spring 2018 in the southern region of the central Mediterranean Sea: near Mazara del Vallo and Lampedusa island. Standard measurements were recorded for each specimen and its organs and sex was determined. The gastrointestinal tract (GIT) was used for plastic detection and identification. The procedure adopted consists in the digestion of the GIT in KOH (aq 10%) for 24 hours at 60°C followed by a density separation and vacuum filtration on cellulose nitrate filters with 8 µm pore size [2]. Where present, plastics (macro- and micro-) were characterized in terms of size, shape and polymer typology through microscopy and µ-Raman spectroscopy. The results obtained indicate that ingestion of plastics is a widespread phenomenon, with microplastics (MP<5mm) abundantly present in all samples and macroplastics (MaP>25mm) in approximately 30% of the specimens collected.

The results of this study represent a first evidence that plastic pollution is an emerging threat to *S. canicula*, the Mediterranean food web and, eventually, human consumers.

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Macrocyclic amidinourea: A novel synthetic strategy for BM1 through a Fukuyama tri-protected polyamine intermediate

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Fungal infections are a significant cause of morbidity and mortality worldwide. The number of people afflicted by serious fungal infections increased every year, as a consequence of the development of antibiotic therapies and often as a result of advanced medical treatments; moreover, current therapy to treat fungal diseases remains unsatisfactory due to the fact that there are few antifungal drugs currently available. Recently our research group reported the discovery and synthesis of a new non-azole antifungal compound bearing a macrocyclic amidinourea, **BM1**,

Figure *1*, endowed with potent antifungal activity against various azole-resistant *Candida* strains [1,2].

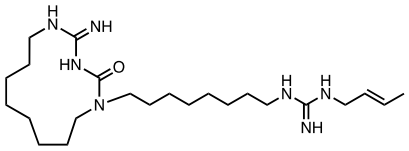

*Figure 1: Chemical structure of compound **BM1**.*

In order to investigate in vitro activity and in vivo safety of **BM1**, greater amount of compound was needed. With the previous synthetic path, we encountered several issues including the cost of the materials and the use of hazardous chemicals. This triggered us to obtained **BM1** with a novel synthetic strategy. Inspirated by Fukuyama's work on amine synthesis and exploiting the Mitsunobu reaction, we obtained grams of the **BM1** compound. Moreover this new synthetic path offers many advantages such as a better handle and purification of the intermediates, lack of hazardous chemicals and good yields [3].

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Tuning of physical-chemical properties of TiO_2 nanotubes for multifunctional applications

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Titanium dioxide nanotubes (TiO_2 NTs) have been widely investigated in the past twenty years due to the variety of possible applications of this material. Important characteristics of TiO_2 NTs are their high surface area and tuneable morphology. These can be combined with key features of TiO_2, such as biocompatibility and photo and electrocatalytic properties. This combination makes TiO_2 NTs perfect candidates for multifunctional applications ranging from biomedical application to sensing and energy devices [1].

Herein, we present TiO_2 NTs grown by anodic oxidation on top of a titanium foil in an EG-based electrolyte with NH_4F [2]. The as-grown amorphous nanotubes were morphologically characterized, as shown in Figure 1a-b. Additionally, the tuneable electronic properties (such as the bang gap, Figure 1c) were investigated varying the post-processing temperatures, while maintaining their amorphous nature.

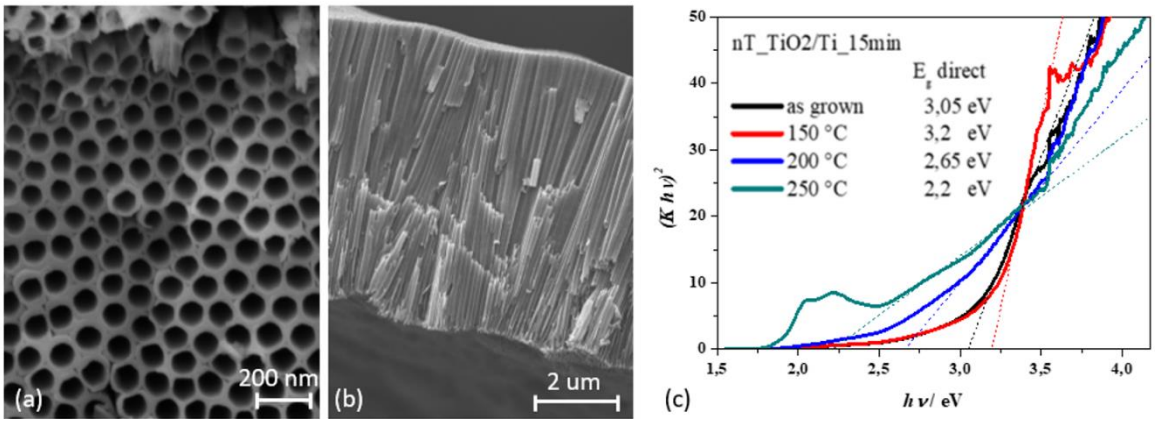

Figure 3: FESEM (a) top view and (b) cross view, (c) UV-VIS curves of the amorphous TiO_2 NTs.

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Poly(glycidyl ether)s recycling from industrial waste and reuse as electrolytes for sodium batteries

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The need to recycle waste products, convert and reuse them for different high-value applications is a very up-to-date, utmost important topic. In this context, here we propose glycidol, a high-value product isolated from epichlorohydrin industry waste, as a starting material for the preparation of two poly(glycidol)s polymer matrices with a chemical structure mimicking that of poly(ethylene oxide), i.e. the most used polymer matrix for non-liquid battery electrolytes.

The materials are characterized from the physico-chemical viewpoint, showing high thermal stability. They are then obtained in the form of ionic conducting polymer electrolytes encompassing different sodium salts and solvent mixtures. Ionic conductivity values exceeding 10^{-5} S cm^{-1} are measured in the "dry" truly solid state at 80 °C, while it approaches 6×10^{-5} S cm^{-1} at ambient temperature in the "wet" quasi-solid state. In addition, poly(glycidol)-based polymer matrices show reasonably wide electrochemical stability towards anodic oxidation.

It envisages their possible use as separating electrolytes in secondary batteries, which is also demonstrated by preliminary charge/discharge cycling tests in lab-scale sodium cells [1]. The present findings pave the way to a circular economy platform starting from industry wastes and ending with post-lithium storage systems.

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Hit optimization for the development of novel ubiquitin-ligase RNF5 inhibitors as therapeutic strategy in cystic fibrosis

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In cystic fibrosis (CF), deletion of phenylalanine 508 (F508del) in the CFTR anion channel is associated to misfolding and premature degradation of the mutant protein [1]. RNF5 is an ubiquitin-ligase promoting F508del-CFTR degradation. Recently, our group reported that genetically suppressing *in vivo* RNF5 increases CFTR activity in intestinal epithelial cells, thus validating RNF5 as drug target for FC. Therefore, through computational methods, we discovered **inh-2**, a drug-like small molecule that inhibits RNF5 (Fig. 1 – a), thus decreasing ubiquitylation of mutant CFTR and causing stabilization of the mature form of CFTR [2].

Therein, we focused on the design and synthesis of a large library of **inh-2** analogues, with the purpose of providing evidence to support RNF5 druggability. The new derivatives were synthetised leaving the central 1,2,4-thiadiazol-5-ylidene core unchanged, while exploring different functional groups in the N-4-benzyl region (Fig. 1 - b). At the same time, *in vitro* experiments were carried out to investigate the activity of the new analogues. Finally, the obtained data were used to perform structure-activity relationship studies (SAR), thus validating the 1,2,4-thiadiazolylidene scaffold as a versatile architecture for the identification of RNF5 inhibitors useful to attenuate CF pathological phenotypes.

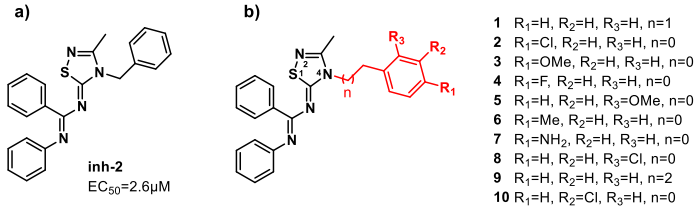

Figure 1: a) **inh-2** structure; b) synthetized **inh-2** analogues.

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Beyond expiration date: naked eye device for milk freshness

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Dairy products provide unique conditions for the growth of microorganisms, responsible of spoilage process, and freshness assessment for such perishable food is mandatory. To gage levels of spoilage, many methods have been developed, like total bacterial counts and methylene blue reduction [1], but they aren't suitable for in-field application.

Nowadays, the development of practical devices to assess food freshness is on the "front burner". Since we have been working on a colorimetric array for meat spoilage [2], here we tested its applicability to milk samples.

We selected a panel of 6 pH indicator dyes, which were covalently bound to ethylene–vinyl alcohol copolymers (EVOH). At first, six sensing spots were dipped in samples of whole, semi-skimmed and skimmed milk. Photos of the array were acquired during the degradation process, Principal Component Analysis on RGB indexes was used to model the data set. Analysing the loadings plot (Fig. 1a), we were able to select the most promising pH indicator, Bromothymol Blue, which can be used by itself to follow the degradation and assess milk freshness, as shown in Fig. 1b.

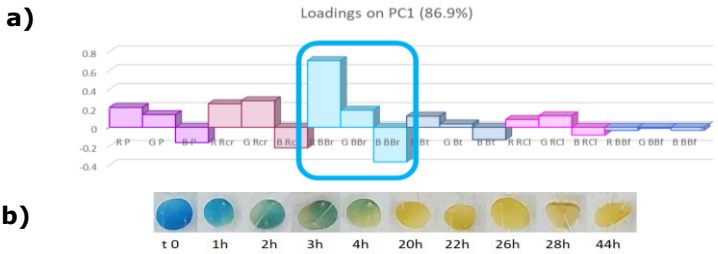

Figure 1: **a)** Loadings plot of the first component of PCA on RGB evolution on 4 different milk samples **b)** evolution of Bromothymolblue-EVOH@ dipped in milk samples.

Since this device shows promising results and interesting features for in-field application, in the future we will validate this method through instrumental analysis and test it with different dairy products.

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New innovative materials from renewable resources

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In recent years, thanks to the raise of public attention towards the environment, the exploitation of biomasses for the production of fuels and chemicals has assumed a central role in the modern chemical industry.

In this research saccharides were used as feedstocks to synthesize new biopolymers and nanocomposites for the conservation of cellulosic artefacts. Starting materials and synthetic procedures were selected taking into account the principles of the Green Chemistry and the future application in the preservation of the cultural heritage.

Allyl saccharide monomers, obtained using allyl bromide to functionalize trehalose, were selected for the synthesis of vinyl acetate copolymers [1] with three different molar ratios between the two monomer units.

Vinyl acetate copolymers were subsequently hydrolysed to the corresponding vinyl alcohol copolymers in order to obtain water soluble products suitable to be used in the treatment of wood and paper and to prevent the hydrolysis of the vinyl acetate groups after the application on the degraded material.

Furthermore, new nanocomposites based on TiO_2 anatase and allyl saccharide/vinyl acetate copolymers were synthesized by grafting the copolymers on properly functionalized nanoparticles. In fact, the titanium dioxide, in the crystalline form of anatase, performs an antifungal function, thanks to its photocatalytic activity promoted by electromagnetic radiation with wavelengths in the UV region.

The synthesis of nanocomposites allows to obtain better properties and performance than the simple mixing of nanoparticles and polymers, obtaining nanocomposites able to combine the antifungal properties of titanium dioxide, with the adhesive capacity of the copolymer.

Also nanocomposites were synthesized with three different molar ratios between the starting monomers and the nanoparticles, to evaluate the different behavior and the different growth of copolymers on the nanoparticles.

All the products were characterized by FT-IR and ^{1}H-NMR spectroscopy and the nanocomposites also by TEM microscopy.

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DLP 3D-printed self-healing hydrogels

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Self-healing (SH) hydrogels are smart soft materials able to autonomously recover their properties after mechanical damage without requiring the presence of an adhesive. Those materials are of increasing importance especially in scaffolds, actuators and sensors [1].

Up to now, the processing of these materials through stereolithographic additive manufacturing technologies (such as Digital Light Processing - DLP) has been challenging because of their opposite requirements in terms of cross-linking density [2]. It would be of great impact to build complex 3D structures with SH hydrogels for their application in biology and underwater environments. In this work, we overcame the incompatibility between 3D printing and self-repairing properties by using an interpenetrated double network, made of chemically cross-linked Acrylic Acid (AAc) and an electrostatically cross-linked Polyvinyl Alcohol (PVA). We propose the use of PVA as mending agent, that provides self-healing behavior thanks to its strong hydrogen bonding [3]. A waterborne formulation, containing a PVA solution, AAc, and a water-soluble photoinitiator, was used to print complex soft samples using a commercial DLP system. Healed samples showed a 72% recovery in mechanical strength, which increased to 91% with the addition of Polyethylene Glycol (PEG) in the formulation. The proposed solution opens the way for new relevant applications of 3D printing such as mendable soft robotics.

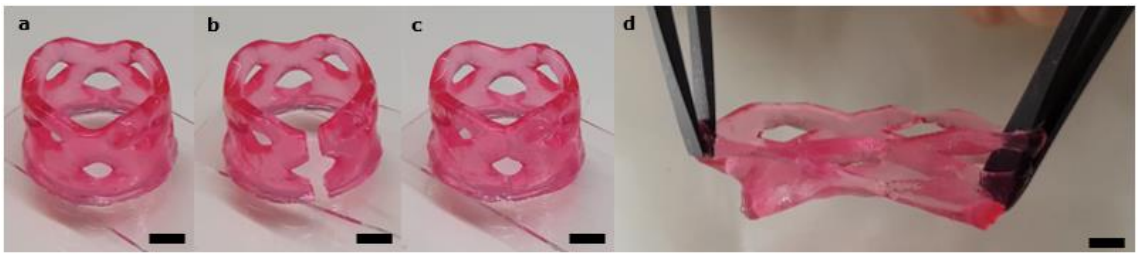

Figure 1: Cylindrical sample (a) as printed (b) cut (c) rejoined (d) stretched after 8 h healing (reference bar 4 mm).

[1] L. Shi, P. Ding, Y. Wang, Y. Zhang, D. Ossipov, and J. Hilborn, *Macromol. Rapid Commun.* **40** (2019) art. no. 1800837.
[2] D.L. Taylor and M. in het Panhuis, *Adv. Mater.* **28** (2016) 9060-9093.
[3] H. Zhang, H. Xia, and Y. Zhao, *ACS Macro Lett.* **1** (2012) 1233-1236.

Smenamide F and G: detection using molecular networking, isolation and stereostructural elucidation

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Caribbean sponges of the genus Smenospongia are a prolific source of chlorinated secondary metabolites. The use of molecular networking as a potent dereplication strategy revealed the presence in the organic extract of *S. aurea* of two new members of the smenamide family [1,2], namely smenamide F and G [3]. The structure of smenamide F and G was determined by spectroscopic analysis (NMR, MS, ECD). The relative and the absolute configuration at C-13, C-15, and C-16 was determined on the basis of the conformational rigidity of a 1,3-disubstituted alkyl chain system (i.e. the C-12/C-18 segment of smenamide F). Both compounds showed selective moderate antiproliferative activity against MCF-7 and MDA-MB-231 breast cancer cell lines.

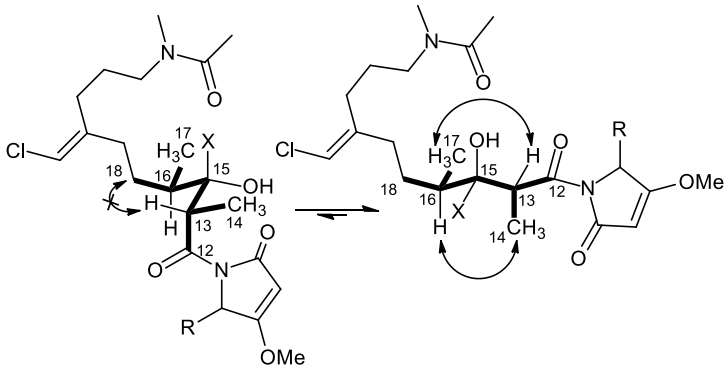

Figure 1: Determination of the relative and the absolute configuration at C-13, C-15, and C-16 of smenamide F and G.

[1] R. Teta, E. Irollo, G. Della Sala, G. Pirozzi, A. Mangoni, and V. Costantino, *Mar. Drugs* **11** (2013) 4451-4463.
[2] A. Caso, A. Mangoni, G. Piccialli, V. Costantino, and V. Piccialli, *ACS Omega* **2** (2017) 1477-1488.
[3] A. Caso, G. Esposito, G. Della Sala, J. R. Pawlik, R. Teta, A. Mangoni, and V. Costantino, *Preprints* (2019) DOI: 10.20944/preprints201910.0091.v1.

Characterization of biochar samples as media for water filtration

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The increase of industrialization has negatively affected the quality of freshwater resources. In this regard, adsorption technologies within the tertiary stages of water treatment plants have proven to be effective and economically feasible approaches for the removal of organic and inorganic contaminants from water compartments. For this purpose, the most used sorbent is activated carbon (AC), able to provide strong chemical interactions with contaminants [1]. Nevertheless, other promising materials such as biochar (BC) were recently considered for the removal of pollutants such as VOC, plasticizers, pesticides and herbicides from waters [2].

BC is the solid by-product of the thermal conversion of biomass wastes. In a circular economy context, BC deserves further insights to elucidate the main adsorption mechanisms involved.

Moving from the above-mentioned assumptions, in this work 10 charcoal samples (3 ACs, 7 BCs) were characterized according to the requirements of international standards on inorganic supports intended for water filtration. Hence, adsorption proprieties (iodine, phenol and methylene blue indexes, which provide information about the surface area of the material), physicochemical properties (ash, moisture, pH, pH at the zero-charge point pH_{pzc}) and release of metals and PAHs were evaluated for each sample. Iodine number, which is a restrictive parameter (> 600 mg/g), ranged between 197 mg/g and 87 mg/g. Ash content (which must not exceed 15%) ranged between 6.2% and 49.4%.

As far as PAH release is concerned, all the BCs tested resulted suitable for the treatment of drinking water, whereas for metals, only one BC did not achieve the requirements.

Furthermore, adsorption capacities of selected BC and AC samples towards emerging and volatile compounds were derived by applying the Freundlich isotherm model, as established by ASTM D5919-96 standard.

Finally, a principal component analysis (PCA) chemometric treatment allowed us the comprehensive overview of the characterization results and to discuss the highlighted correlations among variables.

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Chemical modifications of waste cooking oil (WCO) for the production of biolubricants

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The use of renewable raw materials, such as waste cooking oil (WCO), to operate as an alternative to fossil fuels for the production of lubricants and other valuable chemicals is a an extremely interesting topic both from an economic and scientific point of view [1].

Nevertheless, vegetable oils are thermally less stable, more sensitive to hydrolysis and to oxidation and frequently solidify at low temperatures compared to lubricants of fossil origin.

These problems may be solved via chemical modifications, specifically through transesterification and epoxidation reaction of triglycerides, without compromising their biodegradability [2].

The aim of our research group is to develop a transesterification and epoxidation reaction of WCO under low impact reaction conditions. Several parameters such as solvents, stoichiometric ratios, catalysts, reaction time and temperature were considered to optimize both reactions.

All products were characterized by ^{1}H-NMR, ^{13}C-NMR, e FT-IR spectroscopy.

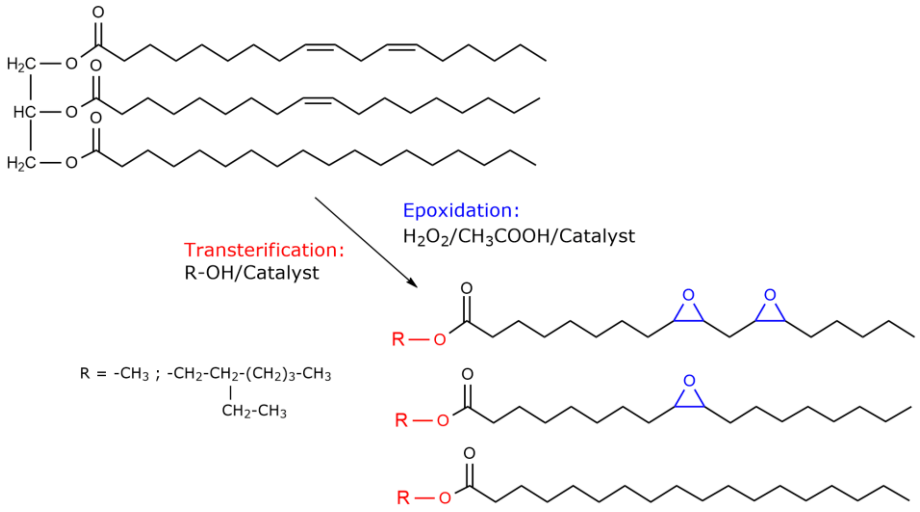

Figure 1: Reaction scheme.

[1] P.N.R. Vennestrøm, C.M. Osmundsen, C.H. Christensen, and E. Taaring, *Angew. Chem. Int. Ed.* **50** (2011) 10502-10509.
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Spectroscopic investigation of coupled QDs dimers

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At the atomistic and sub-nanometer scale, assemblies of colloidal semiconductor quantum dots (QDs) show original electronic collective properties, due to the QD coupling, depending on the number of connected nano-objects and their interparticle distance [1]. While most device implementations use disordered QD aggregates, here the fabrication and characterization of nanostructures composed of a low number of QDs with precise stoichiometry and defined nanometric and sub-nanometric particle-particle spacing are described. Dimers of CdSe QDs in solution are fabricated by engineering QD surface chemistry with ligand treatments that reduce the surface steric hindrance and promote the connection between two QDs by means of alkyl dithiols bifunctional molecules [2]. Alkyl dithiols with different chain lengths are selected to tune the interparticle distance from few nanometers down to sub-nanometers, where strong coupling is expected to be achieved.

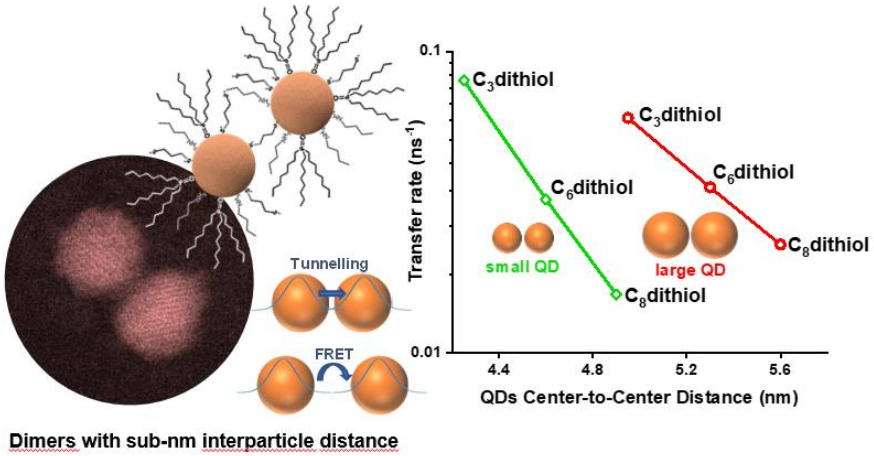

Figure 1: transfer rate trend shortening the interparticle distance of the QDs based dimers at two different size of the nano objects.

[1] D.L. Klein, R. Roth, A.K.L. Lim, A.P. Alivisatos, and P.L. McEuen, *Nature* **389** (1997) 699-701.
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Combined LC-MS/MS and Molecular Networking approach as powerful tool for a fast detection of new lead compounds

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In these last years our search for new lead compounds was achieved thanks to the use of molecular networking, a recently-developed method for automated LC-MS/MS data analysis and mining.

This technique is based on the principle that structurally similar molecules have similar MS/MS fragmentation patterns. The capacity of molecular networking is twofold. On the one hand it allows the identification of structurally related molecules within complex mixtures of substances as can be the extracts, on the other hand it allows easy comparison of MS/MS spectra of the compounds present in the network with a databases of known compounds of which it has been noted the MS/MS spectrum. This process is known as dereplication.

Recently, due to its duality, molecular networking has been used in our studies both to detect the presence of known cyanotoxins in water and bivalve samples and to discover new potential lead compounds in sponge extracts already analyzed with traditional techniques.

Regarding the monitoring of toxic cyanobacteria blooms, molecular networking allowed to detect the presence of lyngbyatoxin in water samples and bivalves collected along Campania coasts [1].

Instead for the organic extracts of sponge samples of *Smenospongia aurea* and *Smenospongia conulosa* in which in the past we found a series of chlorinated mixed-biogenesis NRPS/PKS compounds, the use of high-resolution LC-MS/MS and molecular networking resulted in the discovery of a wide range of such chlorinated compound. In particular four new antiproliferative polyketides, smenolactones A-D [2], and two new hybrid peptide/polyketides, smenamide F and G, were found, subsequently isolated from *S. aurea*, and their structures elucidated.

These findings confirmed molecular networking as a powerful tool in the discovery and development of new drug leads.

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Wearable sensor for pH measurement in sweat samples

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In the last decade, wearable sensors have attracted significant interest for their ability to monitor in real-time and in a non-invasive way the health state of human beings [1]. Wearable sensors have been developed for the detection of various biomarkers such as glucose, lactate, pH and cholesterol, as well as physiological indicators, such as heart rate, temperature and breathing, allowing for potential application in the medical-diagnostic field and fitness monitoring, as well [2]. Most of these physical sensor patches are flexible and biocompatible thanks to the integration of the sensors with data readout and signal conditioning circuits with wireless communication modules for transmitting data to the computing devices [3]. Herein, we developed a novel chemical potentiometric device directly integrated onto the human epidermis for detecting pH in human sweat. This sensor combines a customised electrochemical printed-electrochemical sensor with RFID technology for data transmission to the computer devices, allowing for continuous measurements and long-distance readings. Kapton was chosen as a substrate for production of screen-printed electrodes, because it is commonly used as support for integrated circuits. This device is sensitive to pH variations using electrochemical deposition of an iridium oxide film on the surface of the working electrode as sensitive layer. Once optimised the parameters for the electrochemical deposition of the iridium oxide, the analytical features were assessed using Britton-Robinson buffer. The linearity was observed in the range comprised between 4 to 7 pH described by the following equation $y=(-0.07 \pm 0.01)\ x + (0.87 \pm 0.06)$, $R^2=0.881$. Moreover, the effects of different interfering ions present in sweat such as potassium, chloride, and iodide were evaluated and the results showed no variation of the potentials in presence of these interfering species. The suitability of this device was demonstrated to measure pH in sweat samples in real-time and continuous mode.

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Sustainable low-temperature hydrothermal synthesis of ternary and quaternary transition metal ferrites

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Hydrothermal inorganic synthesis is very important being a sustainable approach with regard to following the principles of Green Chemistry, affording an easy, reproducible, low-temperature synthetic route [1].

Ternary and quaternary spinel ferrites, MFe_2O_4 and $M_{(1-x)}M'_xFe_2O_4$ respectively (where x = 0.2, 0.4, 0.6, 0.8 and M, M' = Co, Ni, Mn, Zn,), have been synthesised through a low temperature (T= 135 °C), green protocol combining the coprecipitation of metal salt precursors via oxalic acid and subsequent hydrothermal treatment [Figure 1].

The obtained powders have been analysed via XRD, XPS and ICP-MS. The analyses have shown that this approach allowed to obtain monophasic, nanocrystalline materials, with excellent compositional control, allowing to tune the value of x, with the possibility to potentially taylor the functional properties of the final materials. Further it has been shown that nanosized crystalline materials can be obtained with treatment times as short as one hour and, moreover, that differences in treatment time can have notable influence on the spinel's final degree of inversion [3]. Further advantages of the protocol include its extreme simplicity, the lack of complex, expensive and/or toxic precursors, the ease with which obtained materials can be purified and its compatibility with scaling up to higher production levels.

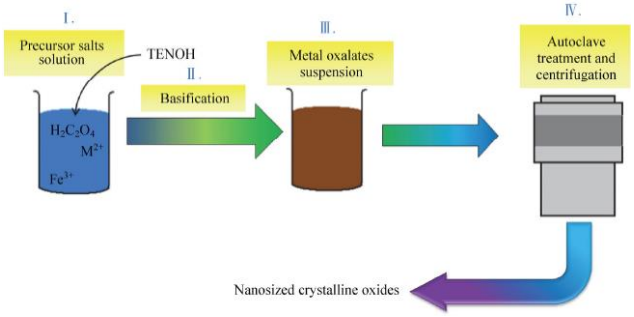

Figure 1: Synthesis scheme of transition metal ferrites [2].

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Crosslinkers for gels and adhesives formulations

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In this work the role of different types of commercial crosslinkers based on polyisocyanates was studied. In particular, this research has focused on the study of the crosslinkers behaviour in the variation of the application properties of adhesives formulations and moreover for their use in gel production.

The polyisocyanates reactivity can lead to the formation of two products: polyurethanes and polyurea. The first one creates a cross-linking with polymeric chains containing hydroxyl groups, the second one creates a hydrophobic network around the same chains. These two competitive reactions may be involved both in gel formation and in improving the performance of adhesives formulations. In this work we have studied different applications of polyisocyanates aimed at reducing the use of substances derived from oil or that could create environmental impact.

New chemical gels were obtained by mixing polyisocyanate-based crosslinkers with pullulan [1], an oligomer of glucose obtained from the enzymatic transformation of starch. The choice of this last compound arise from the idea to study new substances derived from biomass. The gels obtained starting from this compound differ from each other due to different parameters: the types of polyisocyanate used as crosslinker, the different conditions in which they were made (different gel formation temperature and gel formation in an open or closed container) and the different mass ratio between crosslinker and pullulan. The gels obtained were analyzed by FT-IR spectroscopy. Furthermore, the gel fraction (G%) and equilibrium water content (EWC) were evaluated. These properties were compared with those of similar gels obtained using polyvinylalcohol (PVOH) which are potentially applicable in various fields, such as the cultural heritage field.
Crosslinker reacivity was also studied with adhesives formulations based on polyvinyl acetate not modified with agents that could create environmental impact, such as NMA (N-methylolacrylamide). Several polyisocyanates formulations with different hydrophobic or hydrophilic behavior were compared in order to increase the performance of the adhesives formulations to create more effective joints thanks to the creation of a partial cross-linking of the polymeric component chains or through the creation of a hydrophobic network around the chains.

[1] R. S. Singh, G. K. Saini, and J. F. Kennedy, *Carbohyd. Polym.* **78** (2008) 515-531.

In silico study of NLRP3: towards selective inhibition with small molecules

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Inflammasomes are cytoplasmic supramolecular complexes involved in response to exogenous microbial invasions and endogenous damage signals. NLRP3 is the key protein playing a pivotal role in the inflammasome activation. NLRP over-activation is directly connected with many inflammatory diseases. It has been shown that NLRP3 inhibition has therapeutic potential for the treatment of diseases such as Alzheimer´s Disease, atherosclerosis, asthma, gout and inflammatory bowel diseases [1]. Up to date, no experimental 3D structure of the full-length NLRP3 is available, therefore, it is difficult to design possible NLP3 inhibitors by computational approaches. Based on the recently reported low-resolution structure of LRR and NACH domains of NLRP3 (PDB ID:6NPY) and the PYD structure obtained by NMR (PDB ID: 2NAQ) we modeled the structure of the whole enzyme. We identified a potential binding site for the reference compound MCC950. To find new binders for the discovered pocket we next used two different strategies. 1) A selected set of more than 100000 drug-like substances was screened. 2) A set of small molecules structurally similar to MCC950 by the Tanimoto Coefficient was identified.

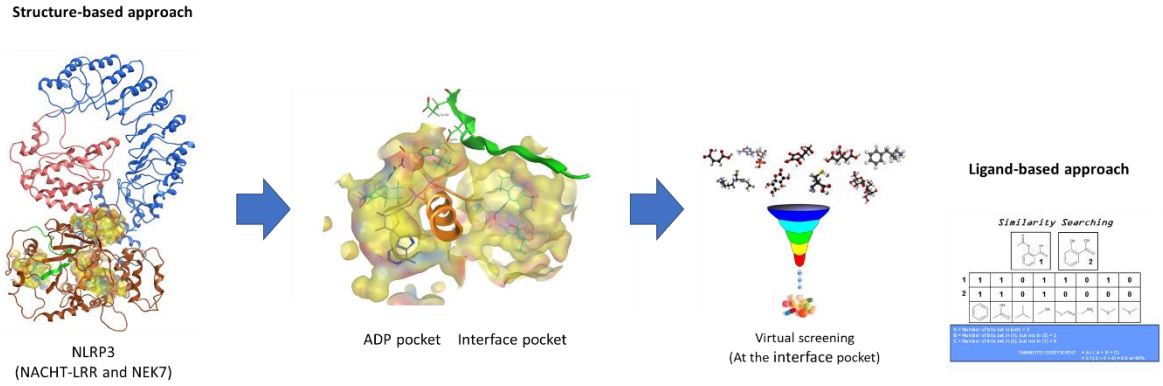

Figure 1: ADP pocket, Ser 331 pocket and interface pocket. ADP (grey), MCC950 (Blue). Walker A motif (orange), Walker B motif (green).

[1] H. Sharif, L. Wang, W.L. Wang, V.G. Magupalli, L. Andreeva, Q. Qiao, A.V. Hauenstein, Z. Wu, G. Núñez, Y. Mao, and H. Wu, *Nature.* **570** (2019) 338-343.

Identification by HS-SPME/GC-MS and activity testing of *Trichoderma* spp. volatile organic compounds against grapevine downy mildew

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Downy mildew, caused by the biotrophic oomycete *Plasmopara viticola,* is one of the most destructive diseases of the grapevine [1]. Fungi of the genus *Trichoderma* are economically important biocontrol agents since they play a crucial role in plant-growth promotion, mycoparasitism of plant pathogens and priming of plant defence. *Trichoderma* spp. also release a high diversity of volatile organic compounds (VOCs), which play a decisive role against plant pathogens [2]. However, the possible contribution of *Trichoderma* VOCs in antagonistic processes against grapevine downy mildew has not yet been investigated.

In this work, VOC emission profiles of three *Trichoderma* strains belonging to *T. asperellum*, *T. atroviride* and *T. harzianum* were analysed using headspace-solid-phase microextraction gas chromatography-mass spectrometry (HS-SPME/GC-MS). Total ion current chromatograms were processed by an open source software [3], and statistical analysis on the obtained raw data was carried out using an in-house R-script. VOCs emitted by the *Trichoderma* strains at specific time-points were selected, and pure compounds were tested against downy mildew by leaf disks assays on susceptible grapevines. The development of downy mildew symptoms was reduced on leaf disks exposed to air treated with two sesquiterpenes, one hydrocarbon, or one heterocyclic compound, indicating the efficacy of these VOCs against downy mildew in plant tissues.

Our data suggest that VOCs emitted by the *Trichoderma* strains under study can effectively be detected and identified by HS-SPME/GC-MS, and can inhibit the development of downy mildew symptoms on susceptible grapevine.

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Design and synthesis of highly potent and selective D-proline-based MMP2 inhibitors

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Matrix metalloproteinases (MMPs) are a family of zinc-dependent neutral endopeptidases, that are key players in the turnover and remodeling of the extracellular matrix (ECM) [1]. Among them, gelatinases A (MMP2) and B (MMP9) are involved in a number of pathological events, including cancer, as they play a primary role in the angiogenic switch [2].

These two enzymes show high degree of structural similarity but opposite effects in the tumor progression, thus there is a high need for the development of novel inhibitors able to discriminate among the two gelatinases.

The synthesis of D-proline-derived hydroxamic acids containing diverse appendages at the amino group, varying in length and decoration allowed to give insight on the MMP2/MMP9 selectivity around the S1' subsite, resulting in the identification of sub-nanomolar compounds with high selectivity up to 730 [3]. Molecular docking studies revealed the existence of an additional hydrophobic channel at the bottom of S1' subsite for MMP2 enzyme useful to drive selectivity towards such gelatinase.

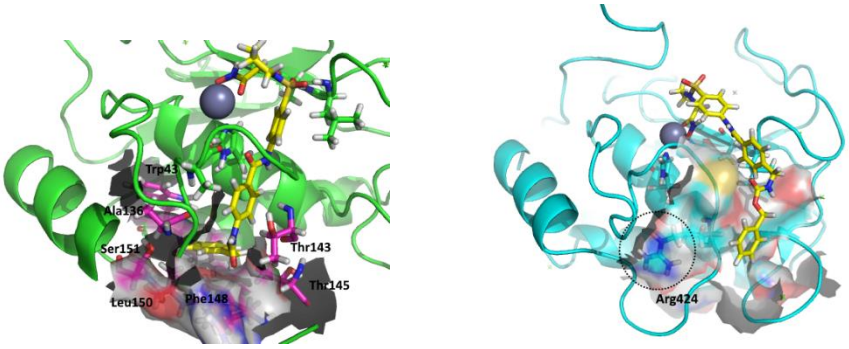

Figure 1: D-proline based inhibitor docked into the active site of MMP2 (PDB: 1HOV) (left), and into the active site of MMP9 (PDB: 1GKC) (right).

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Antioxidant-enriched bio-based polycarbonate for food packaging

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Food composition and nutraceuticals are of remarkable importance in human health and society wellness. Nowadays, consumer demands for healthier and safer food products. Over the last decade there is a growing interest in the development of packaging materials in order to preserve food quality, avoiding lipid oxidation and microbial growth [1]. To reduce lipid oxidation several strategies are already known, such as the addition of antioxidants directly to the food, or the design of novel active packaging. Polyphenols have been widely used as synthetic antioxidants, despite the potential toxicity deriving from the migration of such compounds into the food products. Several studies have been reported to state the capability of releasing these molecules from the packaging itself [2]. To avoid such behaviour, our goal has been to develop a synthetic bio-based polycarbonate from isosorbide and aliphatic diols bearing the antioxidant covalently bound directly to the polymeric chain (Figure 1). In order to guarantee the presence of the antioxidant moiety on the surface, the latter was bound to a perfluoroalkyl diol. This choice aims to avoid the release from the packaging to the food products, with the possibility of restoring its activity after post-use treatment.

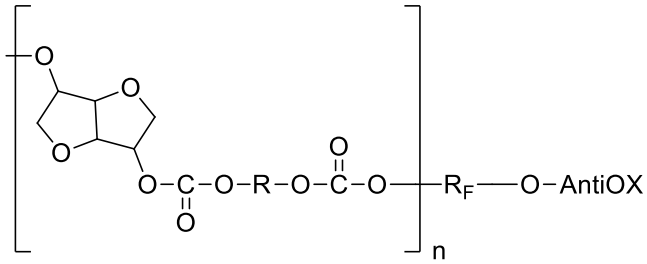

Figure 1: Structure of the bio-based polycarbonate bound to the antioxidant.

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Synthesis of 2-arylbenzonitriles and their reactivity in tandem reactions with carbon nucleophiles and UV studies on aromatic electrophilicity based on Mayr equation

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New methodologies for the synthesis of the ketones 2-cyanobenzophenones and 2-acetylbenzonitriles, based on Suzuki-Miyaura type cross-coupling reactions and mild oxidation of 2-benzylbenzonitriles and 2-ethylbenzonitriles are reported.

The oxidation of diarylmethane have been conveniently performed using NBS/AIBN/H_2O system, via radical di-bromination followed by hydrolysis [**1**].
In the presence of mild carbon- and hetero-nucleophiles, the obtained ketones show a good reactivity allowing the synthesis of wide range of novel 3,3-disubstituted isoindolin-1-ones bearing a tetrasubstituted carbon in yields of 80–99%. All the methodologies are highly efficient and tolerate combinations of functional groups present on both the aromatic rings.

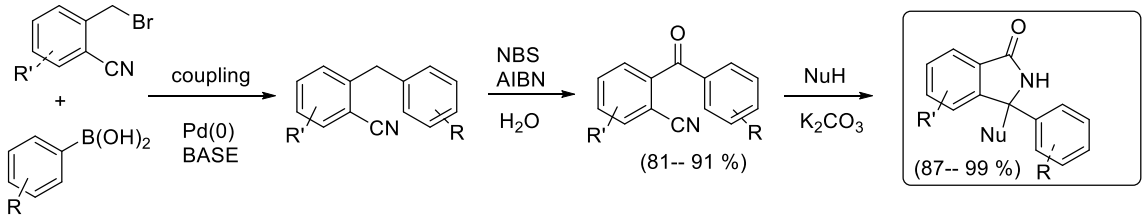

Figure 1: Reaction pathway.

The reaction pathway is a tandem process consisting of an addition step, cyclization at cyano group and subsequent Dimroth-type rearrangement.
The electrophilicity of aromatic ketones were investigated in collaboration with Prof. H. Mayr and Dr. Armin Ofial using Mayr-Patz equation: log $k_2 = s_N$ (N+ E) using testing nucleophiles with known nucleophilicity parameters (N and s_N) [**2**]. All kinetic investigations were performed in anhydrous DMSO solution at 20°C by following the disappearance of the UV/vis absorptions of the carbanion (405 nm) under pseudo-first-order conditions ([$\mathbf{E}^+$] /[$\mathbf{Nu}^-$] > 10). As the carbanions decompose at 20 °C (depending on the method of preparation), they were generated in situ by treatment of their conjugate acids with 1.00−1.05 equiv of t-BuOK. The obtained **E** values serve to understand if a reaction between a couple of nucleophiles and electrophiles is kinetically favored (**N**+**E** < - 5).

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VAMS microsampling and DPX sample pretreatment coupled to mass spectrometry for drugs of abuse testing in biological matrices

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Substance monitoring in biological matrices is a procedure often carried out for legal (e.g., drugs of abuse) and forensic (e.g., poisoning) purposes. This is routinely done by using large volume samples. However, microsampling (5-50 µL of biological fluid) is rapidly becoming an attractive alternative to traditional "macro" sampling, due to numerous advantages and to the possibility of sampling minute amounts of practically any biological fluid of interest (including oral fluid, sweat and tears as well as blood and urine). Microsampling is minimally invasive even if applied to blood, and the subsequent drying step provides increased analyte stability and thus more feasible, inexpensive handling, transportation and storage conditions. Moreover, analysis automation and home- and self-sampling by the subject are much simpler and straightforward. Sample pre-treatment is also usually simplified.

We report herein the development and optimisation of a novel and original microsampling strategy for application to drugs of abuse testing: biomarkers of cocaine consumption alone or in combination with ethanol intake were analysed by means of volumetric absorptive microsampling (VAMS) combined with disposable pipette tip extraction (DPX) and coupled to LC-MS/MS.

Whole blood miniaturised samples were collected by VAMS, an advanced dried microsampling technology based on substrate absorption. All the parameters involved in sampling, storage and extraction steps were optimised in detail. Moreover, an accurate study of sampling volume and analyte stability was carried out to preliminarily ascertain the suitability of the devices to the specific matrix considered.

The microsamples were then subjected to DPX, a miniaturised, high-recovery sample pretreatment procedure developed specifically for this application. Blood levels of cocaine and cocaine/alcohol consumption biomarkers were determined by means of an original, validated LC-MS/MS method. The results were compared to those obtained by classic sampling coupled to reference pretreatment and analysis procedure, obtaining in all cases satisfactory agreement (correlation coefficient > 0.9).

Characterisation of bioactive compounds in wine by-products: toward the valorisation of sustainable resources

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Grape vine (*Vitis vinifera* L.) is one of the most cultivated plants in the world. Regular consumption of grape products is associated with a reduction in the onset of chronic-degenerative diseases [1]. In the European Union most of the harvest is used by the wine industry, generating a large amount of grape processing by-products. Pomace, seeds and stalks are the main processing residues obtained during the winemaking process and represent matrices that could be exploited for sustainable recycling [2]. Aim of this multidisciplinary research project is the extraction, identification and quantitation of bioactive compounds in grape processing by-products, the evaluation of the biological effects of bioactive-enriched extracts and the mapping of the identified bioactive substances by comparing the profiles of different plant parts (pomace, seeds and stalks) and grape cultivars (Albana and Sangiovese). In order to obtain bioactive-enriched samples exploiting eco-sustainable technologies, extraction procedures were developed by means of solid/liquid-, ultrasound- and microwave-assisted extraction (SLE, UAE, MAE). An original LC-MS/MS methodology has been set up, fully validated and applied to the extracts in order to obtain a detailed quali-quantitative profiling of several compound classes (flavonoids, phenolic acids, procyanidins, stilbenoids). Moreover, all the extracts were evaluated for their therapeutic potential on gastrointestinal diseases by exploiting *ex-vivo* animal tissues, and then correlated to their quali-quantitative composition by computational approaches based on molecular networks. The comparative characterisation of bioactive compounds present in grape by-products could be the basis for the valorisation and integrated exploitation of this cheap and easily available alternative source in the nutraceutical, cosmeceutical and pharmaceutical fields.

This research was funded by "Fondazione Cassa di Risparmio di Imola" (Project code: 065.0318-2018.0050; Call year: 2017).

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Chemical behavior of Maytansinol: an intriguing building block

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Microtubule-associated proteins (MAPs) regulate the microtubule polymerization dynamic by unclarified conformational recognition of tubulin. Targeting tubulin founds new application in neurodegenerative diseases to ensure stabilization of microtubule, because in some of these pathologies tau-MAP becomes defective and no longer stabilize microtubules properly [1-2]. Furthermore, binding drug causes small conformational change of tubulin, that can propagate at long distances in the microtubule preventing the appropriate recognition by the MAPs. The result is an abnormal function of microtubule dynamic related to various side effects.

Maytansine is a well-known ligand of tubulin [3] and since its derivatives can influence the dynamics of the microtubules, the aim of project is the synthesis of new several drugs and bifunctional drugs based on Maytansinol, supported by docking study, to modulate the microtubule dynamic. In this way, the correlation between induced structural changes and observed biological effect can shed light and more explain the microtubule dynamic. During the first alcohol acylation step using different conditions, which might seem simple, wide products with and without side chain were obtained as Maytansinoids bringing a potential biological activity.

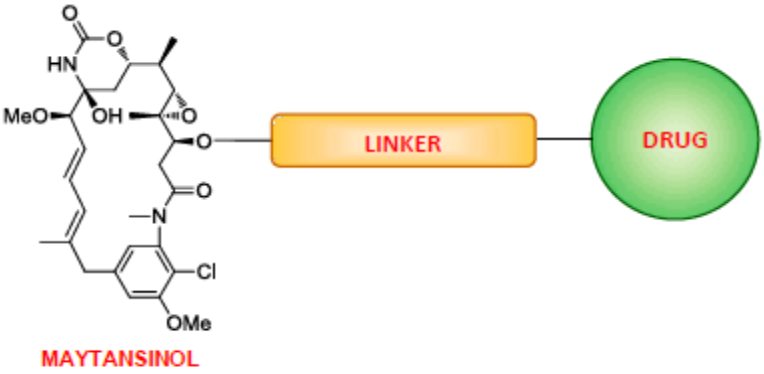

Figure 1: Drugs based on Maytansinol linked to the second drug molecule. Drug can be linked as not.

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Novel PET radiotracer for imaging of CREB binding protein in fibrotic tissue

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cAMP-response element-binding protein (CREB-binding protein or CBP) is an essential transcriptional co-activator protein of the canonical Wnt signalling pathway [1]. Its interaction with the β-catenin-Tcf-complex stimulates the transcription of Wnt target genes, which are involved in tissue development, homeostasis and regeneration. Increased level of CBP has been detected during chronic fibrotic diseases, such as Idiopathic Pulmonary Disease (IPF) [2], making it a potential target for the development of new PET tracers for the imaging in fibrosis patients. We chose ICG-001 (Fig. 1A), a potent and selective inhibitor of CBP [3], as precursor for the development of a novel radiotracer [^{18}F]ICG-001. In this work, we present the synthesis of both the reference compound and cold precursor, and the optimized conditions for the radiosynthesis of the tracer (Fig. 1B).

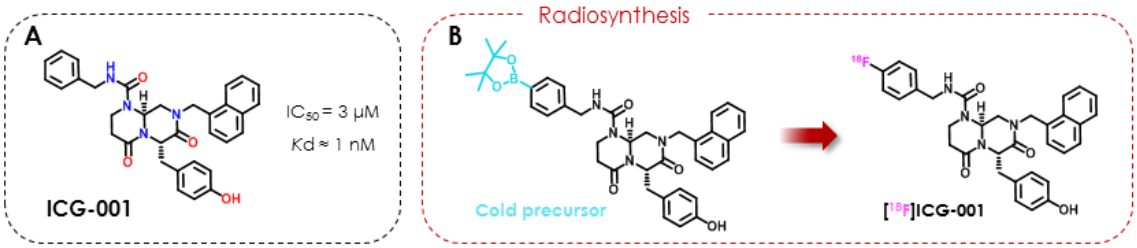

Figure 1: Structure of ICG-001 (A), and scheme of the radiosynthesis reaction (B).

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Formyl peptide receptor 2 agonists for the treatment of neurodegenerative diseases

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Formyl peptide receptor 2 (FPR2) is a G protein-coupled receptor which plays critical roles in neuroinflammatory responses. Lipoxin A4, member of the specialized pro-resolving mediators (SPMs), interacts with FPR2 to contribute to the resolution of inflammatory processes by switching of macrophages from a pro-inflammatory (M1) to an anti-inflammatory and reparative (M2) phenotype. Dysregulation of these events produces continuous release of pro-inflammatory mediators, which causes chronic inflammation. This is a central pathological process in neurodegenerative disease, such as Alzheimer's Disease, Parkinson's Disease, and Multiple Sclerosis. Therefore, mimicking the effects of LXA4 by means of drug-like molecules could have the potential to treat neurodegenerative diseases [1]. We have recently identified the FPR2 agonist MR39, which is able to reduce the production of pro-inflammatory mediators, showed neuroprotective properties in an in vitro model of neuroinflammation, promising in vitro pharmacokinetic properties. Here we report the optimization of MR39 in terms of potency and in vitro pharmacokinetic properties and the effect of our new agonists on viability/metabolic activity, necrotic death, and production of pro-inflammatory mediators in microglial cells under normal conditions and after stimulation with different inflammatory stimuli.

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Transfer hydrogenolysis of Benzyl Phenyl Ether promoted by Ni-HBEA-75 zeolite

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One of the major challenges in the catalytic valorization of lignin is the selective cleavage of the C–O bond [1]. Therefore, in order to develop selective catalytic processes for the production of aromatics from lignin, a complete understanding of the molecular aspects of the basic chemistry and reactivity of aromatic ethers is still crucial. In the last years, the use of zeolite catalysts for biomass valorization has increasingly contributed to the development of more efficient and sustainable processes thanks to their powerful and efficient performances [2].

CTH reactions has recently gained increased attention as an efficient alternative to the direct use of molecular hydrogen by improving the sustainability and economics of hydrogenation reactions [3].

In this contest, the selective cleavage of the C–O bond of benzyl phenyl ether (BPE), as model compound of lignin linkages, using a 10 wt% loading of NiO supported on BEA-75 (Si/Al = 37.5) zeolites, was explored.

Catalysts have been synthesized via ball-milling (mechanochemistry) and reactions were conducted under CTH condition with 2-propanol as H-source - or under hydrogenolysis conditions by using molecular hydrogen.

By using Ni-HBEA-75 catalyst, an appreciable BPE (0.05 M) conversion (40%) into phenol and toluene was achieved after 180 minutes at 240 °C. Being phenol and toluene the only reaction products (100% aromatic yield), it clearly indicated that the cleavage of the etheric C–O bond occurred as the primary reaction route under CTH conditions.

The conversion of BPE increased by increasing the reaction time and a good conversion (68%) and an excellent selectivity towards aromatics was achieved after 12 h.

Transfer hydrogenolysis reactions over 2-phenethylphenylether (PPE) and diphenyl ether (DPE) were also investigated. Catalytic tests show that the cleavage of C-O bond of PPE and DPE is less efficient due to the higher bond dissociation energies (β-O-4=289 kJ/mol and 4-O-5=314 kJ/mol) involved.

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Nanosized delivery systems for therapeutic proteins: a 'grafting from' approach

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The impact of protein therapeutics in healthcare is steadily increasing, due to advancements in the field of biotechnology and a deeper understanding of several pathologies. However, their safety and efficacy are often limited by instability, short half-life and immunogenicity. Nanodelivery systems, including protein-polymer bioconjugates, are currently being investigated for overcoming these limitations [1].

The goal of this work is to design novel protein-polymer conjugates to increase half-life and stability in human body without a significant decrease of their activity. Activator ReGenerated by Electron Transfer (ARGET) Atom Transfer Radical Polymerization (ATRP) in aqueous media have been investigated for conjugating functional polymers to the protein via grafting from technique [2] (figure 1). An ATRP low molecular weight initiator was firstly attached to the protein through a site specific N-terminal bioconjugation reaction [3]. This reductive amination was selected to guarantee product uniformity, and maximize the activity of the therapeutic protein, when the binding domain is far from the N-terminal group. The polymerization conditions were optimized in aqueous solutions to obtain a final PEG-based, functional polymer chains under conditions which are compatible with the protein activity.

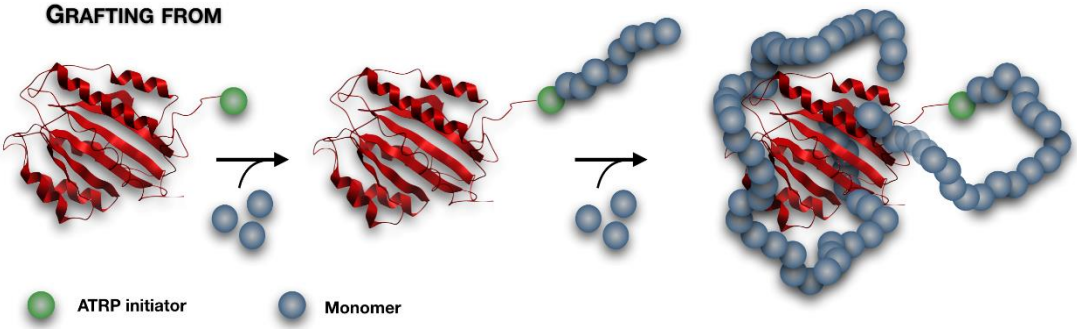

Figure 1: Bioconjugation via grafting from approach.

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Study of the effects induced by the ball milling treatment on different types of hydrocolloids in a starch-based system

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The effects of the ball milling treatment on both conformational structure and viscosity properties of three different hydrocolloids guar gum (GG), tara gum (TG), and methylcellulose (MC) were analyzed, prior to assessing their potential interactions with starch components when they are used alone or in blends into a cornstarch-rice flour system [1]. X-ray diffraction profiles (XRD) showed that the ball milling caused a reduction in the crystallin domain and, in turn, a diminished viscosity of the GG aqueous solutions. On the contrary, despite an increase in its viscosity properties, the effects on the structural evolution of TG were minimum. The milled MC showed an intermediate behavior, exhibiting more reduced crystallinity, but similar viscosity, when compared to its native form. When both milled and un-milled hydrocolloids were singly added into the starch system, the pasting properties of the resulting binary mixtures seemed to be affected by the type of hydrocolloid added rather than to structural changes induced by the treatment. In general, all the hydrocolloids increased the peak viscosity of the binary blends (especially pure GG), but only milled and unmilled-MC showed values of setback and final viscosity similar to that of the individual starch.

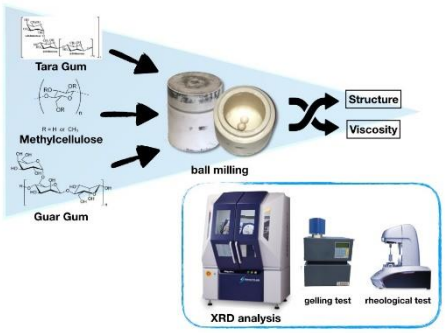

Figure 1: The ball milling treatment on hydrocolloids and subsequent characterization.

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Design and synthesis of small molecules targeting specific DNA arrangements

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The development of DNA ligands targeting specific DNA sites or arrangements is an aim that has been pursued for a long time in medicinal chemistry to identify anticancer agents and chemical probes [1]. G-quadruplex arise from guanine-rich sequences such as those that are present in telomeres and promoter genes. These structures represent a potential target in anticancer and antiviral therapy [2]. Tricyclic aromatic compounds are known ligands for DNA and some of them are selective for G-quadruplex arrangements [3].

In this work, a series of new anthracene-propargylamine derivatives were obtained through an efficient synthesis based on the A3 coupling reaction. These molecule own specific structural features for DNA ligands, as they are completely planar, capable of forming pi-stacking and hydrophobic interactions. Furthermore, to target the negatively charged DNA backbone by electrostatic interaction preserving at the same time the planarity of the molecules, a long linear alkyne arm ending with a tertiary amine, protonated at physiological pH, was introduced. A second set of designed and synthesized molecules includes anthraquinone-based compounds.

All the derivatives in the present study were at first investigated *in silico* by molecular docking, exploring the binding motif with double stranded and G-quadruplex DNA. Pharmacokinetic properties were predicted by computational methods and they follow the most recent guidelines in terms of drug-likeness.

Then, the interaction of the obtained compounds with double stranded and G-quadruplex DNA sequences was studied by electrospray ionization mass spectrometry (ESI-MS), obtaining their selectivity ratio for the two forms. Moreover, collision-induced dissociation (CID) experiments were used to investigate the relative gas-phase kinetic stability of small molecule-DNA complexes, a critical parameter for triggering biological results.

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Transfer hydrogenolysis of lignin and its derived aromatic ethers promoted by the bimetallic Pd-based catalyst

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One of the major challenges in the catalytic valorization of lignin is the selective cleavage of the C–O bond [1]. Therefore, in order to develop selective catalytic processes for the production of aromatics from lignin, a complete understanding of the molecular aspects of the basic chemistry and reactivity of aromatic ethers is still crucial. A lot of research affords have been directed to the study of the catalytic hydrogenolysis of benzyl phenyl ether (BPE), phenethyl phenyl ether (PPE) and diphenyl ether (DPE) that are the simplest model molecules of typical lignin linkages (α-O-4, β-O-4 and 4-O-5 linkages). CTH reactions has recently gained increased attention as an efficient alternative to the direct use of molecular hydrogen by improving the sustainability and economics of hydrogenation reactions. In this context, the present contribution is focused on the sustainable valorization of lignin and its derived molecules, through the application of the transfer hydrogenolysis technology, by using heterogeneous Pd-based catalysts, in order to achieve products with high-added value [2-3]. In particular, the contribution uses heterogeneous bimetallic co-precipitated Pd-based catalysts (Pd-M catalysts), such as Pd/Fe_3O_4, Pd/Co and Pd/Ni, and their textural and structural properties have been deeply elucidated through several characterization techniques (XRD, TEM, SEM, H_2-TPR, XPS and EXAFS) in order to highlight the key factors that influence the unique catalytic results observed. A comparison of the performance of bimetallic Pd-M catalysts used and that of the commercial Pd/C is also included.

The last part is dedicated to the investigation of the transfer hydrogenolisysis reaction of lignin, obtained by organosolv processes, studying the relative conversion, using the most active Pd-based catalyst (Pd/Co), in order to investigate the potential applicability in the direct valorization of lignocellulosic biomasses.

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Pretreatment and chemical characterization of cigarette butts for recycling

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About 5.7 trillion cigarettes are produced all over the world each year. Moreover, from their use, 1.2 million tons of waste as cigarette butts are largely dispersed in the environment [1]. The cigarette butts represent a complex solid matrix, consisting of paper wrapping a cellulose acetate filter and portions of unburnt tobacco. They also contain ashes from combustion and pyrolysis products. There are up to 4.000 more or less volatile and hydrophobic chemical compounds in the butts [2]. Among the many compounds present in the butts, nicotine is one of the major components, alongside with numerous toxic compounds such as phenols and heavy metals like Cu, Pb, Cr, As, Zn, Ni and Cd. In order to reduce the impact resulting from the huge amount of cigarette butts dispersed in the environment, in addition to educational programs, it is important to assess recovery protocols to encourage separate waste cigarette butts collection. In the cigarette butts, there is also the cellulose acetate, which has a great and prolonged environmental impact due to its low biodegradability, but it is potentially recyclable. The aim of this study is to propose a strategy for the pretreatment of cigarette butts in order to separate and recover cellulose acetate. Both cigarette butts and electronic cigarettes were considered. The characterization of contaminants, such as nicotine and heavy metals, shows a greater contaminant loading (from 60 to over 90 wt. %) in the residual tobacco compared to the filter. It was therefore strategic to develop a method for dry separation, by means of vibro-screening, which allows isolating the filter from the tobacco fraction to evaluate the possibility of avoiding the washing phase. Then different washing processes and the effectiveness in contaminants removal were considered. The presence of nicotine, heavy metals, other polar and apolar compounds and was therefore monitored in order to obtain a pollutants-free and therefore recyclable filter.

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In silico intermolecular recognition between 14-3-3ζ/SOS1 and small molecule stabilizers

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14-3-3 is a family of highly conserved regulatory proteins, involved in protein-protein interactions (PPIs) with hundreds of partners, which represents a highly promising target against several human pathologies such as cancer and neurodegenerative disorders [1], [2]. Over the years, two different approaches have been exploited to develop small molecule modulators of 14-3-3 activity: i) PPIs inhibition, and ii) the more innovative PPIs stabilization.

Within the framework of the EU-granted TASPPI project (Grant Agreement 675179), the purpose of this work was to characterize the binding mode of small molecule stabilizers of 14-3-3 PPIs. Based on biophysical screening, two 14-3-3ζ/SOS1 stabilizers were identified. Here, molecular dynamics (MD) simulations were carried out to obtain more information about the binding site on 14-3-3ζ/SOS1 complex as well as to depict the main interactions established by the small molecules with the protein. Starting from a minimum distance of 30 Å between 14-3-3ζ/SOS1 and each small molecule, intermolecular recognition was investigated through 500 ns of unrestrained MD simulations in explicit solvent. Cluster analysis was further used to process the resulting trajectories.

From the representative conformational structure of each complex, a hydrophobic site near the peptide-binding pocket was identified as the possible binding site of both tested compounds. Notably, this site has been already identified in prior experimental works as the possible preferred location for the interaction of fragments [3], thus supporting our theoretical results. Then, computational alanine scanning was carried out to identify the mutations that could impact more strongly on the theoretical affinity of the two molecules, which will be used to verify this binding site at the experimental level (work in progress, results will be available soon).

In this work, computational approach proved highly efficient to integrate an experimental deficit in the identification of the key residues in the interaction between 14-3-3ζ/SOS1 and two small molecules in a site that may have a new role in the identification of 14-3-3 PPIs modulators.

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Biocatalyzed oxidations in continuous flow reactors and their application in the synthesis of Captopril

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The integration of biocatalysis (either enzymes and whole-cells) and flow chemistry can lead to more controlled, sustainable and productive procedures for both pharmaceutical and fine chemical industries.

In this context, biocatalytic redox reactions play a major role, since they often occur with stereo- and regio- selectivity under mild conditions. Although the exploitation of oxidoreductases in flow reactors has many advantages (e.g. selectivity and sustainability), one important issue should be considered: oxidoreductases' functioning relies on expensive cofactors that are often not spontaneously regenerated in the catalytic cycle. We addressed this issue using whole cells, as the presence of native metabolic pathways, as well as endogenous cofactors, can be self-sufficient.

In our studies, immobilized whole cells of *Acetobacter Aceti* were exploited to perform the stereo- and regio- selective in-flow oxidation of different achiral 1,3-diols to yield chiral hydroxyacids. In order to ensure the oxygen supply, a segmented air-water flow regime was applied [1].

Among others, it was possible to obtain (*R*)-3-hydroxy-2-methylpropanoic acid, whose isolation was achieved using a catch-and-release strategy. The obtained chiral acid was then used for the synthesis of Captopril, a widely used anti-hypertensive drug, which was obtained through three sequential chemical steps performed in a continuous flow environment [2].

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Evaluation of *in vitro* and *in vivo* pharmacokinetics of novel broad-spectrum antiviral compounds against enveloped viruses

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The exponential increase of the number of emerging viral pathogens contrasts with our limited resources to develop therapies and highlights the need to develop broad-spectrum antivirals that target common components of large classes of viruses. We previously reported some rhodanine and aminothiazolone derivatives characterized by sub-micromolar activities against HIV-1 infected cells and different enveloped viruses including resistant strains [1-3].

Their selective action on enveloped viruses, time of addiction and binding experiments, suggested a mechanism of action on an early step of virus replication. We hypothesized a mechanism that causes changes in the fluidity of the lipidic bilayer, thus compromising the efficiency of the virus-cell fusion and preventing viral entry [3].

We report herein a panel of novel promising derivatives showing broad spectrum antiviral activity on clinically relevant pathogens including HSV and Flu. The *in vitro* ADME properties were assessed in order to early select the most promising lead candidate. We thus evaluated pharmacokinetic parameters of the most promising compound which was administrated *iv* at the dose of 25 mg/Kg and 12.5 mg/Kg.

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Low impact acetalization reactions

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Acetalization reaction are widely used in the protection of carbonyl groups during multistep synthesis, as well as intermediates in the monoprotection of diols. These reactions are usually carried out in toluene as a solvent with *p*-toluensulfonic acid as a catalyst, under Dean-Stark conditions [1].

The aim of this work is to develop an alternative low impact acetalization procedure. As substitute to toluene as a solvent, cyclopentyl methyl ether (CPME) [2] and 2-methyltetrahydrofuran (2-MeTHF) [3] were successfully used. These solvents are emerging as a green alternative due to their features, *i.e.*, low toxicity, high boiling point and resistance to peroxide formation.

Ammonioum salts, which are cheap, easily available, insoluble in the organic solvents and mildly acidic, were successfully employed as heterogeneous recoverable catalysts.

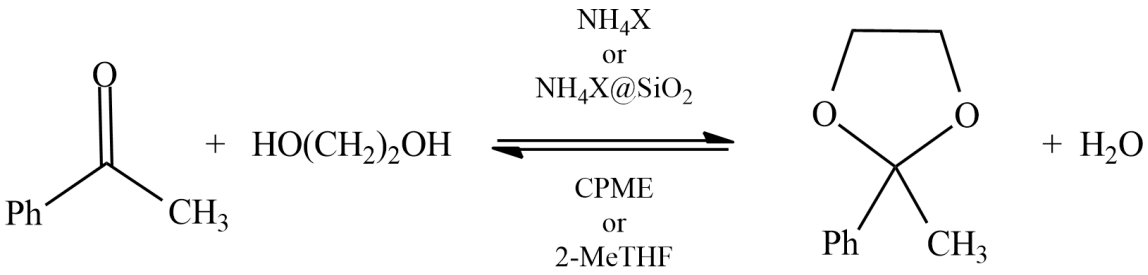

Figure 1: Acetalization of acetophenone.

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Synthesis of new organocatalysts derived from bile acids and their use in aqueous solvent

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Bile acids **1** are a very important class of natural surfactants, showing themselves and their derivatives as self-assembling materials. The morphology of the aggregates is dependent upon the substituents present both on the rigid steroid backbone and on the side chain. For this reason, they are very suitable for nanochemistry, sensing and drug delivery applications [1].

In the last years, our group has been involved in a project concerning the preparation of bile acid derivatives bearing amino acid moieties either on the C-3 or on the lateral chain of the steroid polycyclic ring [2].

Click chemistry approach was also used as useful method to link the steroid backbone to different aromatic units, such as naphthalene and anthracene, which could be good lipophilic "solvents" for the reagents used in the organocatalized reactions in aqueous solutions.

Our interest in conducting water-catalyzed organoreactions stems from the fact that water is the green solvent "par excellence" and it has been proved that it accelerates the rates of many reactions [3].

In this work, we present a variety of organocatalysts derived from bile acid bearing amino acid moieties (**Figure 1**), which we subsequentially have tested in aldolic reactions in water.

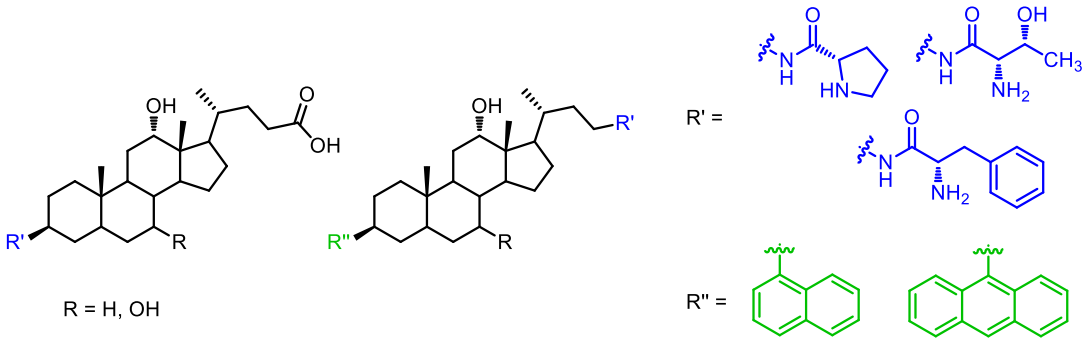

Figure 1: Bile acids' derivative organocatalysts.

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Optimization of analytical protocols for the determination of microplastics in marine sediments and oysters

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Microplastics (MPs) are plastic fragments particles having, in general, less than 5.0 mm. Recently, pollution from MP has received increased attention due to potential threat to marine ecosystem and human health. In addition, a correlation between the use of fishing nets and the presence of microfibers has been revealed in the last years. These fibers could aggregate to originate clusters, which can precipitate contaminating marine sediments, or else they could be ingested by a wide range of marine organisms, including bivalves cultured for human consumption, such as oysters. In both cases, the monitoring of the presence of MPs by proper protocols is necessary.

According to the above-mentioned assumptions, the aim of the presented work was to optimize protocols for the extraction of different types of MPs (PE-LD particles; PA; PE-HD both in irregular- and sphere-shaped particles) from marine sediment and oyster samples. For sediments, moving from NOAA, one of the most applied procedures, a new protocol was developed to treat samples with different organic matter content. An iterative method, based on two different density separation steps and one oxidation step, was developed. Good recoveries ranging from 84.0% (PA, fibers) to 100% (PE-HD, irregular particles) were achieved, with a RSD of ca. 1% (3 replicates). For oysters, the oxidation of the fat component, necessary to extract MPs, was innovatively achieved through an oxidation step with H_2O_2 and Fe solution (after the careful tune of volumes and reaction temperatures to control the exothermic reaction), followed by a density separation step. The oxidation lead to the complete degradation of the organic matrix within 1 h, thus representing a considerable improvement over the time required by other common oxidation procedures using KOH (e.g. 24 h). MPs recoveries from oyster samples were in the range 84.5% (PA, fibers) - 100% (PE-HD, irregular particles), with low RSD% (ca. 1.1%, 3 replicates). Finally, the optimized methods were successfully applied in the determination of MPs in sediments and oysters sampled in Atlantic Ocean coast.

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Bivalent ligands of Sigma-1 receptor (S1R) as a tool for studying the oligomerization process

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The biological response following ligand-S1R interaction appears to be related to the oligomerization status of the receptor. S1R agonists seem to stabilize monomers and dimers that act as chaperones, whereas antagonists bind to higher oligomer complexes, maintaining them in repository forms [1]. The equilibrium of S1R in different states of oligomerization, may explain its multiple interactions with such a wide number of heterogeneous classes of proteins. To investigate S1R oligomerization process and the biological function of S1R oligomers, we designed and synthetized a series of homo- and hetero-bivalent S1R ligands. Since S1R agonists are known to exert neuroprotective effects, and S1R can form homo-dimeric structures upon interaction with agonists, we reasoned that promoting dimerization through bivalent agonists might enhance ligand's activity. The designed bivalent compounds consist in two units of (*R*)-RC-33 (a potent and selective S1R agonist developed by our group) [2] tethered by different linkers.

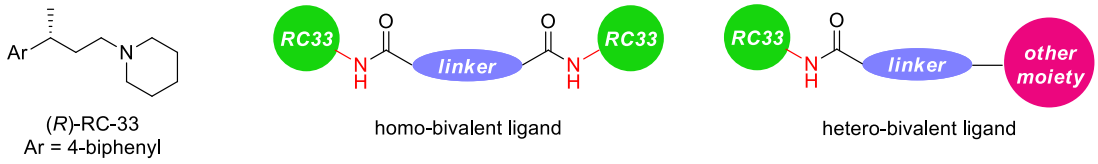

Figure 1: Design of bivalent ligands.

The S1R affinity of the bivalent ligands was evaluated using radioligands and their interaction with S1R studied performing docking experiments. The ongoing molecular dynamics studies combined with future functional assays will contribute to shed light on the S1R oligomeric states.

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Chemical evaluation of Tobacco Heating System

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Both traditional and electronic cigarettes' smoke contains several chemicals resulting toxic and/or carcinogenic for humans.

Based on the evidences we decided to investigate on a new commercially available electronic cigarette with a temperature regulation software, which heats tobacco without burning it. This fact should reduce the production of smoke compounds responsible of several human diseases.

Chemical analyzes have been carried out both on tobacco before and after the heating. Furthermore, analyzes were carried out on the smoke generated by the electronic cigarette.

The compounds, relevant for human health, analyzed in this study were the polycyclic aromatic hydrocarbons, metals, aldehydes, benzene and its derivatives, phenols and aromatic amines. In addition, we determined the nicotine content in the pre- and post-heating tobacco and in the smoke generated by the electronic cigarette.

The analyzes were performed by using an homemade, inexpensive smoke machine thanks to the use of low-cost recovery components, anyway carrying out the analysis under standard conditions (puff of 2 s and 35 mL of volume; interval between two successive puffs: 30 s).

The results obtained by the analysis on the smoke generated by the tobacco heating system were then compared with those relating to the traditional reference cigarettes [1,2] smoked under standardized conditions. Our data confirmed that in the smoke from the tobacco-heating device the content of the searched analytes was reduced in comparison with those from the burning of the traditional cigarette.

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Catalytic conversion of levulinic acid into γ-valerolactone under transfer hydrogenation conditions

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In the last years, important progresses were established in the field of lignocellulose biorefinery for the production of biofuels and biochemicals. So far, among various added value chemicals that can be obtained from biomasses, γ-valerolactone (GVL) has been considered to be a versatile platform chemical that can be used as a fuel additive, a solvent for biomass processing, and a precursor for the production of alkanes and valuable chemicals [1].

Many methods for the production of GVL have been reported. Generally, GVL is currently produced by the hydrogenation of levulinic acid (LA) and its esters in the presence of molecular hydrogen [2]. However, these hydrogenation strategies suffer from high H_2 pressure and a low catalyst stability or reactivity which limit their large-scale application to a certain degree. In this regard, one of the most interesting approaches is the catalytic transfer hydrogenation (CTH) [3]. In CTH reactions, the use of an indirect H-source reduces most of the problems related to the use of high-pressure molecular hydrogen (e.g. purchase, transport, safety hazards, and pricey infrastructure), thus improving the sustainability of industrial processes (at the present time, several H-donor molecules can be obtained from renewable feedstocks).

This study focusses on the production of γ-valerolactone from levulinic acid in the presence of Pd/C and Ru/C as heterogeneous catalysts, both under classic hydrogenation conditions as well as using methanol, ethanol and 2-propanol as solvent/H-donor. The experimental evidence shows that GVL formation occurs through the Meerwein–Ponndorf–Verley (MPV) reaction with 2-propanol being the best H-donor solvent due to its higher tendency of secondary alcohols to release hydrogen.

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MS-based molecular networking leads to the identification of a new cyclic heptapeptide from the sponge *Stylissa caribica*

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A major challenge in natural product research is the fast identification of new bioactive secondary metabolites from complex mixtures. MS-based molecular networking in the field of natural products is a helpful supplement to the traditional dereplication methods [1]. This innovative strategy provides a visual representation (the network) of the structural similarity between molecules, as inferred by the relatedness of their LC−MS/MS data determined by a computational algorithm [2].

The strength of molecular networking for fast dereplication will be shown in the study of extracts from the marine sponge *Stylissa caribica*. The Bahamian sponge *Stylissa caribica* has been extensively investigated by many research groups, and a wide range of brominated pyrrole-imidazole alkaloids and cyclic peptides were identified from it. Still, the molecular networking approach allowed the fast identification of a new cyclic heptapeptide related to stylissamide A. The structure elucidation of the unknown compound was performed based on liquid chromatography-high resolution MS/MS spectra and 1D and 2D NMR spectroscopic data. The absolute configuration of the seven amino acid residues was assigned by advanced Marfey's methodology, revealing for all amino acids the L-configuration.

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Iron oxide/OxyHydroxide thin films: electrochemical studies

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Iron oxides/oxyhydroxides are abundant materials and their films are useful in many scientific and technological applications. These compounds are implicated in corrosion processes as different species (green rust (GR), amorphous ferric phase, …) [1].

The corrosion layer growth and evolution are difficult processes to follow because of unclear species involved in its formation. Iron corrosion is one of the most important process for artefacts conservation.

It is worth studying in order to find new methodologies for the cultural heritage preservation. To allow an *in situ* study of the corrosion process and its involved species, an electrochemical simulation was carried out [2].

For this purpose, GR films are electrodeposited on GC working electrode and they are electrochemically reduced by cyclic voltammetry.

The studies aim is understanding the green rust film behaviour in several experimental conditions to evaluate its resistance, support electrolytes concentration impact, pH influence and Cl- ion rule. This investigation could help the restorers to optimize the decloruration process that is the wide used process in order to stop the corrosion process in the iron artefacts.

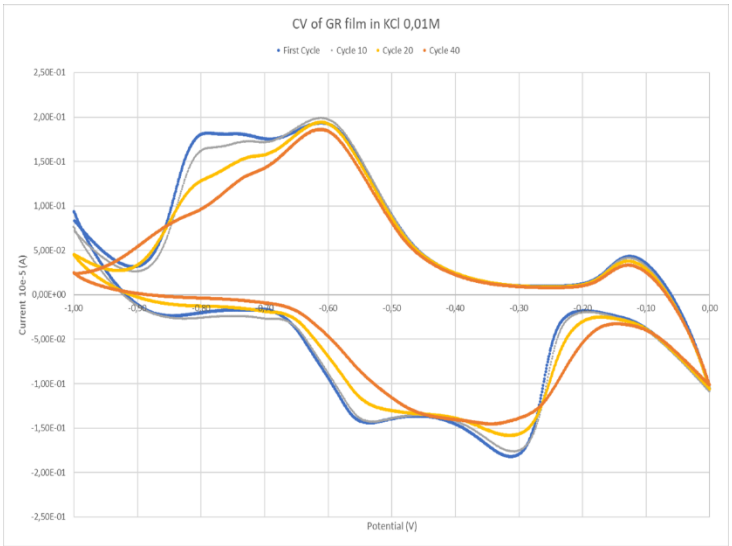

Figure 1: Cyclic Voltammogram of GR film in KCl 0.01M.

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Comics & Science: what a tool for chemical dissemination

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The role of comics in science communications has been subject of a number of recent papers [1]. While some debate on an accepted definition of what constitutes a science comics is still ongoing, the role of comics in science outreach is now universally recognized [2].

Here we present the *Comics&Science* comic books published by CNR Edizioni and edited by Roberto Natalini and Andrea Plazzi. The *Comics&Science* concept was implemented in the first place as a section of the *Lucca Comics&Games festival*, followed by the printed series in 2013.

Comics&Science's philosophy is to have science elements, ideas and "bits" integrated into cartoons by the best professional writers and artists. The story must be fun, entertaining and overall artistically and aesthetically significant. Each issue is completed by articles and pieces about and around the topics touched by the story. A *Comics&Science* issue almost always starts with the cartoonist visiting a research lab/facility. Tipically, the artist has little or no formal scientific background and up to now this has proved to be an effective starting point for exchanging opinions and a cross-debate of sorts.

Figure 1: Snapshots from C&S issues.

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Study of isosteric substitutions of the 1,4-benzodioxane oxygen atoms in benzamides FtsZ inhibitors

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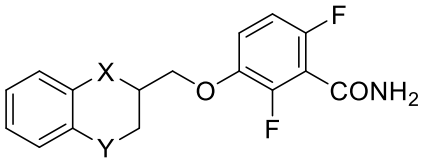
Multi-Drug Resistant bacterial infections are predicted to cause more than 10 million deaths each year by 2050. Among several factors, the development of this global health-threatening problem is primary caused by the lack of new antibiotics being developed [1].

In this context, targeting the cell division system can be the strategy to bypass antibiotic resistance. In particular, FtsZ is an optimal target: it is a crucial protein for the bacterial division system, it is highly conserved between bacteria and mycobacteria and shares only less than 20% of sequence with its human functional homologue (β-tubulin).

In the last year we developed a class of potent FtsZ inhibitors with an 1,4-benzodioxane-benzamide structure characterized by high activity (MIC < 1 μg/mL vs both MSSA and MRSA). The oxygen atoms of the benzodioxane ring were successively replaced with bioisosteric atoms like Nitrogen, Sulfur and Carbon (Figure 1) [2-3].



X = **Y** = O
X = **Y** = S
X = **Y** = NMe
X = **Y** = CH_2
X = S, **Y** = O
X = O, **Y** = S
X = CH_2, **Y** = O
X = O, **Y** = CH_2
X = NMe, **Y** = O
X = O, **Y** = NMe

Figure 1: General structure of benzodioxane-benzamides analogues.

Here we report the synthesis and the biological results of these derivatives. We demonstrated the importance of the Oxygen in 1- position in the 1,4-benzodioxane moiety in the maintaining of the antimicrobial activity. Conversely, the nature of the heteroatom at 4- position can differently modulate the antimicrobial activity of the derivative.

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[2] V. Straniero, M. Pallavicini, G. Chiodini, C. Zanotto, L. Volontè, A. Radaelli, C. Bolchi, L. Fumagalli, M. Sanguinetti, G. Menchinelli, G. Delogu, B. Battah, C. De Giuli Morghen, and E. Valoti, *Eur. J. Med. Chem.* **120** (2016) 227-243.
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Application of an electro-activated glassy-carbon electrode to the determination of Diclofenac in water solution

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The occurrence of pharmaceuticals in the environment and in surface waters is a problem of increasing concern and it is mainly caused by discharges from municipal wastewater treatment plants. The reason is that the purification processes, such as those based on activated sludge, are often unable to efficiently remove these pollutants [1]. Specifically, Diclofenac (henceforth, DCF:2-[2-(2,6-dichloroanilino)phenyl] acetic acid) has been found to be rather unaffected by the purification process. Thus, it is often detected in the plant's effluents and in the receiving water bodies.

The aim of this work is to develop a screening electrochemical method that employs an activated GCE (Glassy Carbon Electrode) to determine DCF in surface waters [2]. To understand the electrochemical behavior of the molecule on the activated GCE surface, a study using Cyclical Voltammetry (CV) and Differential Pulse Voltammetry (DPV) was conducted. The voltammetric signal due to the DCF was studied as a function of the pH. The best results in terms of both sensitivity and linear response were obtained using a 2 mM phosphoric buffer at pH 2. The Red/Ox mechanism involving the molecule was studied. The analysis of the DCF voltammograms and the literature data [3] allowed us to identify the Red/Ox pairs involved in the voltammetric process. The signal due to the reduction of the oxidation sub-product of DCF showed a linear response by increasing the DCF concentration. This is an optimal condition for the construction of a calibration curve and for the determination of DCF by Differential Pulse Voltammetry (DPV). The DPV parameters were optimized by using a Design of Experiment approach and the linearity of the response was assessed in ultra-pure water.

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LCA, LCC and socio-economic impact on GOAST-Green Organic Agents for Sustainable Tanneries-project

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Life GOAST project is a European project funded by LIFE Programme, which focuses a novel leather tanning technology. In particular, Goast technology aims to develop a more sustainable tanning process based on the combination of polymer based chemicals and protocol which allows to produce Chrome-Free high-quality leather. In order to assess environmental, economic and human health potential impacts of the whole GOAST tanning strategy, Life Cycle Assessment (LCA), Life Cycle Costing (LCC) and socio-economic impact, have been performed.

The LCA involves a first study of LCA of leather tanned with new tanning agent compared with the LCA of leather chrome-based. The research aims to demonstrate that the removal of chrome from tanning chain allows to reduce its environmental impacts without affecting on leather quality.

Complementary to LCA, in LIFE GOAST project, the LCC analysis aims to understand and compare costs throughout the life cycle stages of the leather tanning process performed with the two alternative methods, the innovative and the chrome-based.

Finally, the Socio-Economic action has the objective to build a framework in order to assess both the economic sustainability and the socio-economic impacts on the community deriving from the use of the GOAST tanning. The socio-economic analysis involves a survey of the impact on two different stakeholders, companies and workers. To accomplish with this objective, two web-based questionnaire surveys have been designed and administered: one for companies and the other for workers.

Synthesis of alloy NPs by laser ablation and investigation of their properties for biomedical imaging

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In this study, we used the technique of laser ablation synthesis in liquid solution (LASiS) to synthesize alloy nanoparticles to be employed as biocompatible multimodal contrast agents (MCAs) in biomedical imaging, such as magnetic resonance imaging (MRI) and x-ray computed tomography (CT). This synthetic technique permits to obtain nanomaterials characterized by a metastable phase that are difficult to obtain by chemical method [1].
The MCAs show two advantages: first it's possible to do the imaging of the same area with two complementary techniques (MRI and CT) and second, it's possible to reduce the total dose administered to the patient [2].

The elements in which we focalized our attention are Gold (Au), and Iron (Fe). The choice of these materials was dictated by their important chemical-physical properties and for their ability to be used in biomedical field: 1) all these two elements are biocompatible, a key point for biomedical applications; 2) iron has excellent magnetic properties, for this reason it's a very good contrast agent for MRI; 3) gold is easily functionalizable with biocompatible polymers and exhibits excellent X-ray absorption, necessary for CT.

The synthetized nanoparticles are characterized by different techniques: TEM was used to study their size distribution and to monitor the change in structure over time; XRD was performed to determine the crystallographic structure of the material; ICP was use to understand the ratio between the elements in the alloys; VSM permited to check the magnetic properties of the samples. Lastly, the preliminary biocompatibility test confirm that our materials are suitable for in vivo test.

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ElementaLe Watson! Alla scoperta della tavola periodica

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The exhibition provides a guided discovery to the fundamental chemistry of some elements of the Periodic Table. The discovery through simple experiments (flame essays, luminescence, redox reactions, solubility) is interspersed by selected pieces of The Periodic Table of Primo Levi. In detail:

-the similar appearance of salts of the first group lead to the difference in light emission (flame essays);

-the same approach applies to the elements of the second group;

-the light emission is applied to the discovery of noble gases, the matter that we cannot see or touch;

-the colour of some metals are the starting point of experiments and a discussion about the identification of the elements of the eleventh group (redox and precipitation reactions);

-finally, the differences between carbon and silicon are highlighted by acid-base reactions.

Each experiment is accompanied by a movie that shows the text of the selected piece of The Periodic Table of Primo Levi and some pictures of materials containing the elements involved in the experiment.

The public is asked to attend the experiments and to choose the placement of the elements in the right place in a blank grid-shaped as the Periodic Table. The Mendeleev's classification criterion, based on the atomic mass of elements, is highlighted as well as the effort made in classification based on macroscopic observations of the matter behaviour.

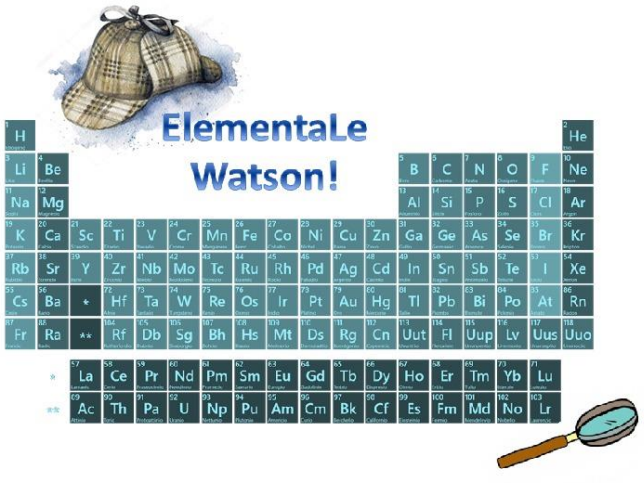

Figure 1: Laboratory's logo

Ab initio study of Li-rich layered transition metal oxides as positive electrodes in Li-ion batteries

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In the last decades, remarkable industrial and academic research efforts have been focusing on lithium-ion batteries (LIBs) for portable electronics and electric vehicles (EV) [1]. Generally speaking, LIBs are more expensive than other battery chemistries, but they provide the highest power and energy densities as well as longer cycle. However, this technology requires further development in terms of safety and performance to establish itself in the automotive market. Thus, new materials and chemistries at the positive/negative electrode sides as well as at the electrolyte side are necessary to overcome the state-of-the-art and the commercial benchmarks.

Over-stoichiometric Li-rich nickel manganese cobalt (LNMC) oxides are a family of promising positive electrode materials with large specific capacity and high working potential. The crystal structure and cation ordering of LNMC are a matter of controversy. In the literature the structure of these materials is identified as solid solution, with an $R\bar{3}m$ crystal structure [2] with partial supercell ordering of lithium ions, or as a nano-mosaic constituted of coexisting solid-solution phases with $R\bar{3}m$ and $C2/m$ structures [3]. Here we present a preliminary analysis of mono-component stoichiometric $LiMO_2$ (M=Mn, Co, Ni) layered phases with $R\bar{3}m$ and $C2/m$ structures (see the figure 1 below). Our aim is to analyse the relative thermodynamic stability of these lattices and the peculiarities of the electronic structures. We apply a state-of-art quantum mechanical approach, based on density functional theory (DFT) and periodic boundary conditions ; in particular, we use DFT+U methods, which corrects for the large self-interaction error (SIE) caused by the approximate form of standard exchange-correlation density functional when applied to strongly localized unpaired electrons, ad in the d manifold of Mn, Co and Ni.

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Unexpected reactivity of methylammonium and formamidinium in aged organometal halide perovskites solution

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Organometal halide perovskites have revolutioned the field of optoelectronics during the past 10 years. Today's best perovskite solar cells (PSC) use a mixture of formamidinium (FA), methylammonium (MA), and cesium (Cs) as a monovalent cations [1-2]. The resulting triple-cation perovskite compositions enables more reproducible and stable device performances over time. However, it is commonly accepted in the scientific community that the complex precursors solution needs to be freshly prepared and readily used to avoid undesirable, and not well understood so far, decrease of device performances [1]. Nuclear Magnetic Resonance (NMR) spectroscopy is a key tool to investigate the solution chemistry of the perovskite precursors [3]. Here, through this technique, we unravel an unexpected reactivity between MA and FA in solution leading to the formation of the new species (N-methyl-formamidinium). We have explored different experimental conditions that deeply modify the reaction kinetics and we have correlated the presence of the new species with the performances of PSCs in inverted architecture (p–i–n configuration), fabricated from precursor solutions at different aging times. The relationship between the solution chemistry and the optoelectronic properties of the final devices allows to draw up a guideline for the stabilization over time of the precursors solution with the aim of optimizing the fabrication of high performing PSCs.

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Using information solutions to understand the potential risks and control strategies of substances

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This presentation will cover the ways in which information solutions, such as Reaxys, can be used to better understand the potential risk that substances pose to human health and the environment. By having a greater understanding of these potential risks, an effective strategy for their control can be devised.

New Tools for Medicinal Chemistry

Manuela Vacatello

Research Technology Specialist for Chemistry at Merck
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At Merck we collaborate with chemists to make new chemistry available globally. New chemistry that helps accelerate discovery in important fields that improve human life, like for example in drug discovery.

Here are introduced some innovative products at different stages of the drug discovery workflow, as in lead discovery, reaction design, synthesis and new reaction platforms such as photocatalysis.

Metal oxide and perovskites in industrial coating matrix for electrochemical water splitting

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Industrie De Nora S.p.A., Milan, Italy 20158
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Hydrogen (H_2) is one of the promising solutions for sustainable and green energy problem. One of the most efficient ways of producing H_2 at low cost and high purity is the electrochemical water splitting into H_2 and O_2. However, the process is still not optimal because of the sluggish kinetic of the anodic oxygen evolution reaction (OER) due to the well-known scaling relation restriction [1]. Thus, it is important to develop efficient OER catalysts with large surface area, abundant active sites and good stability using simple and economical synthesis method.

In this work, metal oxide (IrO_2) and perovskites ($LaMnO_3$ and $LaNiO_3$) were synthesized using glycine combustion technique [2]. These synthesized powders were integrated in the coating matrix for alkaline water electrolysis. OER was investigated under industrial relevant conditions (high temperature and high pH) at varying current densities up to 10 kA/m^2 (1000 mA/cm^2). Results from the electrochemical tests (Figure 1) showed the catalytic activity of the materials. Overpotential values, η, of the coated Ni substrate were 40 to 60 mV lower than the uncoated Ni substrate. In summary, the study has demonstrated the feasibility of integrating electrocatalysts in the industrial coating matrix deposited on metallic substrates as an anode for alkaline water electrolysis.

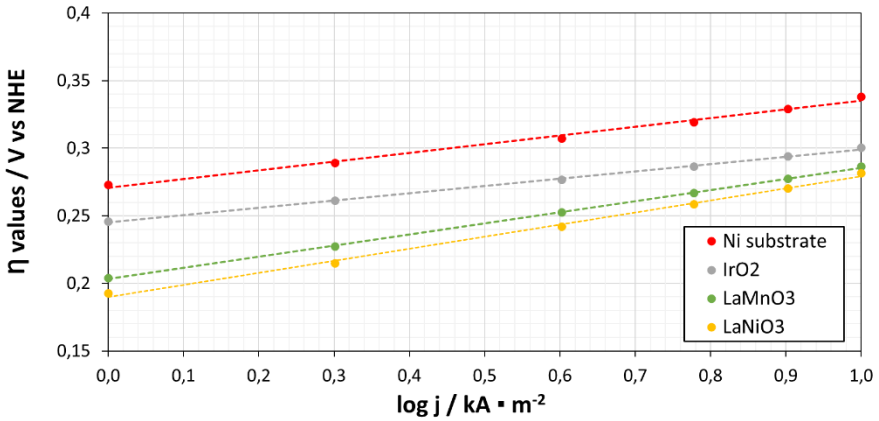

Figure 1: Tafel plots of bare Ni, IrO_2, $LaMnO_3$ and $LaNiO_3$ in KOH solution.

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The value of academic-industrial collaborations: Reaxys Research and Development (R&D) network

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The increase in demand for structured, annotated and reliable chemical reactions' data is due to improvements of machine learning (ML) algorithms and continuous growth in computer processing power. Reaxys R&D Network is the network of academic research groups, each of which is using the real-world Reaxys chemistry and/or medicinal chemistry data to design and improve methods and models that advance research and scientific discoveries in chemistry and medicinal chemistry fields. For example, the data is used for reaction predictions/optimizations, historical analyses of reactions and substances, chemical space visualisation and drug discovery. Most notably, reaction predictions, specifically retrosynthesis, found a lot of interest in the industry showing the potential to change how chemists may work in the future.

In the past few years Elsevier has been working relentlessly with the Italian Chemical Society (SCI) to increase awareness of its diverse solutions, launching various awards to financially support junior and senior researchers in the chemical and biological fields, promoting usage of Elsevier's products and sponsoring chemistry related conferences. One of the latest activities was creation of a survey about Italian researchers' attitudes towards data access and data sharing in the chemical and biological fields. By understanding methods and applications used, types of experimental data generated, as well as challenges faced by Italian researchers, the results of this survey will shape future initiatives to support best practices in research data sharing. Finally, together with SCI we want to attract excellent teams to initiate interesting projects using experimental and published data combined with ML technologies creating and improving predictive applications for the benefit of chemical, biological and pharmacological sciences.

Come preparare un buon cv e come affrontare un'intervista di successo in un'azienda privata

Roberta Costantini[a] and Federica Ladogana[b]

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Sei soddisfatto del tuo CV? Sei pronto per affrontare un colloquio di selezione? I recruiter di Merck mettono a disposizione la loro esperienza maturata in aziende private per dare consigli pratici su come scrivere un buon curriculum, quali tipi di interviste esistono e come affrontare un colloquio di successo!

Mentoring Young Researchers: the Elsevier's Role

Marta Da Pian, Carlos Rodriguez del Rio, Elena Herzog, Alica May, Agne Karose, and Juan Pablo Aita Vassallo

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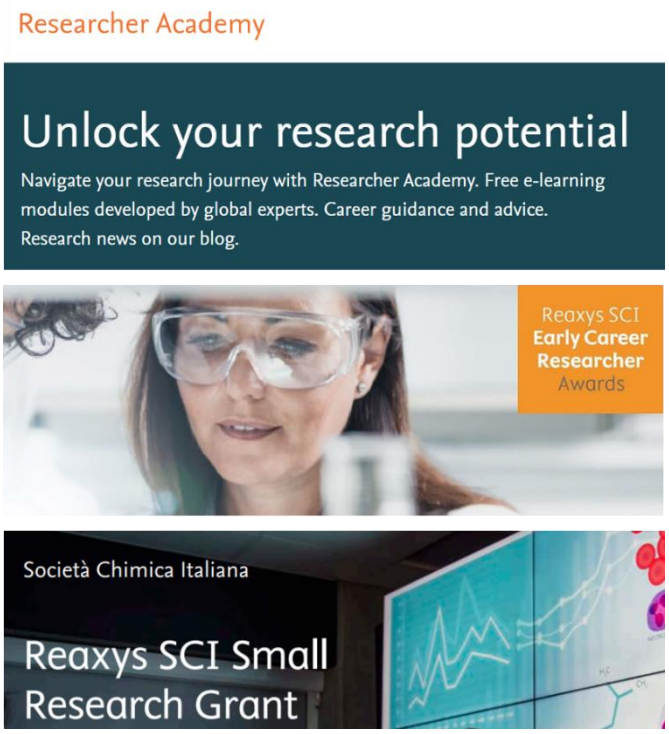
Have you ever felt the pressure of pursuing an academic career and wondered what are the requirements to be a successful researcher? Have you ever felt lost among ideas not knowing how to shape them in a grant application? Then you know how crucial it is to receive the right guidance in the path you chose. A mentor can help you deal with your career challenges whether it is choosing between academia and industry, or writing a good manuscript and publishing it in the most appropriate journal. These are just a few examples of what the Researcher Academy [1] platform offers to young scientists. And it is not the only initiative that Elsevier organizes to recognize and assist young researchers. Together with Società Chimica Italiana Elsevier also organizes the Reaxys SCI Early Career Researcher Award [2] and the Reaxys SCI Small Research Grant [3] to support early career chemists.



[1] https://researcheracademy.elsevier.com/
[2] https://www.elsevier.com/awards/reaxys-sci-small-research-grant
[3] https://www.elsevier.com/awards/reaxys-sci-early-career-researcher-awards

EYCN – The European Young Chemists' Network

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The European Young Chemists' Network (EYCN), the young member's division of EuChemS, is a motivated team of young scientists from 25 different European countries 27 Societies.

The EYCN spent the last years working towards promoting the exchange of knowledge, experience, new ideas and projects among young chemists coming from academia and companies. One of the aims is also to improve the visibility of chemistry, bring it closer to a wider audience and to people from outside the research field - such as industry, business and management. Moreover, the EYCN wants to support young chemists at the beginning of their career with awards and activities focused on developing soft-skills and expanding their possibilities. EYCN sponsors award all around Europe and every two years, we announce the Young Chemist Award (EYCA) in collaboration with SCI and the FNCF. The EYCN organizes career days and has promoted the Young Chemists Crossing Borders exchange program (YCCB) in collaboration with the Younger Chemists Committee of the American Chemical Society (ACS YCC) since 2011 [1].

The EYCN hosted the 2nd European Young Chemists' Conference (EYCheM) in Bremen (DE) last March. Our network offers a mentoring program for Marie Curie fellowship and ERC starting grant applicants during the last ECC7 Congress, and these seminars are online on our YouTube Channel!. If you wish to get in touch with us, please visit our website www.eycn.eu, or contact us using our social media profiles on Facebook (@EYCN), Twitter (@YoungChemists) or LinkedIn.
We look forward to collaborating with you!

Figure 1: EYCN Delegates attending the 14th Delegates Assembly in Bremen (DE)

[1] U. I. Zakai, N. LaFranzo, C. Dunne, and J. Breffke, *ChemViews Mag* (2015)

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Società Chimica Italiana

Società Chimica Italiana (SCI) is a scientific association that includes nearly 4000 members. It was founded in 1909 and erected as a Legal Institution with R.D. n. 480/1926.

Società Chimica Italiana

SCI members carry out their activities in universities, public and private research institutes, schools, industries, or as freelancers. They are joined not only by the interest in chemical sciences, but also by the desire to contribute to the cultural and economic growth of the national community, within a global framework, improving the quality of human life and the protection of the environment.

SCI is organized in Divisions and Sections: Divisions are *thematic* branches, gathering members working in the same field or sharing the same scientific interests; Sections are *local* branches, gathering people working or living in the same territory.

For new members

All the participants to the *Merck Young Chemists' Symposium* are (or are going to be) SCI members.

Those who were not yet SCI members before the conference, must fill the request form included in the Conference bag in order to complete the membership procedure.

Those who chose the 1-year subscription will be enrolled until 31/12/2020; those who chose the 2-year subscription will be SCI members up to the end of 2021.

SCI Giovani / SCI Young

All SCI members younger than 35 years old belong to *SCI Giovani*, an interdisciplinary group organizing multiple iniziatives precisely devoted to youngers, such as prizes, workshops, and the very congress you are attending.

Società Chimica Italiana
Gruppo Giovani

You can find all the information about these activities on our website

https://www.soc.chim.it/sci_giovani/home

as well as on our social media pages

@SCI Giovani

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